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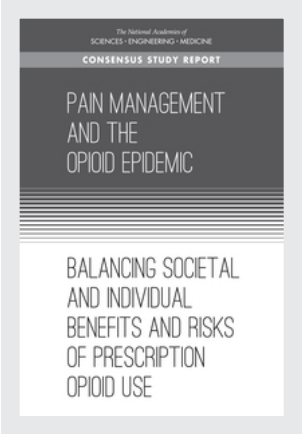

Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use (2017)

DETAILS

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PAIN MANAGEMENT AND THE OPIOID EPIDEMIC

BALANCING SOCIETAL AND INDIVIDUAL BENEFITS AND RISKS OF PRESCRIPTION OPIOID USE

Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse

Richard J. Bonnie, Morgan A. Ford, and Jonathan K. Phillips, *Editors*

Board on Health Sciences Policy

Health and Medicine Division

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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 **KRISTINE M. GEBBIE,** Flinders University, and **SARA ROSENBAUM,** The George Washington University. 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.

Preface

Nature and human ingenuity have spawned a class of opioid drugs that alleviate pain and, not coincidentally, induce feelings of well-being. Unfortunately, overprescribing and misuse of these drugs pose serious risks to individuals who consume them and the population at large. Industrial and postindustrial societies have been grappling with the challenge of balancing these benefits and risks for more than 150 years. Alarmingly, rates of opioid use disorder (OUD) and opioid overdose deaths have reached unprecedented levels over the past two decades, and have risen much faster in the United States than in most other countries.

U.S. Department of Health and Human Services data suggest that at least 2 million Americans have an OUD involving prescribed opioids and nearly 600,000 have an OUD involving heroin, with about 90 Americans dying every day from overdoses that involve an opioid. Recognizing the magnitude of the problem, the U.S. Food and Drug Administration (FDA) asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to characterize the epidemic and to recommend actions that the FDA and other public and private organizations should take to address it, balancing society's interest in reducing opioid-related harms with the needs of individuals suffering from pain. It was my privilege to chair a committee of talented experts chosen by the National Academies to carry out this important charge.

Few communities have been left untouched by the recent surge of opioid-related deaths. Perhaps at no time in modern history has there been broader public understanding of the nature and consequences of substance use disorder, including OUD. Indeed, the broad reach of the epidemic has

blurred the formerly distinct social boundary between use of prescribed opioids and use of heroin and other illegally manufactured ones. These unfortunate developments may have finally reframed the "cops versus docs" debate that has characterized U.S. drug policy since World War II.

It has become clear (and is well-documented in this Consensus Study Report) that the opioid epidemic will not be controlled without deploying multiple policy tools. Increasing access to treatment for individuals with OUD is imperative, together with a substantial program of research to develop new nonaddictive treatments for pain. The committee urges the FDA to reshape and monitor the legal market for opioids and to facilitate use of safe and effective agents for treating persons with OUD and reducing overdose deaths. In addition, the professional societies, insurers, health care organizations, pharmaceutical manufacturers, and state and federal agencies collectively responsible for shaping prescribing practices should attend to the multiple weaknesses in the nation's health system that led to this epidemic. Meanwhile, law enforcement agencies will continue to be responsible for curtailing trafficking in illegally manufactured opioids, most recently the low-priced, high-potency fentanyl manufactured in clandestine labs domestically and also streaming into the country from abroad. Although criminal drug law enforcement was beyond the scope of this report, the need for improved tools for tracking the dynamic interaction between the legal and illegal markets is one of its core themes.

The Controlled Substances Act, which provides one of the two prongs of federal statutory regulation of opioids (the other being the Food, Drug, and Cosmetic Act), was enacted by Congress in 1970, as part of an omnibus drug policy bill that also established the National Commission on Marijuana and Drug Abuse, for which I had the honor of serving as Associate Director. The Commission's second report, issued in 1973, championed strong roles for federal public health agencies, and for federally funded scientific research, in a coordinated national policy for substance use disorder prevention and treatment. Perhaps the tragic effects of the opioid epidemic will reinvigorate federal leadership and provide the impetus for comprehensive and sustained national action.

Richard J. Bonnie, *Chair*
Committee on Pain Management and Regulatory Strategies
to Address Prescription Opioid Abuse

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The National Academies of Sciences, Engineering, and Medicine's (the National Academies') Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse and its supporting staff thank the representatives of the study sponsor, the U.S. Food and Drug Administration, including Robert Califf, Sharon Hertz, Joshua Lloyd, and Douglas Throckmorton, who gladly provided the committee with background information, responded to questions, and participated in the committee's open sessions and workshops. We also thank the many other individuals who shared their expertise and information during the committee's workshops (see Appendix A for the names of the speakers). Their contributions informed the committee's deliberations and enhanced the quality of this Consensus Study Report. The study staff, including board director Andrew Pope, study director Morgan Ford, associate program officer Jonathan Phillips, and administrative assistant Thelma Cox, were central in shepherding the report through all its stages. The committee would also like to thank senior program officers Anne Claiborne and Clare Stroud for the guidance they provided throughout the study, as well as science writer Erin Hammers, who helped to draft portions of the report. Special thanks are also due to Rona Briere and Alisa Decatur for their editorial support. We also appreciate the many staff at the National Academies who contributed to the production and review of the report, including Daniel Bearss, Clyde Behney, Christie Bell, Chelsea Frakes, Ellen Kimmel, Janice Mehler, Bettina Ritter, Lauren Shern, and Taryn Young. The committee and staff also extend their gratitude to Greta Gorman, Nicole Joy, Sarah Kelley, An Nguyen-Gia, and Jennifer Walsh for their assistance with report communications and release activities.

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Acronyms and Abbreviations

ACA	Patient Protection and Affordable Care Act
ADAM	Arrestee Drug Abuse Monitoring
ADF	abuse-deterrent formulation
ADP	adenosine diphosphate
ANDA	Abbreviated New Drug Application
APAP	N-Acetyl-p-Aminophenol (acetaminophen)
ARRIVE	Animals in Research: Reporting In Vivo Experiments
ASAM	American Society of Addiction Medicine
ASIC	acid-sensing ion channel
ATP	adenosine triphosphate
BH4	tetrahydrobiopterin
BMT	buprenorphine maintenance therapy
CASP6	caspase-6
CB	cannabinoid receptor
CBT	cognitive behavioral therapy
CDC	U.S. Centers for Disease Control and Prevention
CDSS	clinical decision support system
CEWG	Community Epidemiology Working Group
CGMP	Current Good Manufacturing Practice
CHARM	Children and Recovering Mothers
CI	confidence interval
CNCP	chronic noncancer pain
CNS	central nervous system

CoEPE	Center of Excellence in Pain Education
COMM	Current Opioid Misuse Measure
COX	cyclooxygenase
CRPS	complex regional pain syndrome
CSA	Controlled Substances Act
CSF1	colony-stimulating factor 1
DA	dopamine
DAMP	damage-associated molecular pattern
DATA	Drug Addiction Treatment Act of 2000
DAWN	Drug Abuse Warning Network
DDD	defined daily dose
DEA	U.S. Drug Enforcement Administration
DIRE	Diagnosis, Intractability, Risk, Efficacy tool
DoD	U.S. Department of Defense
DOJ	U.S. Department of Justice
DOPR	delta opioid receptor
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
DTC	direct-to-consumer
DUR	drug utilization review
ECHO	Extension for Community Healthcare Outcomes
EEG	electroencephalogram
EMR	electronic medical record
EP3	E prostanoid receptor 3
EpFA	epoxy fatty acid
ER/LA	extended-release/long-acting
ERK	extracellular signal-regulated kinase
ETASU	elements to assure safe use
FAAH	fatty acid amide hydrolase
FAERS	FDA's Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
FDASIA	FDA Safety and Innovation Act of 2012
FDCA	Food, Drug, and Cosmetic Act
FQHC	federally qualified health center
GI	gastrointestinal
GPR	G protein-coupled receptor
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GTP	guanosine triphosphate

HCV	hepatitis C virus
HHS	U.S. Department of Health and Human Services
HIV	human immunodeficiency virus
HMGB1	high mobility group box 1 protein
ICD	*International Classification of Diseases*
IL-6	interleukin-6
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IND	Investigational New Drug
IOM	Institute of Medicine
IPRCC	Interagency Pain Research Coordinating Committee
IR	immediate-release
KOPR	kappa opioid receptor
MAT	medication-assisted treatment
MCH	maternity care home
MED	morphine equivalent dose
MME	morphine milligram equivalents
MOMS	Maternal Opioid Medical Supports
MOPR	mu (μ) opioid receptor
MPGES	microsomal prostaglandin E synthase
NAc	nucleus accumben
NAS	neonatal abstinence syndrome
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NDA	New Drug Application
NDEWS	National Drug Early Warning System
NeuPSIG	Neuropathic Pain Special Interest Group
NFLIS	National Forensic Laboratory Information System
NGF	nerve growth factor
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NMDA	*N*-Methyl-D-aspartate
NMPR	nonmedical pain relief
NNT	number needed to treat
NorBNI	norbinaltorphimine
NSAID	nonsteroidal anti-inflammatory drug
NSDUH	National Survey on Drug Use and Health
OIH	opioid-induced hyperalgesia

ONDCP	Office of National Drug Control Policy
OPRM1	opioid receptor mu1
OR	opioid receptor
ORT	Opioid Risk Tool
OTA	opioid treatment agreement
OTC	over-the-counter
OUD	opioid use disorder
PAMP	pathogen-associated molecular pattern
PDMP	prescription drug monitoring program
PG	prostaglandin
PGE	prostaglandin E
PHN	postherpetic neuralgia
POATS	Prescription Opioid Addiction Treatment Study
POMAQ	Prescription Opioid Misuse and Abuse Questionnaire
PPA	patient–provider agreement
PPRECISE	Preclinical Pain Research Consortium for Investigating Safety and Efficacy
PRR	pattern recognition receptor
PVB	paravertebral block
PWID	people who inject drugs
QALY	quality-adjusted life year
QL	quantity limit
RA	rheumatoid arthritis
RADARS	Researched Abuse, Diversion, and Addiction-Related Surveillance
RAGE	receptor for advanced glycation end products
RCT	randomized controlled trial
REMS	Risk Evaluation and Mitigation Strategy
RF	radiofrequency
RICO	Racketeer Influenced and Corrupt Organizations Act
RMTg	rostromedial tegmental nucleus
SA	short-acting
SAFE	Safety, Appropriateness, Fiscal Neutrality, and Effectiveness
SAMHSA	Substance Abuse and Mental Health Services Administration
SCOPE	Safe and Competent Opioid Prescribing Education
SCS	spinal cord stimulation
sEH	soluble epoxide hydrolase
SIF	safe injection facility

SIH	supervised injectable heroin
SIS	Spine Intervention Society
SMB	state medical board
SNP	single-nucleotide polymorphism
SNRI	serotonin–norepinephrine reuptake inhibitor
SOAPP	Screener and Opioid Assessment for Patients with Pain
SSRI	selective serotonin re-uptake inhibitor
SUD	substance use disorder
TCA	tricyclic antidepressant
TEDS	Treatment Episodes Data Set
THC	tetrahydrocannabinol
TIRF	transmuscosal immediate-release fentanyl
TLR	toll-like receptor
TNF	tumor necrosis factor
TPP	thrombotic thrombocytopenic purpura
TRPA1	transient receptor potential cation channel, member A1
TRPV	transient receptor potential cation channel, subfamily V
TTX	tetrodotoxin
VA	U.S. Department of Veterans Affairs
VGSC	voltage-gated sodium channel
VHA	Veterans Health Administration
VTA	ventral tegmental area
WHO	World Health Organization

Summary[1]

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. In March 2016, the U.S. Food and Drug Administration (FDA) asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to convene an ad hoc committee to

- update the state of the science on pain research, care, and education since publication of the 2011 Institute of Medicine (IOM) report *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, including the evolving role of opioids in pain management;
- characterize the epidemiology of the opioid epidemic and the evidence on strategies for addressing it;
- identify actions the FDA and other organizations can take to respond to the epidemic, with a particular focus on the FDA's development of a formal method for incorporating individual and societal considerations into its risk-benefit framework for opioid approval and monitoring; and
- identify research questions that need to be addressed to assist the FDA in implementing this framework.[2]

[1]This summary does not include references. Citations for the findings presented in the summary appear in subsequent chapters of the report.

[2]The full statement of task is presented in Chapter 1 of the report.

In the context of the growing opioid problem, the FDA launched an Opioids Action Plan in early 2016. One component of the FDA plan is to reassess the agency's risk-benefit framework for opioid approval and monitoring. The FDA commissioned this study specifically to inform this reassessment.

The committee interpreted its charge as focusing primarily on prescribed opioids, although its analysis of the epidemiology of the opioid epidemic and strategies for addressing it took into account the diversion of prescription opioids into illicit markets and the impact of use of prescription opioids on use of illicit opioids, such as heroin. This analytical approach was necessary because markets for these drugs have been found to be interrelated. Furthermore, as the FDA cannot address the opioid problem on its own, the committee directs a number of its recommendations at other stakeholders, such as federal agencies other than the FDA, state agencies, and payers, among others.

BACKGROUND

Over the past 25 years, the United States has experienced a dramatic increase in deaths from opioid overdose, opioid use disorder (OUD), and other harms in parallel with increases in the prescribing of opioid medications for pain management. During the period from 1999 to 2011, the annual number of overdose deaths from prescription opioids tripled (see Figure S-1). While the annual number of deaths from prescription opioids remained relatively stable between 2011 and 2015, overdose deaths from illicit opioids (including heroin and synthetic opioids such as fentanyl) nearly tripled during this time period, driven in part by a growing number of people whose use began with prescription opioids. Drug overdose is now the leading cause of unintentional injury deaths in the United States, and most of these deaths involve an opioid. As of 2015, 2 million Americans aged 12 or older had an OUD involving prescription opioids, and nearly 600,000 had an OUD involving heroin.

Pain is a complex syndrome, often difficult to measure or treat, and is associated with comorbidities (e.g., depression); disability; and social costs, such as work absenteeism and increased utilization of medical resources. Accordingly, meeting the needs of the tens of millions of U.S. residents suffering from pain (including acute pain, chronic pain, or pain at the end of life) requires access to a broad armamentarium of therapies for pain management.

The vast majority of people who are prescribed opioids do not misuse them. However, opioids can produce feelings of pleasure, relaxation, and contentment, leading to an overreliance on these drugs in many patients and to misuse and OUD in others. Moreover, many lawfully dispensed opioids

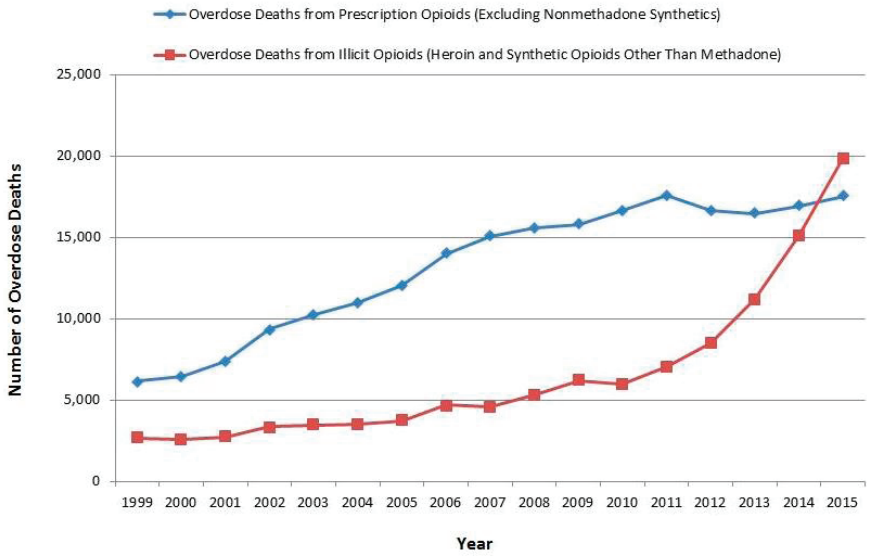


FIGURE S-1 Number of overdose deaths from prescription and illicit opioids, United States, 1999–2015.

make their way into the hands of people for whom they were not intended, including participants in illicit markets. As a result, harms associated with use of prescription opioids affect not only patients with pain themselves but also their families, their communities, and society at large.

The complexity of pain is matched by the complexity of achieving appropriate use of opioids in the context of the often suboptimal clinical management of pain within the fragmented U.S. health care delivery system. A further complication is the stigma associated with OUD and the persistent poor access to evidence-based OUD treatment services. The committee believes it is possible to stem the still-escalating prevalence of OUD and other opioid-related harms without foreclosing access to opioids for patients suffering from pain whose providers have prescribed these drugs responsibly.

PAIN MANAGEMENT AND PROGRESS AND FUTURE DIRECTIONS IN RESEARCH ON PAIN AND OPIOID USE DISORDER

Opioids are prescribed in a variety of settings for treatment of both acute and chronic pain. However, data demonstrating benefits of long-

term use of opioids to manage chronic noncancer pain are lacking, while the evidence clearly demonstrates that long-term use of opioids is associated with an increased risk of OUD and overdose as well as a number of other adverse outcomes (e.g., cardiovascular events, fractures). In studies in which OUD has been carefully defined, rates of OUD among individuals who were prescribed opioids to help them manage their pain have averaged about 8 percent, and estimates of combined rates of misuse, OUD, and aberrant behaviors thought to be indicative of OUD among people taking opioids for pain have ranged from 15 to 26 percent. Because of these risks, no widely accepted guideline for opioid prescribing recommends the use of opioids as a first-line therapy for management of chronic noncancer pain.

A number of nonopioid pharmacologic treatments can be used successfully to manage pain. While each such alternative has its own indications and risks, 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.

Nonpharmacologic interventions for pain treatment, including acupuncture, physical therapy and exercise, cognitive-behavioral therapy, and mindfulness meditation, also are powerful tools in the management of chronic pain. Many are components of successful self-management. While further research is needed for some nonpharmacologic interventions to better understand their mechanism of action and optimal frequency and intensity, they may provide effective pain relief for many patients in place of or in combination with pharmacologic approaches. Interventional therapies[3] also have been found to be beneficial for the management of some forms of pain (e.g., low back and neck pain) in the context of a multidisciplinary approach. Research on interventional therapies is still developing.

Several advances in understanding pain and its treatment have occurred since the release of the 2011 IOM report *Relieving Pain in America*. The basic mechanisms related to MOPR (μ opioid receptor)-biased analgesia, inflammation, pain transmission, innate immunity, and treatment of neuropathic pain are now better understood. Likewise, progress in preclinical and translational research includes several developments related to the creation of nonaddictive alternatives to the opioid analgesics currently on the market. The movement toward pragmatic, practice-based trials is a critical step forward in clinical pain research. The ideal balance of opioid reduction in the context of more comprehensive pain management (e.g., stepped care models) continues to be investigated. Precision medicine (broadly defined)

[3]Interventional pain management involves the use of invasive techniques, such as joint injections, nerve blocks, spinal cord stimulation, and other procedures, to reduce pain.

has the potential to improve clinical pain research and management, but is another area in which continued research is needed.

Little is known about why individuals who use prescribed opioids to alleviate pain develop opioid dependence or OUD, yet these outcomes have become a driving force in the opioid epidemic. Better identification of individuals at risk of OUD requires better characterization of the neurobiological interaction between chronic pain and opioid use. In particular, research on the interactions among pain, emotional distress, and reward, including pain-induced alterations in the reward pathway, would help in understanding and reducing the misuse potential of opioids.

Chronic pain and OUD are complex human conditions affecting millions of Americans and causing untold disability and loss of function. Yet despite the prevalence of pain and OUD and related costs to society and repeated calls to action (including the 2011 IOM report), research on pain remains poorly resourced.

Recommendation 3-1. Invest in research to better understand pain and opioid use disorder. Given the significant public health burden of pain and opioid use disorder (OUD) in the United States, the National Institutes of Health, the Substance Abuse and Mental Health Services Administration, the U.S. Department of Veterans Affairs, industry, and other relevant research sponsors should consider greater investment in research on pain and OUD, including but not limited to research aimed at

- improving understanding of the neurobiology of pain;
- developing the evidence on promising pain treatment modalities and supporting the discovery of innovative treatments, including nonaddictive analgesics and nonpharmacologic approaches at the level of the individual patient; and
- improving understanding of the intersection between pain and OUD, including the relationships among use and misuse of opioids, pain, emotional distress, and the brain reward pathway; vulnerability to and assessment of risk for OUD; and how to properly manage pain in individuals with and at risk for OUD.

TRENDS IN OPIOID USE AND HARMS

The level and type of risk to a patient from a given opioid are influenced by specific features of the medication itself, including the compound; the formulation (whether the medication is an extended- or immediate-release formulation and/or a combination product [coformulated with naloxone, acetaminophen, or aspirin]); and the route of administration. How opioids are prescribed (e.g., on an "as-needed" basis) also may influence the

risk of overdose. Studies consistently demonstrate that the risk of overdose increases in a dose-response fashion, that is, with increasing morphine-equivalent milligram doses.

It is also important to recognize that people who inject drugs are vulnerable to harms related to drug use that can be reduced by safe access to injection materials. New medications with "abuse liability" will be used by people with established patterns of injecting drugs. Tracking the toll of expected nonmedical use of specific products on the health of people who inject drugs is of public health importance.

Another critical feature of the opioid crisis is that the prescription and illicit opioid epidemics are intertwined; indeed, a majority of heroin users report that their opioid misuse or OUD began with prescription opioids. In addition, the declining price of heroin, together with regulatory efforts designed to reduce harms associated with the use of prescription opioids (including the development of abuse-deterrent formulations [ADFs][4]), may be contributing to increased heroin use.

Recommendation 4-1. Consider potential effects on illicit markets of policies and programs for prescription opioids. In designing and implementing policies and programs pertaining to prescribing of, access to, and use of prescription opioids, the U.S. Food and Drug Administration, other agencies within the U.S. Department of Health and Human Services, state agencies, and other stakeholders should consider the potential effects of these interventions on illicit markets—including both the diversion of prescription opioids from lawful sources and the effect of increased demand for illegal opioids such as heroin among users of prescription opioids—and take appropriate steps to mitigate those effects.

Gaps exist in the reporting of data with which to accurately describe the epidemiology of pain, OUD, and other opioid-related harms in the United States, including how pain and OUD relate to one another and how often they co-occur. Closing these data gaps would improve understanding of pain, OUD, and overlapping prescription and illicit opioid use and enable more effective and measurable policy interventions.

Recommendation 4-2. Improve reporting of data on pain and opioid use disorder. The Substance Abuse and Mental Health Services Administration, the U.S. Food and Drug Administration, the National

[4]Abuse-deterrent formulations are opioid medications designed to reduce the likelihood that they will be "abused." For example, some opioid pills have properties that make them difficult to manipulate (e.g., crush) or that render them ineffective or unpleasant once manipulated.

Institutes of Health, and the U.S. Centers for Disease Control and Prevention should collaborate to identify best practices and reporting formats that portray the epidemiology of both pain and opioid use disorder accurately, objectively, and in relation to one another.

Recommendation 4-3. Invest in data and research to better characterize the opioid epidemic. The National Institute on Drug Abuse and the U.S. Centers for Disease Control and Prevention should invest in data collection and research relating to population-level opioid use patterns and consequences, especially nonmedical use of prescription opioids and use of illicit opioids, such as heroin and illicitly manufactured fentanyl.

OPIOID APPROVAL AND MONITORING BY THE U.S. FOOD AND DRUG ADMINISTRATION

The FDA traditionally has taken a product-specific approach to drug approval decisions by focusing on the data generated and submitted by a drug's manufacturer and balancing the benefits revealed by those data against the risks known (and unknown) at the time of the agency's review. While this approach works well in most cases, the committee believes it is necessary to view regulatory oversight of opioid medications differently from that of other drugs because these medications can have a number of consequences not only at the individual level but also at the household and societal levels.

Recommendation 6-1. Incorporate public health considerations into opioid-related regulatory decisions. The U.S. Food and Drug Administration (FDA) should utilize a comprehensive, systems approach for incorporating public health considerations into its current framework for making regulatory decisions regarding opioids. The agency should use this approach, in conjunction with advisory committee input, to evaluate every aspect of its oversight of prescription opioid products in order to ensure that opioids are safely prescribed to patients with legitimate pain needs and that, as actually used, the drugs provide benefits that clearly outweigh their harms. When recommending plans for opioids under investigation; making approval decisions on applications for new opioids, new opioid formulations, or new indications for approved opioids; and monitoring opioids on the U.S. market, the FDA should explicitly consider

- benefits and risks to individual patients, including pain relief, functional improvement, the impact of off-label use, incident opioid use disorder (OUD), respiratory depression, and death;

- benefits and risks to members of a patient's household, as well as community health and welfare, such as effects on family well-being, crime, and unemployment;
- effects on the overall market for legal opioids and, to the extent possible, impacts on illicit opioid markets;
- risks associated with existing and potential levels of diversion of all prescription opioids;
- risks associated with the transition to illicit opioids (e.g., heroin), including unsafe routes of administration, injection-related harms (e.g., HIV and hepatitis C virus), and OUD; and
- specific subpopulations or geographic areas that may present distinct benefit-risk profiles.

To implement the systems approach proposed by the committee, it will be necessary to broaden the evidence used to demonstrate safety and efficacy during approval and for post-market monitoring. Specific means for meeting this need may extend beyond the protocolized setting of traditional clinical trials to encompass use of data from less traditional sources, such as online forums. The agency should consider reports of family members or other third parties affected by the drug, as well as data on outcomes in subpopulations that are at high risk of OUD or that exhibit mental health comorbidities common in patients with pain. Outcomes of interest include impact on function and long-term efficacy for pain reduction. Other data that could inform the agency's decisions include the estimated impact of an opioid medication on the demand for and availability of all other prescription and illicit opioids, as well as interactions with other drugs (both prescription and illicit) commonly used with opioids or by people who use opioids illicitly. The FDA also should take steps to ensure that clinical development programs examine the full range of public health considerations.

Recommendation 6-2. Require additional studies and the collection and analysis of data needed for a thorough assessment of broad public health considerations. To utilize a systems approach that adequately assesses the public health benefits and risks described in Recommendation 6-1, the U.S. Food and Drug Administration (FDA) should continue to require safety and efficacy evidence from well-designed clinical trials while also seeking data from less traditional data sources, including nonhealth data, that pertain to real-world impacts of the availability and use of the approved drug on all relevant outcomes. The FDA should develop guidelines for the collection of these less traditional data sources and their integration in a systems approach.

Recommendation 6-3. Ensure that public health considerations are adequately incorporated into clinical development. The U.S. Food and Drug Administration (FDA) should create an internal system to scrutinize all Investigational New Drug (IND) applications for opioids. This review should examine whether public health considerations are adequately incorporated into clinical development (e.g., satisfactory trial design; see Recommendation 6-2). In implementing this recommendation, the FDA should rarely, if ever, use expedited development or review pathways or designations for opioid drugs and should review each application in its entirety.

The committee believes a commitment to transparency is critical to maintain balance between preserving access to opioids when needed and mitigating opioid-related harms and to maintain public trust.

Recommendation 6-4. Increase the transparency of regulatory decisions for opioids in light of the committee's proposed systems approach (Recommendation 6-1). The U.S. Food and Drug Administration should commit to increasing the transparency of its regulatory decisions for opioids to better inform manufacturers and the public about optimal incorporation of public health considerations into the clinical development and use of opioid products.

The committee also believes aggressive use of the FDA's currently available authorities, such as Risk Evaluation and Mitigation Strategies (REMS), safety labeling changes, and risk communications, is critical to supporting the safe and effective use of opioids.

Recommendation 6-5. Strengthen the post-approval oversight of opioids. The U.S. Food and Drug Administration should take steps to improve post-approval monitoring of opioids and ensure the drugs' favorable benefit-risk ratio on an ongoing basis. Steps to this end should include use of risk evaluation and mitigation strategies that have been demonstrated to improve prescribing practices, close active surveillance of the use and misuse of approved opioids, periodic formal reevaluation of opioid approval decisions, and aggressive regulation of advertising and promotion to curtail their harmful public health effects.

Evidence on the effectiveness of the current REMS for opioids is limited. To improve the evidence on this REMS, the FDA could continue to evaluate the data on its performance, collecting additional data if needed, and then modify features of the REMS accordingly so that it more optimally ensures the evidence-based use of opioids.

Consistent regulatory oversight of opioid products under the committee's proposed approach will necessarily raise concerns about the safety and efficacy of products currently approved for market. The committee believes the FDA has the authority and responsibility to reexamine the opioid class of drugs to ensure that these drugs remain safe and effective. The committee believes this could be accomplished in a relatively short time frame because the review would be limited to a single drug class for which substantial evidence already exists.

Recommendation 6-6. Conduct a full review of currently marketed/approved opioids. To consistently carry out its public health mission with respect to opioid approval and monitoring, the U.S. Food and Drug Administration should develop a process for reviewing, and complete a review of, the safety and effectiveness of all approved opioids, utilizing the systems approach described in Recommendation 6-1.

The process for U.S. Drug Enforcement Administration (DEA) scheduling of drugs also could benefit from the explicit incorporation of the public health considerations discussed in this report. The FDA and the DEA are already required to take "risk to public health" into account in making scheduling decisions, but the considerations included under this heading have not been enumerated in detail. Moreover, the ultimate impact on health outcomes related to these decisions remains largely unknown.

Recommendation 6-7. Apply public health considerations to opioid scheduling decisions. To ensure appropriate management of approved opioids, the U.S. Food and Drug Administration and the U.S. Drug Enforcement Administration should apply the same public health considerations outlined in Recommendation 6-1 for approval decisions to scheduling and rescheduling decisions, and study empirically the outcomes of scheduling determinations at the patient and population health levels.

STRATEGIES FOR ADDRESSING THE OPIOID EPIDEMIC

A constellation of policies, interventions, and tools related to lawful access to opioids and clinical decision making are available for use in reducing or containing opioid-related harms while meeting the needs of patients with pain. These strategies include those that (1) restrict the lawful supply of opioids, (2) influence prescribing practices, (3) reduce demand, and (4) reduce harm. The committee offers several recommendations based on its review of the evidence regarding the effectiveness of these strategies.

Each of these strategies entails costs and trade-offs. The committee believes the restrictions, policies, and practices recommended leave adequate space for responsible prescribing and reasonable access for patients and physicians who believe an opioid is medically necessary.

It also is important to keep in mind that restrictions on lawful access to prescription opioids can have other untoward effects: any policy designed to shrink the incidence of future OUD (and other harms) due to use of prescribed opioids by curtailing legal access to these medications will inevitably drive some people who already have OUD into the illegal market. In the committee's view, it is therefore ethically imperative to couple a strategy for reducing lawful access to opioids with an investment in treatment for the millions of individuals who already have OUD.

Strategies for Restricting Supply

One recent controversy concerns whether any opioid should be permitted on the market unless it is an ADF. The committee applauds the FDA's current cautious approach toward ADFs because the evidence is insufficient to warrant a recommendation on this question at this time. The potential for benefit remains counterbalanced by recent examples of unexpected harm. Ongoing studies will help clarify the optimal role for ADFs as a strategy for reducing misuse of prescription opioids.

States and localities also have regulatory authority over the practice of medicine in their jurisdictions unless their actions are preempted by federal action, and they have exercised that authority to stem the opioid epidemic. Overall, although further research is warranted, limited evidence suggests that state and local interventions aimed at reducing the supply of prescription opioids in the community (e.g., regulations limiting days' supply of opioid medications) may help curtail access. It should be emphasized, however, that none of these studies investigates the impact of reduced access on the well-being of individuals suffering from pain whose access to opioids was curtailed.

The available evidence suggests that drug take-back programs in the United States can increase awareness of the need for the safe disposal or return of many unused drugs, but effects of these programs on such downstream outcomes as diversion and overdose are unknown. Many drug take-back programs in the United States are once-per-year events. International examples and the recent success of a year-round disposal program at one pharmacy chain support policies expanding such programs to reduce the amount of unused opioids in the community.

Recommendation 5-1. Improve access to drug take-back programs. States should convene a public–private partnership to implement drug

take-back programs allowing individuals to return drugs to any pharmacy on any day of the year, rather than relying on occasional take-back events.

Strategies for Influencing Prescribing Practices

Current efforts to improve pain education and knowledge about prescription opioid misuse and OUD among prescribers are inadequate. Any meaningful effort to improve pain management will require a fundamental shift in the nation's approach to mandating pain-related education for all health professionals who provide care to individuals with pain. Prescribing guidelines may be able to improve provider prescribing behavior, but may be most effective when accompanied by education and other measures to facilitate implementation.

Recommendation 5-2. Establish comprehensive pain education materials and curricula for health care providers. State medical schools and other health professional schools should coordinate with their state licensing boards for health professionals (e.g., physicians, nurses, dentists, pharmacists), the National Institutes of Health's Pain Consortium, the U.S. Food and Drug Administration, the U.S. Centers for Disease Control and Prevention, and the U.S. Drug Enforcement Administration to develop an evidence-based national approach to pain education encompassing pharmacologic and nonpharmacologic treatments and educational materials on opioid prescribing.

Insurance-based policies have substantial potential to reduce the use of specific prescription drugs, although their impact on health outcomes remains uncertain.

The judicious deployment of insurer policies related to opioid prescribing would benefit from a commensurate increase in coverage of and access to comprehensive pain management, encompassing both pharmacologic and nonpharmacologic modalities.

Recommendation 5-3. Facilitate reimbursement for comprehensive pain management. Public and private payers should develop reimbursement models that support evidence-based and cost-effective comprehensive pain management encompassing both pharmacologic and nonpharmacologic treatment modalities.

Evidence suggests that prescription drug monitoring programs (PDMPs) can help address the opioid epidemic by enabling prescribers and other stakeholders to track prescribing and dispensing information. State laws

differ widely with respect to access to PDMP data, with some states denying access to certain stakeholders that could use the data to monitor opioid use and related harms. Some states do not require prescribers and/or dispensers to check PDMP information. As a result, PDMP data currently are not being used to their full potential.

Recommendation 5-4. Improve the use of prescription drug monitoring program data for surveillance and intervention. The U.S. Department of Health and Human Services, in concert with state organizations that administer prescription drug monitoring programs, should conduct or sponsor research on how data from these programs can best be leveraged for patient safety (e.g., data on drug–drug interactions), for surveillance of policy and other interventions focused on controlled substances (e.g., data on trends in opioid prescribing, effects of prescriber guidelines), for health service planning (e.g., data on discrepancies in dispensing of medications for treatment of opioid use disorder), and for use in clinical care (i.e., in clinical decision making and patient–provider communication).

Strategies for Reducing Demand

The committee's recommended changes to provider education and payer policy should be accompanied by a change in patient expectations with respect to the treatment and management of chronic pain. The committee was struck in particular by the relative lack of attention to the impact of educating the general public (i.e., all potential patients) about the risks and benefits of opioid therapy and the comparative effectiveness of opioid and nonopioid analgesics and nonpharmacologic interventions.

Recommendation 5-5. Evaluate the impact of patient and public education about opioids on promoting safe and effective pain management. The nation's public health leadership, including the surgeon general, the U.S. Centers for Disease Control and Prevention, and heads of major foundations and professional organizations, should convene a body of experts in communication and in pain and opioid use disorder to evaluate the likely impact (and cost) of an education program designed to raise awareness among patients with pain and the general public about the risks and benefits of prescription opioids and to promote safe and effective pain management.

Medication-assisted treatment is the standard of care for OUD, even for special populations such as pregnant and postpartum women. Although several efficacious medications for treatment of OUD are available, they are

underutilized because of an array of factors, including insufficient numbers of providers eligible to provide OUD treatment, coverage barriers, and other limitations on access.

Recommendation 5-6. Expand treatment for opioid use disorder. States, with assistance from relevant federal agencies, particularly the Substance Abuse and Mental Health Services Administration, should provide universal access to evidence-based treatment for opioid use disorder (OUD), including use of medication, in a variety of settings, including hospitals, criminal justice settings, and substance use treatment programs. Efforts to this end should be carried out with particular intensity in communities with a high burden of OUD. State licensing bodies should require training in treatment for OUD for all licensed substance use disorder treatment facilities and providers.

Recommendation 5-7. Improve education in treatment of opioid use disorder for health care providers. Schools for health professional education, professional societies, and state licensing boards should require and provide basic training in the treatment of opioid use disorder for health care providers, including but not limited to physicians, nurses, pharmacists, dentists, physician assistants, psychologists, and social workers.

Recommendation 5-8. Remove barriers to coverage of approved medications for treatment of opioid use disorder. The U.S. Department of Health and Human Services and state health financing agencies should remove impediments to full coverage of medications approved by the U.S. Food and Drug Administration for treatment of opioid use disorder.

Strategies for Reducing Harm

Life-saving medication for treating opioid overdose is available. The provision of naloxone to overdose victims by laypersons or health professionals in the prehospital setting is the standard of care, and community-based programs and other first responder agencies have adopted this protocol for treating opioid overdose. Mechanisms for increasing naloxone prescribing and dispensing, equipping first responders, and possibly enabling direct patient access (e.g., over-the-counter status) are warranted, but are impeded by high and unpredictable medication costs.

Recommendation 5-9. Leverage prescribers and pharmacists to help address opioid use disorder. State medical and pharmacy boards should

educate and train their members in recognizing and counseling patients who are at risk for opioid use disorder and/or overdose, and encourage providers and pharmacists to offer naloxone when an opioid is prescribed to these patients or when a patient seeks treatment for overdose or other opioid-related issues.

Recommendation 5-10. Improve access to naloxone and safe injection equipment. To reduce the harms of opioid use, including death by overdose and transmission of infectious diseases, states should implement laws and policies that remove barriers to access to naloxone and safe injection equipment by

- permitting providers and pharmacists to prescribe, dispense, or distribute naloxone to laypersons, third parties, and first responders and by standing order or other mechanism;
- ensuring immunity from civil liability or criminal prosecution for prescribers for prescribing, dispensing, or distributing naloxone, and for laypersons for possessing or administering naloxone; and
- permitting the sale or distribution of syringes, exempting syringes from laws that prohibit the sale or distribution of drug paraphernalia, and explicitly authorizing syringe exchange.

FINAL THOUGHTS

Years of sustained and coordinated effort will be required to contain the current opioid epidemic and ameliorate its harmful effects on society. Trends indicate that premature deaths associated with the use of opioids are likely to climb and that opioid overdose and other opioid-related harms will dramatically reduce quality of life for many people for years to come. Access to evidence-based treatment for OUD and efforts to prevent overdose deaths and other harms should therefore be increased substantially and immediately as a public health priority. Action by the nation's political and public health leadership also is warranted to reduce the occurrence of new cases of prescription opioid-induced OUD through the implementation of scientifically grounded policies and clinical practices to promote responsible opioid prescribing and through advocacy for research aimed at identifying and developing nonaddictive alternatives to opioids for treatment of pain. The FDA has a crucial role to play in these efforts.

1

Introduction

Over the past 25 years, the United States has experienced an unprecedented increase in opioid use disorder (OUD), opioid overdose, and other opioid-related harms. As of 2015, 2 million Americans aged 12 years or older had an OUD involving prescription opioids, and about 600,000 had an OUD involving heroin, an illicit opioid (HHS, 2016a). Drug overdose, driven primarily by opioids, is now the leading cause of unintentional injury death in the United States (more than 60 percent of overdose deaths in 2015 involved a prescription or illicit opioid) (Rudd et al., 2016). This increase in opioid-related deaths has occurred in tandem with an equally unprecedented increase in prescribing of opioid medications for purposes of pain management.

Millions of Americans experience acute and/or chronic painful conditions each year, and many of them are prescribed opioids. The vast majority of these patients do not misuse these drugs. Yet the pain-relieving and other effects of opioids (e.g., the feelings of pleasure, relaxation, and contentment opioids can produce) (NIDA, 2017) may lead to an overreliance on these drugs in many patients and to misuse and OUD in others. Moreover, many lawfully dispensed opioids make their way into the hands of people for whom they were not intended, including participants in illicit markets. As a result, the harms associated with use of prescription opioids (including OUD, overdose, and death) affect not only the patients with pain themselves but also their families, their communities, and society at large. The purpose of this report is to assess the nation's response to what is, by any measure, a grievous public health problem.

STUDY CHARGE

When the U.S. Food and Drug Administration (FDA) approved the opioid analgesic OxyContin in 1995, the drug had not been shown to be more efficacious or safe than short-acting oxycodone, which was already on the market. The idea promoted by OxyContin's manufacturer was that it was less likely to lead to addiction and misuse because of its time-release formulation. Yet, as discussed below, OxyContin was widely diverted, and many people became addicted to it. In 2013, the FDA approved Zohydro ER (extended-release) (hydrocodone bitartrate), an opioid without abuse-deterrent properties, although several abuse-deterrent formulations (ADFs) were by then available. The approval of this drug exacerbated frustration among some stakeholders that the societal impacts of opioids were not being sufficiently accounted for. In 2014, the FDA approved an ADF version of Zohydro to replace the original version.

In the wake of these decisions and in light of concerns about the growing opioid problem, the FDA launched an Opioids Action Plan in early 2016. In this plan, the agency described actions it would take in its role as the federal agency responsible for protecting the public's health by ensuring the efficacy and safety of drugs in the United States (Califf et al., 2016; FDA, 2016a,b). The actions outlined in the FDA plan include the following:

- Expand the use of advisory committees, including by
  - convening an expert advisory committee before approving any new drug application for opioids without abuse-deterrent properties;
  - consulting an advisory committee on ADFs when they raise novel issues; and
  - assembling and consulting with a pediatric advisory committee regarding a framework for pediatric opioid labeling before any new labeling is approved.
- Develop changes to immediate-release (IR) opioid labeling, including additional warnings and safety information incorporating elements similar to the ER/long-acting (LA) opioid labeling, to give providers better information about the risks of opioids and how to prescribe safely.
- Strengthen the requirements for drug companies to generate post-market data on the long-term impact of ER/LA opioids.
- Update the Risk Evaluation and Mitigation Strategy (REMS) program[1] requirements for opioids based on advisory committee rec-

[1]A REMS is a safety strategy used by the FDA "to manage a known or potential serious risk associated with a medicine to enable patients to have continued access to such medicines by managing their safe use" (FDA, 2017a).

ommendations and review of existing requirements to decrease inappropriate prescribing.[2]
- Expand access to and encourage the development of ADFs of opioid products.
- Support better treatment by making naloxone more accessible and supporting the U.S. Centers for Disease Control and Prevention (CDC) guideline for prescribing opioids for chronic pain (discussed later in this chapter) (Dowell et al., 2016).
- Reassess the risk-benefit approval framework for opioids to incorporate risks of opioids to patients as well as to others who obtain them (FDA, 2016a,b).

As part of efforts to implement its Opioids Action Plan, the FDA asked the National Academies of Sciences, Engineering, and Medicine (the National Academies) to establish an ad hoc committee to advise the agency on the development of "a regulatory framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the broader public health consequences of abuse and misuse" (Califf et al., 2016). This specific task was embedded in a broad charge (see Box 1-1). Specifically, the committee was asked to provide an update on the state of the science of pain research, care, and education since publication of the 2011 Institute of Medicine (IOM) report *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research* (IOM, 2011), including the evolving role of opioids in pain management and practices for reducing their misuse; to characterize the epidemiology of the opioid epidemic; and to review the evidence on approaches for addressing the problem. Based on its review of the evidence, the committee was to identify regulatory actions the FDA can take to address the opioid epidemic, with a focus on the agency's development of a formal method (a regulatory framework) for incorporating the broader public health impacts of opioids into its future opioid approval decisions. The committee also was asked to outline steps that can be taken by other stakeholders (e.g., prescribers; professional societies; federal, state, and local government agencies). In addition, the committee was charged to identify important research questions that need to be addressed to assist the FDA with the development of its regulatory framework.

In spring 2016, the National Academies convened an 18-member committee to carry out this task. Members included individuals with expertise

[2]ER/LA opioids are currently subject to a REMS program that requires sponsors to fund continuing medical education for providers on the appropriate use of these products at low or no cost. The FDA has stated that it is expanding the REMS requirements to include IR opioids as well (FDA, 2017b).

BOX 1-1
Statement of Task

The Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine will convene an ad hoc committee to develop a report that will inform the U.S. Food and Drug Administration (FDA) as to the state of the science regarding prescription opioid abuse and misuse, including prevention, management, and intervention, and to provide an update from the 2011 Institute of Medicine (IOM) report *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, which includes a further characterization of the evolving role that opioid analgesics play in pain management. The report additionally will make recommendations on the options available to the FDA to address the prescription opioid overdose epidemic, from both the individual and public health perspectives, and to otherwise further advance the field.

Specifically, the report will address the following items:

- Provide an update on the state of the science of pain research, care, and education since the 2011 IOM report and characterize the evolving role of opioid analgesics in pain management.
- Review the available evidence on best practices with regard to safe and effective pain management, including practices to reduce opioid abuse and misuse, including an assessment of possible barriers to implementation of those best practices by prescribers and patients.
- Characterize the epidemiology of prescription opioid abuse and misuse, to include an assessment with regard to patient characteristics (such as indication, acute versus chronic pain; formulation, immediate-release versus extended-release; duration of use; and dose) and approaches to address the problem (such as approval of abuse-deterrent opioids, FDA communication strategies, prescription drug monitoring programs, and state or local policies) and review the available evidence on differences in pain experiences and treatment effectiveness across subpopulations.

in pain management, basic pain research, epidemiology, medical anthropology, substance use disorder (SUD), nursing, law, drug development, public health, health policy and policy modeling, and decision science. Two consultants with expertise in health care and food and drug law were appointed to contribute to the regulatory components of this report.

STUDY APPROACH

The committee conducted an extensive review of the scientific literature relevant to its statement of task. This literature review entailed English-language searches of a number of databases, including the Cochrane Database of Systematic Reviews, Embase, Google Scholar, Medline, PubMed,

- Given the state of the available data, identify important research questions to be addressed to assist the FDA in meeting the goal of further developing a framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the broader public health consequences of opioid abuse and misuse.
- Given the state of the available data, identify additional actions the FDA and others should consider now, with a particular focus on those actions the FDA can undertake, to balance the needs of pain patients and the need to address opioid misuse and abuse. Areas of particular focus include
  - FDA actions to be taken as a part of development, review and approval, and safe use of pain medicines, such as:
    - Development of a formal method to incorporate the broader public health impact of opioid abuse in future FDA approval decisions regarding opioids
    - The development of nonopioid pain medicines to treat severe pain
    - The development of abuse-deterrent opioids
    - The incorporation of prevention strategies into safe opioid prescribing, including modification of the standard opioid indication statements
    - The development of medicines for medication assisted treatment for patients with opioid use disorder
    - The development of medicines to treat opioid overdose
    - The education of prescribers and patients about safe use of pain medications
    - The education of prescribers and patients about appropriate medication storage and disposal
  - Actions by prescribers, professional societies, and government agencies (local, state, and federal).

Scopus, and Web of Science. In addition to research published in peer-reviewed journals and books, the committee reviewed reports issued by government agencies and other organizations.

FDA representatives provided the committee with a number of background materials describing the agency's current processes and activities related to regulation of prescription drugs, including opioids. Among these materials were FDA guidance documents, presentations from FDA science board and advisory committee meetings, and research articles.

In addition, the committee held two public workshops to hear from researchers and agency representatives on topics germane to its task. The first workshop featured presentations on and discussion of topics relevant to the first four bullet points in the committee's statement of task (see

Box 1-1); these presentations are summarized in a Proceedings of a Workshop—in Brief titled *Pain Management and Prescription Opioid-Related Harms: Exploring the State of the Evidence* (NASEM, 2016). The second workshop focused on the regulatory aspects of the committee's charge, including how the FDA might incorporate public health considerations into its regulatory framework for evaluation of prescription drugs.

Additional detail on the committee's literature search and workshops can be found in Appendix A.

DEFINITIONS AND TERMINOLOGY

In recent years, several factors have increased attention to the language of SUD. Patient advocacy groups have long advocated for language describing SUD that avoids stigma and negative stereotypes. In 2013, the fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) replaced the categories of "abuse" and "dependence" with the single term "substance use disorder." This change led major addiction journals to publish guidelines for clinical, nonstigmatizing language that is viewed as acceptable terminology for manuscripts. On October 4, 2016, the Office of National Drug Control Policy (ONDCP) released a guidance document titled *Changing the Language of Addiction* (ONDCP, 2017). And in a related effort, the American Society of Addiction Medicine (ASAM) proposed a series of definitions aimed at the development of a vocabulary that is humanizing, nonstigmatizing, medically defined, and precise. This proposed terminology is a partial basis for the definitions presented in Box 1-2, which reviews both acceptable language and language that has been identified as no longer acceptable.

BOX 1-2
Key Definitions

Addiction refers to "a primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Addiction is characterized by inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response" (ASAM, 2011). The criteria for substance use disorder in the fifth edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-5) are contained in the category of Addictions and Related Disorders; the

BOX 1-2 Continued

preferred term for the disease, and the one used in this report, is **substance use disorder** (or **opioid use disorder**).

The severity of a substance use disorder can differ across individuals and across time for the same individual. Different from opioid use disorder and addiction, **dependence** in this report refers to a state associated with withdrawal symptoms upon cessation of repeated exposure to a drug. It is important to note that a person who is physically dependent on a drug may not meet the definition of addiction. **Tolerance** refers to the diminishing effect of a drug resulting from the repeated administration of a given dose.

Abuse (as in substance abuse or substance abuser) is no longer acceptable terminology, as research has found the term to be associated with negative and stigmatizing perceptions. Accordingly, the committee avoids use of this term except when quoting other sources; when referring to abuse-deterrent formulations of opioids (those with properties designed to prevent misuse [e.g., properties to prevent crushing so the drug can be snorted or dissolving so it can be injected]); and when referring to statutes, such as the Controlled Substances Act, that use this term. The term **misuse** is commonly used to describe any use of a prescription medication beyond what is directed in a prescription. It encompasses such specific behaviors and motivations as (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. Some have argued that use of the term "misuse" to encompass both medical and nonmedical motivations (such as "to get high") is misleading and imprecise. While the American Society of Addiction Medicine (ASAM) acknowledges this problem, it prefers "misuse" as the umbrella term encompassing a continuum of use patterns based on degree of risk, ranging from "low-risk" and "at-risk" use to "harmful use" and addiction. Under the ASAM approach, once a patient misusing prescription medication meets the criteria for an opioid use disorder, the term "misuse" is no longer appropriate. **Diversion** refers to the transfer of regulated prescription drugs from legal to illegal markets. The term is not used in this report to refer to the sharing of drugs with friends, family members, or other contacts for medical or nonmedical purposes.

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.

Finally, the acronym **MAT** refers to the use of medication in the treatment of opioid use disorder, regardless of whether the medication is used in conjunction with counseling and behavior therapies. This acronym may refer either to **medication for addiction treatment**, where medications are used without counseling and behavior therapies, or to **medication-assisted treatment**, where medication is used in conjunction with these therapies. Current medications approved for treatment of opioid use disorder are methadone, buprenorphine, and naltrexone. The terms **substitution therapy** and **replacement therapy** are not accurate and therefore are not used in this report.

STUDY CONTEXT

Historical Context

Opioids have been used for medicinal and recreational purposes for millennia. While the use of opioids for treatment of acute severe pain has generally been accepted, their use for managing chronic noncancer pain has been controversial since the 19th century, with the popular view shifting over the decades between broad acceptance and a more restrictive perspective (Rosenblum et al., 2009). The tension between the desire to make opioids available to those who may benefit from them and the recognition that opioids are addictive drugs with societal consequences began with medical developments that occurred during the 1800s (Booth, 1986; Musto, 1999; Rosenblum et al., 2009). These developments included the extraction of morphine from opium in 1803 and the development of the hypodermic needle (which can be used to inject morphine to relieve neuralgic pain) in the 1850s (Rosenblum et al., 2009). Morphine was used widely for pain management during the American Civil War, and many soldiers developed OUD. With few effective alternatives, moreover, many medical professionals used morphine to treat chronic pain conditions. This and the nonmedical use of opioids were major drivers of an opioid addiction epidemic that took place in the latter 19th century (Courtwright, 2015).

By the late 1800s, scientists were starting to recognize the problem of OUD, and a policy response began to emerge. What is thought to be the first accurate and comprehensive description of addiction to morphine was produced in 1877. In hopes of developing a less addictive alternative to morphine, heroin (diacetylmorphine) was synthesized in 1874 (although it was later found to be more potent than morphine) (Rosenblum et al., 2009). Medical professionals became increasingly critical of the use of opioids to treat pain and lobbied successfully for state and local laws to control the sale of opioids and other narcotics. Consumption of medicinal opioids declined as a result (Courtwright, 2015).

Reform efforts continued in the early 20th century. The Harrison Narcotics Act, enacted by Congress in 1914, required persons who imported, produced, sold, or dispensed opium-based drugs (as well as coca-based drugs) to register, pay a tax, and keep detailed records that officials could use in enforcing laws to restrict opioid transactions to legitimate medical channels. This act had the effect of criminalizing the use of opium for nonmedical purposes (Courtwright, 2015; Hoffman, 2016).[3] The use of heroin

[3]The Harrison Narcotics Act has since been replaced by the Controlled Substances Act, enacted in 1970.

for medicinal and other purposes was specifically banned by the Heroin Act, enacted by Congress in 1924.

The consensus among medical professionals for most of the 20th century was that opioids should not be used for the management of chronic pain because of the lack of evidence regarding their effectiveness for this type of pain and the risk of OUD (Rosenblum et al., 2009). Research aimed at developing new and potentially less addictive opioids continued, however, and Percocet and Vicodin—which combined semisynthetic opioids with acetaminophen—became available in the 1970s for relief of moderate to moderately severe pain. These and most other prescription opioids are now regulated under the Controlled Substances Act (CSA) of 1970 as Schedule II drugs—those with a "high potential for abuse which may lead to severe psychological or physical dependence" (DEA, 2017b).[4]

Liberalization of Prescribing in 1990s

Medical practice in the United States began to shift markedly toward more liberal use of opioids for chronic noncancer pain following the development and marketing of new formulations of opioid drugs in the 1990s (Compton and Volkow, 2006; Rosenblum et al., 2009). As noted earlier, in 1995 the FDA approved OxyContin (oxycodone controlled-release), which allowed dosing every 12 instead of every 4 to 6 hours (FDA, 2017c). The drug's manufacturer (Purdue Pharma) marketed it aggressively to providers and patients in the years following its release to the market in 1996. Purdue claimed in some of its promotional materials that the risk of addiction to the drug was small (Van Zee, 2009).

Around the same time, there was growing recognition in the medical community that many individuals with chronic pain were being treated inadequately (Pokrovnichka, 2008). In 1996, the American Academy of Pain Medicine and American Pain Society issued a joint consensus statement titled *The Use of Opioids for the Treatment of Chronic Pain*, describing potential benefits of using opioids for management of chronic (including noncancer) pain (Haddox et al., 1997; Hoffman, 2016). Advocates representing the interests of pain patients suggested that pain be considered a "fifth vital sign" in an effort to improve pain assessment and treatment (Campbell, 1996), and some health care organizations incorporated this concept into guidelines and clinical practice (Mularski et al., 2006). There

[4]Some opioids are not classified in Schedule II. These include opioids containing less than 90 milligrams of codeine per dosage unit (e.g., Tylenol with Codeine®) and buprenorphine (used in the treatment of OUD), which are Schedule III drugs—those that have "a potential for abuse less than substances in Schedules I or II" and whose "abuse may lead to moderate or low physical dependence or high psychological dependence" (DEA, 2017b).

were also concerted efforts by pain specialists to persuade state medical boards and state legislatures to remove legal impediments to medically accepted pain treatment (Hoffman, 2016).[5] This shift in professional understanding was accompanied by a public campaign to call public and professional attention to the prevalence of pain and its seriousness as a public health problem.

Congress declared 2001–2011 the "Decade of Pain Control and Research" (Brennan, 2015). The 2010 Patient Protection and Affordable Care Act (ACA) directed the U.S. Department of Health and Human Services (HHS) to work with the IOM to increase recognition of pain as a public health problem (IOM, 2011). In response, HHS, through the National Institutes of Health (NIH), commissioned an IOM committee to review the science on pain and recommend actions to advance the field. The resulting report, *Relieving Pain in America*, provided a blueprint for "transforming the way pain is understood, assessed, treated, and prevented" (IOM, 2011, p. 2).

In the context of Purdue's substantial promotional expenditures and these changing professional attitudes, sales of OxyContin rose from $48 million in 1996 to more than $1 billion by 2000 (Van Zee, 2009). Sales of prescription opioids are estimated to have quadrupled between 1999 and 2010 (CDC, 2011), driven in part by OxyContin during the early portion of this period (GAO, 2003). However, problems began to emerge around 2000, with reports of widespread diversion, tampering, and misuse of OxyContin (Cicero et al., 2005; GAO, 2003; Hoffman, 2016). In response, the FDA changed the OxyContin label in 2001 "to add and strengthen warnings about the drug's potential for abuse and misuse" and in 2003 issued a warning letter to the manufacturer regarding promotional materials that omitted and minimized the drug's safety risks (FDA, 2017c).[6] The U.S. Drug Enforcement Administration (DEA) prosecuted many physicians for illegal distribution of OxyContin (Hoffman, 2016).[7]

Nonetheless, sales of prescription opioids continued to increase (Pan, 2016). Data from the National Prescription Audit show that the number of opioid prescriptions dispensed from U.S. outpatient retail pharmacies

[5]Liberalization of prescribing was resisted in some quarters, and worries about possible discipline by state medical boards or even prosecution by the U.S. Drug Enforcement Administration (DEA) continued to affect professional practice during this period.

[6]Purdue Pharma was eventually prosecuted and, in 2007, paid a $600 million settlement after pleading guilty for its misrepresentation of OxyContin's addiction and abuse potential.

[7]The DEA reported investigating 247 OxyContin diversion cases between October 1999 and March 2002, which led to 328 arrests. Between May 2001 and January 2004, the DEA arrested approximately 600 people for violation of laws related to distribution, dispensing, or possession of OxyContin. Of these, 60 percent were doctors, pharmacists, or other professionals (Hoffman, 2016).

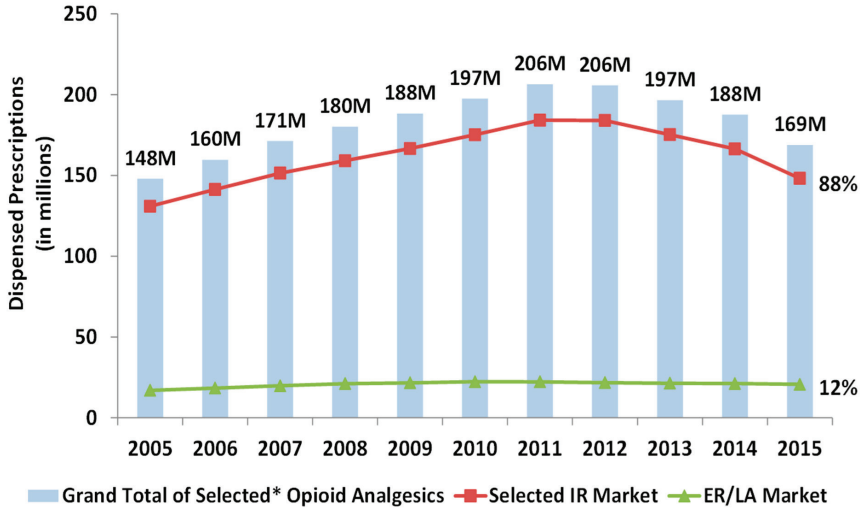


FIGURE 1-1 Nationally estimated number of prescriptions dispensed for extended-release/long-acting (ER/LA) and selected immediate-release (IR) opioid analgesics (oral solids and transdermal products) from U.S. outpatient retail pharmacies, 2005–2015.
*ER/LA opioid molecules include buprenorphine transdermal patch, fentanyl transdermal patch, hydrocodone ER, hydromorphone ER, morphine ER, oxycodone ER, oxymorphone ER, tapentadol ER, and methadone (all approved and marketed ER/LAs at the time). IR opioid molecules include hydrocodone IR combination analgesics (hydrocodone in combination with acetaminophen, ibuprofen, or aspirin), oxycodone IR combination analgesics (oxycodone in combination with acetaminophen, ibuprofen, or aspirin), oxycodone IR, hydromorphone IR, morphine IR, tapentadol IR, and oxymorphone IR. Buprenorphine indicated for medication-assisted treatment is not included.
SOURCE: Staffa, 2017.

for all approved and marketed ER/LA and some of the most common IR opioid analgesics grew from 148 million in 2005 to 206 million by 2011. Opioid dispensing during this period was driven primarily by IR opioids (which work quickly and often are prescribed for short-term, intermittent, or "breakthrough" pain) rather than ER/LA opioids such as OxyContin (see Figure 1-1).[8] Sales of OxyContin increased from just over $1 billion in

[8]The preponderance of IR opioid prescribing may be the result of many factors, including but not limited to the effect of hydrocodone IR combination products being Schedule III drugs/refillable until 2014 (when they were reclassified as Schedule II drugs), the number of prescriptions for acute pain after injuries/surgeries/procedures, the comfort of many providers with short-acting drugs, an overall practice of using relatively low doses of drugs, and the preferences of patients to have control over when they take their drugs.

2000 to $1.84 billion in 2003 and then declined in the wake of the FDA actions described above until 2006, after which there was another increase in sales until 2010 (Public Citizen, 2007).

Public Health Consequences

During the years coinciding with the growth in opioid prescribing, the United States experienced an increase in deaths from opioid overdose and in admissions to treatment associated with opioid use. According to CDC data, there was a 1.9-fold increase in the total number of deaths from prescription opioids (excluding nonmethadone synthetics) between 1999 and 2011 (see Figure 1-2). While the number of overdose deaths from prescription opioids remained relatively stable between 2011 and 2015, overdose deaths from illicit opioids (e.g., heroin and synthetic opioids such as fentanyl) continued to increase, related in part to a growing number of people with OUD in connection with prescription opioids. Overdose deaths from illicit opioids increased rather steadily during 1999 to 2015, growing 6.4-fold over that period (see Figure 1-2). Poisoning, driven largely by opioids, became the leading cause of death due to injury in the United States in 2008, surpassing motor vehicle crashes (Warner et al., 2011). The annual

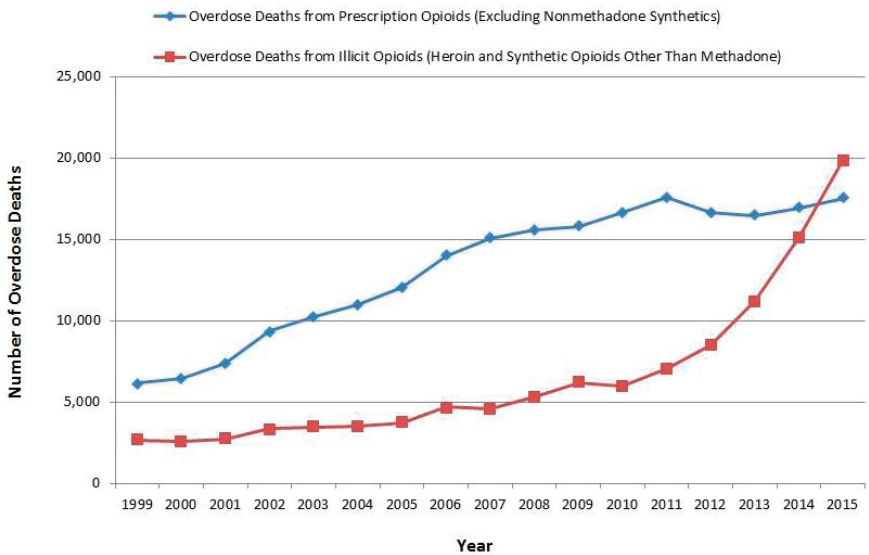


FIGURE 1-2 Number of overdose deaths from prescription and illicit opioids, United States, 1999–2015.
SOURCE: NCHS, 2016.

incidence of hospitalization for prescription opioid poisoning among children and adolescents aged 1–19 increased 165 percent (from 1.4 to 3.7 per 100,000) between 1997 and 2012 (Gaither et al., 2016). Between 2003 and 2013, the proportion of admissions to treatment associated primarily with nonheroin opioid use and heroin use increased from 3 to 9 percent and 15 to 19 percent, respectively (SAMHSA, 2015).

Policy Responses

By the end of the first decade of the 21st century, alarm about the opioid epidemic was growing in public health circles. An increasing number of medical organizations were urging greater caution in prescribing opioids in light of the growing opioid problem and the lack of evidence that the drugs are effective for long-term pain management (VonKorff et al., 2011). At the federal level, in 2009, the FDA held public and stakeholder meetings to discuss opioid-related harms; partnered with the Substance Abuse and Mental Health Services Administration (SAMHSA), the DEA, and others on efforts to improve the safe use and disposal of opioids; and launched a Safe Use Initiative to reduce preventable harms from opioids and other drugs. In 2010 the agency approved an ADF of OxyContin (FDA, 2017c). During approximately 2013–2015, ONDCP and HHS ramped up efforts to reduce OUD and opioid overdose, including the creation of an HHS opioid initiative in 2015 (HHS, 2015). CDC's 2016 Guideline for Prescribing Opioids for Chronic Pain explicitly declares that nonpharmacologic and nonopioid therapies are preferred for treating chronic pain (Dowell et al., 2016). And in December 2016, the U.S. Congress passed the 21st Century Cures Act, which included $1 billion in funding over 2 years for grants to states targeting opioid prevention and treatment activities.

State and local governments also have scaled up efforts to identify problematic prescribing (e.g., via prescription drug monitoring programs [PDMPs], discussed in Chapter 5), prevent diversion of prescription opioids, and increase access to naloxone and to treatment for OUD. Some jurisdictions have declared public health emergencies (e.g., Massachusetts Department of Public Health, 2014; Virginia Department of Health, 2016).

In the context of these federal and state policy initiatives, the total number of prescriptions for opioid analgesics dispensed from outpatient retail pharmacies decreased between 2012 and 2015.[9] Large health care providers and professional associations also have recently suggested that pain no longer be considered a vital sign (Frieden, 2016; Lowes, 2016).

[9]It is important to note, however, that opioid prescribing practices, and therefore trends in dispensing, vary widely among states and other localities.

Some have suggested that routine pain assessment is not in the best interest of providers and may contribute to overprescribing (Lowes, 2016).

International Context

Historically, the United States has consumed a large majority of the world's supply of opioid drugs. An older figure that continues to be cited is that approximately 80 percent of the world's supply of opioid drugs is consumed in the United States (Manchikanti and Singh, 2008). According to another estimate, 90 percent of the world's supply of morphine, fentanyl, and oxycodone was used in the United States, Canada, Australia, and New Zealand in 2009, and in that same year, the United States consumed 83 and 99 percent of the world's oxycodone and hydrocodone, respectively (Hauser et al., 2016). Based on available data (UNODC, 2017), other countries, including Mexico and countries in Central and South America, Africa, and Asia, appear to have a considerably lower prevalence of past-year use of both prescription and illicit opioids, although this does not necessarily mean that these countries are free of problems related to opioids.

Consumption of opioid drugs has increased globally since the 1980s. Data indicate that in more recent decades, increases in consumption have been highest in the United States and to a lesser extent in other industrialized nations. For example, during 2000–2010, opioid consumption increased 400 percent in the United States, compared with 65 percent in Great Britain and 37 percent in Germany (Hauser et al., 2014). In Australia, where the prevalence of opioid use also is high, opioid dispensing increased nearly four-fold between 1990 and 2014 (from 4.6 to 17.4 defined daily doses/1,000 population/day) (Karanges et al., 2016). Spain saw a 14-fold increase in opioid daily doses between 1992 and 2006 (Garcia del Pozo et al., 2008).

The responses in countries experiencing high rates of opioid misuse, OUD, and opioid overdose have varied. Some are noteworthy for their public health orientation. In the Canadian province of British Columbia (Canada has the second highest rate of opioid consumption after the United States), harm reduction strategies implemented to reduce opioid overdose included making the opioid overdose reversal drug naloxone available outside of pharmacies without a prescription and opening supervised injection facilities (SIFs) (British Columbia was the first region in North America to open a SIF, in 2003) (Voon, 2016). The British Columbia Ministry of Health also issued guidelines for the clinical management of OUD to foster improved linkage to medically supervised treatment (Dunlap and Cifu, 2016). SIFs, which have been found to be associated with reductions in syringe sharing and overdose fatality (Kerr et al., 2005; Marshall et al., 2011), are operating as well in several other countries that have experi-

enced significant opioid misuse problems, including Spain, Australia, and Germany, and are now being considered in the United States.

Some countries have reduced criminalization of drug use, with positive results. Portugal, while not having opioid-related problems at the levels seen in other countries, became the first country to decriminalize the possession and use of drugs in 2001, making these violations administrative as opposed to criminal offenses (Greenwald, 2009). Individuals who are addicted to heroin or other drugs are offered access to treatment, which is widely available through health centers, hospitals, and pharmacies, as well as to needle exchange and other services. Since these changes were implemented, the country has seen more people enter treatment, and HIV transmission rates have declined among injection drug users (EMCDDA, 2016).

The United States' response to the opioid epidemic also has taken on an increasingly public health focus. Examples include efforts to make OUD treatment, naloxone, syringe exchange, and other services more widely available, and the promulgation of guidelines for prescribers that emphasize greater caution in opioid prescribing and recommend referral to evidence-based treatment for patients with OUD. As discussed in this report, these strategies are at various stages of implementation and evaluation.

Statutory Context

Opioid regulation lies at the intersection of two federal statutes, each with its roots in the early 20th century. The first is the Food, Drug, and Cosmetic Act (FDCA), a successor to the groundbreaking Pure Food and Drug Act of 1906, which now requires manufacturers of medical drugs and devices to prove that they are safe and effective for their intended uses before they may be marketed to consumers. The second applicable statute is the CSA, enacted in 1970 as a successor to the Harrison Narcotics Act of 1914, mentioned above. The CSA was designed to provide an overarching framework for tight federal regulation, including both public health oversight and aggressive enforcement, for all drugs with "potential for abuse," whether or not intended for medical use. Previously, those functions had operated relatively autonomously, with drug development and prescription control under the FDA, and enforcement responsibility originally lodged in the U.S. Department of the Treasury and later transferred to the U.S. Department of Justice (Spillane, 2004). Enforcement duties under the CSA are now exercised by the DEA, but the CSA also retains a significant role for HHS, usually acting through the FDA, in the regulation of controlled substances with medical uses.

The CSA created tiered levels of control and reporting responsibilities based on the potential danger posed by a given drug, and established a structure for coordinating regulatory and enforcement action (Spillane,

2004). The act also was designed to create a "big tent" for all drugs that might be subject to misuse and to explicitly subject such drugs as barbiturates and amphetamines to the same control as narcotics. Each controlled substance is assigned to a specific schedule. Schedule I substances are strictly limited and may be used only in some highly controlled research contexts, if at all. Schedule II substances are subject to production quotas and registry requirements for importers and exporters. Drugs assigned to the lower schedules are subject to progressively diminished levels of control. A controlled substance may be prescribed only for a "legitimate medical purpose" by a practitioner licensed by the DEA "acting in the usual course of his professional practice." The CSA gives the DEA the power to revoke licensure when a physician is determined to have violated that standard, and offending practitioners may be subject to criminal prosecution.

The primary focus of the CSA was ambiguous from the outset: the Nixon administration saw it principally as a way to control street use of illicit drugs, while its congressional sponsors saw it as a vehicle for limiting overproduction and overprescription of legally marketed drugs based on balancing the dangers of abuse against the health benefits of legitimate medical use (Spillane and McAllister, 2003, p. S8). To its congressional sponsors, the CSA represented a key step in the direction of a national public health approach to drug abuse and addiction. The second step, taken in the Drug Abuse Office and Treatment Act of 1972, established a Special Action Office for Drug Abuse Prevention in the White House and enacted sweeping federal protection of the confidentiality of SUD treatment records that continues to serve as a centerpiece of national policy.

The DEA was created in 1973 to carry out the U.S. Department of Justice's responsibility for enforcing the CSA (Senate Committee on Government Operations, 1973, pp. 5–6). It was believed that making one agency accountable would "maximize coordination between Federal investigation and prosecution efforts." The new agency was to draw on Federal Bureau of Investigation expertise with organized crime, and to provide a single focal point for enforcement with state, local, and international authorities (Senate Committee on Government Operations, 1973, pp. 5–6). The DEA enforces both the criminal and noncriminal regulatory requirements of the CSA, but it does so as a law enforcement agency; it is not designed to function as a public health agency, nor does it pretend to be one (DEA, 2017a).

Over the four and a half decades since its passage, the CSA has been amended many times, usually to increase law enforcement authority. The Comprehensive Crime Control Act of 1984 and the Anti-Drug Abuse Acts of 1986 and 1988 added provisions to deal with synthetic compounds and new enforcement mechanisms, such as forfeiture provisions, and introduced mandatory minimum sentences. The Illicit Drug Anti-Proliferation

Act of 2003 amended the CSA to deal with MDMA (*3,4-methylenedioxymethamphetamine*, or ecstasy) and other club drugs. The Ryan-Haight Act of 2008 amended the CSA to regulate online pharmacy distribution. The Secure and Responsible Drug Disposal Act of 2010 requires the DEA to establish programs for voluntary disposal of controlled substances that are no longer required by patients. And the Synthetic Drug Abuse Prevention Act of 2012 not only mandated restrictive scheduling for various synthetic drugs but also streamlined the scheduling process so that newly approved drugs could enter the market more quickly.

Among the many important issues that have surfaced during the opioid crisis are whether the public health goals of the CSA envisioned by its architects have been achieved, and whether regulatory activities carried out by the FDA and the DEA under the FDCA and the CSA have been suitably coordinated and harmonized. One issue of particular interest in the context of this report is surveillance. As a key component of its public health aims, the CSA mandated the collection of epidemiologic data on use and abuse of the drugs controlled by the act and on other substances that might warrant control. The first such effort, the Drug Abuse Warning Network (DAWN), created in 1972 and discontinued in 2011, revealed a problem that continues to this day: it is difficult to break down the data by specific drug products (Mansbach et al., 2010; Spillane, 2004), which is essential to determining the nature and level of misuse for specific substances. The discontinuation of DAWN in 2011 left a substantial gap in the nation's capacity to monitor, anticipate, and respond to the opioid epidemic as it unfolded.

Recent Federal Policy Initiatives

As noted above, the IOM's 2011 report *Relieving Pain in America* highlighted the public health significance of pain and the need for fundamental changes in pain policy and practice (IOM, 2011). The report details the landscape of pain in the United States of that time, including such key factors as its overall prevalence; its personal, economic, and social consequences; and the significant shortcomings of prevailing treatment approaches. The report also describes the status of some of the available pain treatment approaches, including pharmacologic options, injection-based interventions, surgery, rehabilitative strategies, psychological therapies, and complementary modalities. The report presents highlights of then-current knowledge about pain mechanisms and the impact of interacting comorbid conditions such as depression, anxiety, and SUD, as well as areas in which knowledge was critically lacking. While the report ably describes the contemporary state of the art, however, important advances have since occurred on many fronts.

One element of this committee's charge was to "provide an update on the state of the science of pain research, care, and education since the 2011 report and characterize the evolving role of opioid analgesics in pain management," a task that the committee carries out in several chapters of this report. The subsections below summarize three major federal policy activities related to pain management and opioids that have taken place since the 2011 report was published and that provide additional context for the present study: the ongoing formulation of a National Pain Strategy, promulgation of a guideline for opioid prescribing under the auspices of the CDC, and ONDCP's development of a comprehensive plan for managing the opioid crisis.

National Pain Strategy

One of the principal recommendations of the 2011 IOM report was that HHS develop "a comprehensive population health-level strategy for pain prevention, treatment, management, and research" (IOM, 2011, p. 102). In response, the HHS assistant secretary requested that the Interagency Pain Research Coordinating Committee (IPRCC) develop a National Pain Strategy to provide a blueprint for transforming pain prevention, care, education, and research. After several years of work, the National Pain Strategy was published in 2016 (HHS, 2016b). The document's findings and recommendations fall into six primary areas: population research, prevention and care, disparities, service delivery and reimbursement, professional education and training, and public awareness and communication.

The National Pain Strategy highlights difficulties surrounding the use of opioids in pain management. Its recommendations include augmenting the use of population-level data to inform national policy on opioid use, including regulatory actions undertaken by the FDA and the DEA. Perhaps more significant, the Strategy lists as an objective, "Develop and implement a national educational campaign to promote safer use of all medications, especially opioid use, among patients with pain" (HHS, 2016b, p. 48). The document, however, makes no specific recommendations to the FDA.

The work of the IPRCC is far from complete. The committee, composed of 7 federal and 12 nonfederal members, is engaged in several ongoing tasks, including summarizing advances in pain research, identifying critical gaps in the research, and advising NIH and other federal agencies on how best to streamline research efforts and improve the collection and dissemination of information on pain research and treatment.

U.S. Centers for Disease Control and Prevention's Guideline for Prescribing Opioids for Chronic Pain

In parallel with the efforts of the IPRCC, the CDC issued its Guideline for Prescribing Opioids for Chronic Pain in 2016, offering a detailed set of recommendations for prescribing opioids to adults for chronic pain (Dowell et al., 2016). Specific issues addressed by the guideline include (1) when to consider opioids for chronic pain; (2) what types and doses of opioids to use, as well as when to consider tapering off the drugs; and (3) how to assess patient-specific risks. The CDC developed the guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and its recommendations are based on a systematic review of the scientific evidence, as well as consideration of benefits and harms, values and preferences, and resource allocation. The guideline was specifically developed for primary care clinicians, including physicians, nurse practitioners, and physician assistants, prescribing opioids to patients with chronic pain (>3 months' duration) in outpatient settings. It acknowledges the existence of other sets of opioid prescribing guidelines, such as those issued by the American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel and the U.S. Department of Veterans Affairs (Chou et al., 2009; VA and DoD, 2010). The CDC guideline, however, has the advantage of reflecting more recent data on the effectiveness and risks of prescription opioids. In addition to review of the direct clinical evidence and complementary contextual evidence, the CDC process engaged federal partners and other stakeholders, and entailed subjecting the guideline to peer review and publishing it for public comment prior to dissemination.

The guideline ultimately published provides 12 recommendations concerning the use of opioids for the management of chronic pain (see Box 5-3 in Chapter 5) (Dowell et al., 2016). The guideline generally can be regarded as more conservative than many previous sets of recommendations on this topic. Some of its specific provisions should be noted. First, the guideline stresses the general approach of using nonopioid and nonpharmacologic therapy for chronic pain. In fact, it stresses that opioids are not first-line medications for the treatment of chronic pain. This recommendation is based on the finding that nonpharmacologic therapies appear to have efficacy similar to that of pharmacologic therapies, at least for the first several months of treatment, as well as a superior long-term risk profile. Second, the guideline recommends that when opioid therapy is used, IR rather than ER/LA opioids be prescribed and at relatively low doses. The guideline generally recommends doses below 50 morphine milligram equivalents (MME)/day and suggests careful justification of doses above 90 MME/day. Finally, the guideline stresses the evaluation of risks prior to opioid initiation, careful ongoing evaluation of those risks, and regular assessment of

response to the therapy. The guideline specifically mentions the potential for adverse interactions between opioids and such sedatives as benzodiazepines as it is now clear that such interactions contribute to many opioid-related deaths (Park et al., 2015).

Some have cautioned that the CDC guideline may have unintended consequences in terms of unduly limiting access to opioid medications (e.g., Guerriero and Reid, 2016; Pergolizzi et al., 2016). It should be noted, however, that additional publications providing separate analyses of the use of opioids for low back pain, a common indication, have become available since the CDC guideline was published (Abdel Shaheed et al., 2016; Qaseem et al., 2017). Consistent with the CDC findings and recommendations, these more recent analyses also find little evidence of meaningful pain relief provided by opioids for low back pain.

Office of National Drug Control Policy's Comprehensive Plan

ONDCP was created in 1989 by the Anti-Drug Abuse Act of 1988 to coordinate activities of the DEA, the FDA, the CDC, the National Institute on Drug Abuse (NIDA), and SAMHSA. In 2011, ONDCP issued a four-pronged comprehensive plan for managing the opioid crisis aimed at balancing the need to curb opioid-related harms with the needs of individuals for adequate pain treatment (ONDCP, 2011, p. 2).

The first prong entailed educating the public and health care providers. Practitioners seeking DEA registration for prescribing controlled substances would have been required to receive training on responsible opioid prescribing practices. Opioid REMS would have been required to include effective educational materials, and efforts would have been made to enhance education in health professional schools as well as continuing education through state and federal agencies. Second, the plan called for improved monitoring through state-authorized PDMPs. The plan noted that standardized monitoring programs with enhanced interoperability (with each other and with national monitoring systems) and access were needed in all 50 states. The plan also encouraged legal changes to allow more sharing of clinical data and innovative use of electronic health records. Third, the plan recommended new actions to increase environmentally responsible disposal of prescription drugs to prevent misuse and diversion. Finally, the plan recommended methods for improving enforcement, including a Model Pain Clinic Regulation Law and improved coordination among federal, state, and local agencies for investigation of illicit trafficking and illegitimate prescribing and prosecution of offenders (ONDCP, 2011).

In 2014, the DEA issued a new rule that largely addressed the goals of the 2011 ONDCP plan's drug disposal requirements. The DEA also has created a DEA 360 program, developed "Tactical Diversion Squads," and

formulated the HIDTA (High Intensity Drug Trafficking Areas) Heroin Response Strategy, all of which are designed to improve enforcement while taking a "balanced public health and public safety approach" (White House, 2016, p. 68). However, the ONDCP plan's education goals, which would have linked DEA registration and training requirements, have not been implemented, and the REMS education goals have been underutilized. ONDCP has pointed to the new CDC practice guideline as evidence of progress in education (White House, 2016, p. 66), but adherence to those recommendations is voluntary. Similarly, while progress has been made in expanding PDMPs—now in 49 states—and new federal monitoring plans have been developed, a lack of standardization and interoperability and poor access impede the effectiveness of these systems.

Ethical Context

The statement of task for this study (see Box 1-1) directed the committee to recommend policy actions by the FDA and other policy makers that would properly "balance the needs of pain patients and the [societal] need to address opioid misuse." This deceptively simple statement entails many technical challenges related to measurement quantification that are explored in this report. However, it also exposes a genuine ethical quandary that is fundamental to this entire report: How exactly does a regulator (or this committee) weigh and balance, for any particular regulatory action limiting access to opioids, the otherwise avoidable suffering that patients with pain would experience against the harms, not only to those individuals and their families but also to society, that would be prevented by the restriction? The "societal need to reduce opioid misuse" is particularly challenging in ethical terms because much of the harm to society arising from opioid misuse is attributable to diversion of the prescribed drugs from lawful markets and to the operation of black markets. Are these two sets of needs morally commensurate? Are they convertible to a common metric?

The task is made somewhat easier if one recognizes that the point of contention regarding the use of opioids in serving the "needs of pain patients" focuses almost entirely on treatment of chronic noncancer pain. As long as the quantity prescribed, dispensed, and administered is suitably limited, there is little disagreement about the need for opioids for treatment of patients with acute pain within controlled settings such as hospitals (e.g., the perioperative use of opioids for many types of surgeries), or for treatment of patients with cancer or terminal conditions. The area of dispute concerns long-term use of take-home doses for chronic noncancer pain by people who are not terminally ill.

It is instructive to attempt to operationalize the balancing task at the policy level. On the one hand, the policy maker must quantify or other-

wise characterize the aggregate reduction in pain experienced by patients if opioids are prescribed and used for these chronic indications. As discussed in Chapter 2, this is a difficult task because of a lack of data on the effectiveness of opioid therapy for long-term (>1 year) outcomes related to pain, function, and quality of life (Chou et al., 2015; Dowell et al., 2016)—notwithstanding the reported experience of many patients and their providers who believe the drugs are beneficial. On the other hand, policy makers must quantify or otherwise characterize the harms that would not have occurred had prescribing of opioids been more restricted. These harms include death from overdose and other harms to patients who become addicted to opioids in the course of treatment, and importantly, it also includes harms due to the misuse of drugs that have been diverted from lawful channels to people other than the patients to whom the drugs are prescribed.

This policy balance between benefits and harms inevitably involves many uncertain parameters requiring considerable speculation: the numbers of patients with pain who will be affected, the nature and intensity of the pain that will be experienced or mitigated under different sets of assumptions about access to the drugs, and the effect of more or less restrictive regulatory approaches on access to the drugs by persons other than the patients to whom they have been prescribed and the harms that might subsequently occur. Converting all these postulated impacts to a common metric, such as quality-adjusted life years (QALYs), would be one way to proceed, although this approach would require overcoming many technical challenges. Moreover, other outcomes at the societal level might be difficult to quantify, such as the impact of one or another policy on public trust in the medical profession and the health care system. Loss of confidence can arise from perceived overprescribing or perceived underprescribing.

This analytic approach of identifying, quantifying, and balancing relevant outcomes at the societal level is the only way policy makers can think clearly about such a complex issue and make their arguments transparent and open to critical review by others. However, one of the confounding features of the policy discourse on the regulation of opioids and opioid prescribing is that many physicians and patient advocates ground their arguments not in an aggregated balance of benefits and harms at the population level but in the patient-centered ethics of clinical medicine (ethics "at the bedside," so to speak). When viewed from the perspective of an individual physician and an individual patient seeking treatment for chronic pain, regulations restricting access to opioids may be objectionable because they are perceived as unduly constraining the options available to physicians seeking to alleviate the suffering of each patient under their care. This ethical duty entails making an individualized judgment about each patient's needs, recognizing that the needs of a particular patient may differ from those of the "average" patient experiencing a particular type of pain; that

the patient's response to treatment may differ from the "typical" response in relation to both specific risks and potential benefits; and that these effects in any particular case are difficult to quantify, especially when there is so little evidence about long-term use of opioids for chronic noncancer pain. From this perspective, the duty to exercise individualized clinical judgment lies at the heart of the physician–patient relationship. Individualized decision making is all the more important in the context of pain, given its inherently subjective nature, and in the context of the ethical paradigm of shared decision making.

In thinking about the task of balancing the aggregated needs of patients in pain at the societal level and the need to prevent harms associated with misuse of opioid analgesics, the committee was sensitive to the ethical tension between the population perspective of public health and the patient-centered perspective of clinical ethics. The bottom line is that these two perspectives address two different questions. The committee's charge was to answer the societal question: What should the FDA and other government entities do when acting to further society's collective interest? The committee was not charged with asking what physicians and other prescribers should do or what options they should have available for particular clinical indications. This does not imply, however, that the ethics of clinical medicine are irrelevant: the framework used by policy makers in balancing the aggregated needs of patients with pain against society's collective interest in preventing opioid-related harms must be sensitive to the impact of alternative policies on public confidence in the health care system, including trust in the physician–patient relationship.

STUDY SCOPE AND EMPHASIS AND REPORT ORGANIZATION

Study Scope and Emphasis

The breadth of the committee's charge posed several challenges. First, the charge envisioned two fairly distinct tasks—an update of the science of pain research, care, and education since the IOM's 2011 report, including the evolving role of opioids in pain management, and a "new" report summarizing the "state of the science" on the use and misuse of prescription opioids and on approaches for addressing the problem. The committee interpreted its charge as focusing primarily on the misuse of prescribed opioids, the occurrence of OUD, and the associated public health harms, with updates to the 2011 report being limited to those bearing on indications for opioid prescribing, alternatives to opioids for pain management, physician education, and priorities for research.

A second challenge was the multiple audiences for this report. The charge requested that the committee provide advice not only to the FDA but

also to other policy makers and stakeholders. The committee understood that the FDA's primary reason for requesting this report was its desire for an expanded framework for review, approval, and monitoring of opioids that would encompass the societal harms resulting from opioid prescribing, and accordingly attempted to develop such a framework. However, the FDA knows it cannot address the opioid problem on its own, and its charge to the committee clearly invited a broader view of the report's intended audience. The committee chose to take this broader view because it was convinced that successful efforts to prevent, ameliorate, and minimize the public health harms associated with use and misuse of prescription opioids will require coordinated action at all levels of government and by a diverse array of stakeholder organizations.

A third challenge was that the committee was charged with addressing a complex, multifaceted problem that can be viewed through many lenses. The approach the committee took to carrying out this charge was shaped by the expertise of the its members and its interpretation of the charge. Accordingly, the committee focused on improving the treatment of pain and on responding to the policy challenges presented by the opioid epidemic. Many other relevant topics could have been included, such as why this epidemic has occurred. However, the committee was not directed to investigate the causes of the prescription opioid problem or to judge how it could have been avoided or ameliorated. Indeed, in its initial conversations with FDA officials, the committee was specifically advised that the purpose of this report was not to place blame for the current state of affairs.

Not surprisingly, however, questions about who bears responsibility for the current situation surfaced repeatedly in the committee's public workshops. Some observers, for example, suggested that the 2011 IOM report underemphasized then-emerging opioid-related harms as it highlighted the prevalence and cost of inadequately treated pain. Other speakers argued that the FDA has not been aggressive enough in its regulatory decisions, while still others directed attention to the systemic failures of the nation's health care system.

Nonetheless, the committee did not aim to assign responsibility for past mistakes. Its task was to review and assess approaches and actions that the FDA and others have taken, and could take, to resolve the problem and prevent such problems from arising in the future. To this end, the committee naturally posits a predictive model concerning what interventions might work. In so doing, it relies on a traditional multifactorial causal model commonly used in public health, encompassing considerations ranging from structural factors to individual susceptibility. Using this approach, certain hypotheses about causes of the epidemic are inescapable. For example, the data presented earlier in this chapter make a prima facie case that heavy promotion of opioid prescribing by drug manufacturers (including misleading

claims by some) and substantially increased prescribing by physicians were key contributors to the increase in misuse, OUD, and accompanying harms.

It is also clear, however, that overprescribing was not the sole cause of the problem. While increased opioid prescribing for chronic pain has been a vector of the opioid epidemic, researchers agree that such structural factors as lack of economic opportunity, poor working conditions, and eroded social capital in depressed communities, accompanied by hopelessness and despair, are root causes of the misuse of opioids and other substances and SUD (Carpenter et al., 2016; Compton et al., 2014; Nagelhout et al., 2017). It was beyond the scope of the committee's task to review and offer recommendations for mitigating the effects of these underlying structural determinants of opioid misuse and OUD. Nonetheless, the committee believes it is extremely important to keep these determinants in mind while reading this report, which focuses largely, although not entirely, on the supply side of the equation (increased prescribing of opioids) rather than on the more complex structural and environment factors that contribute to the demand side of the equation.

Report Organization

This report is divided into six chapters. Part I, consisting of Chapters 2 and 3, updates the 2011 IOM report. Chapter 2 describes the scope of the problem of pain in the United States and the state of the science on pain management, with an emphasis on the evolving role of prescription opioids and other forms of treatment in pain management. Areas for future research on pain and its management and on OUD to assist the FDA with the development of a framework for opioid approval and monitoring are discussed in Chapter 3. Part II, consisting of Chapters 4, 5 and 6, characterizes the opioid epidemic and the nation's response to it. Chapter 4 describes the epidemiology of opioid use and misuse, OUD, overdose, and other harms from both prescription and illicit opioids (e.g., heroin). Chapter 5 reviews the evidence regarding the effectiveness of strategies being used to address the opioid epidemic and makes recommendations where indicated. Specific topics covered include regulating the types of products approved for use (e.g., ADFs); restricting legal access to approved drugs; modifying prescribing practices; providing patient education; increasing access to treatment for OUD; and reducing harms from opioid use, such as by providing naloxone to prevent opioid overdose and making clean needles available for injection drug users to reduce transmission of HIV and hepatitis C virus. Finally, based on content presented in earlier chapters, Chapter 6 outlines steps the FDA can take to improve its regulation of opioids, including an approach for improving incorporation of individual and public health risks and benefits into future FDA approval and monitoring of these drugs.

REFERENCES

Abdel Shaheed, C., C.G. Maher, K.A. Williams, R. Day, and A.J. McLachlan. 2016. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: A systematic review and meta-analysis. 2016. *JAMA Internal Medicine* 176(7):958-968.

ASAM (American Society of Addiction Medicine). 2011. P*ublic policy statement: Definition of addiction. Short definition of addiction*. http://www.asam.org/quality-practice/definition-of-addiction (accessed May 1, 2017).

Booth, M. 1986. *Opium: A history*. New York: St. Martin's Press.

Brennan, F. 2015. The U.S. Congressional "Decade on Pain Control and Research" 2001-2011: A review. *Journal of Pain and Palliative Care Pharmacotherapy* 29(3):212-227.

Califf, R.M., J. Woodcock, and S. Ostroff. 2016. A proactive response to prescription opioid abuse. Special Report. *New England Journal of Medicine* 374:1480-1485.

Campbell, J.N. 1996. APS 1995 Presidential address. *The Journal of Pain* 5(1):85-88.

Carpenter, C.S., C.B. McClellan, and D.I. Rees. 2016. Economic conditions, illicit drug use, and substance use disorders in the United States. *Journal of Health Economics* 52:63-73.

CDC (U.S. Centers for Disease Control and Prevention). 2011. Vital Signs: Overdoses of prescription opioid pain relievers—United States, 1999-2008. *Morbidity and Mortality Weekly Report* 60(43):1487-1492.

Chou, R., G.J. Fanciullo, P.G. Fine, J.A. Adler, J.C. Ballantyne, P. Davies, M.I. Donovan, D.A. Fishbain, K.M. Foley, J. Fudin, A.M. Gilson, A. Kelster, A. Mauskop, P.G. O'Connor, S.D. Passik, G.W. Pasternak, R.K. Portenoy, B.A. Rich, R.G. Roberts, K.H. Todd, and C. Miakowski. American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. 2009. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *The Journal of Pain* 10(2):113-130.

Chou, R., J.A. Turner, E.B. Devine, R.N. Hansen, S.D. Sullivan, I. Blazina, T. Dana, C. Bougatsos, and R.A. Deyo. 2015. The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of Internal Medicine* 162(4):276-286.

Cicero, T.J., J.A. Inciardi, and A. Muñoz. 2005. Trends in abuse of Oxycontin and other opioid analgesics in the United States: 2002-2004. *The Journal of Pain* 6(10):662-672.

Compton, W.M., and N.D. Volkow. 2006. Major increases in opioid analgesic abuse in the United States: Concerns and strategies. *Drug and Alcohol Dependence* 81(2):103-107.

Compton, W.M, J. Gfoerer, K.P. Conway, and M.S. Finger. 2014. Unemployment and substance outcomes in the United States, 2002-2010. *Drug and Alcohol Dependence* 142:350-353.

Courtwright, D. 2015. Preventing and treating narcotic addiction—A century of federal drug control. *New England Journal of Medicine* 373(22):2095-2097.

DEA (U.S. Drug Enforcement Administration). 2017a. *DEA mission statement*. https://www.dea.gov/about/mission.shtml (accessed April 23, 2017).

DEA. 2017b. *List of controlled substances*. https://www.deadiversion.usdoj.gov/schedules (accessed February 7, 2017).

Dowell, D., T.M. Haegerich, and R. Chou. 2016. CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. *Morbidity and Mortality Weekly Report* 65(No. RR-1):1-49.

Dunlap, B., and A.S. Cifu. 2016. Clinical management of opioid use disorder. *Journal of the American Medical Association* 316(3):338-339.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2016. *Portugal country overview*. http://www.emcdda.europa.eu/countries/portugal (accessed March 17, 2017).

FDA (U.S. Food and Drug Administration). 2016a. *Fact sheet—FDA opioids action plan*. http://www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm (accessed January 5, 2017).

FDA. 2016b. FDA News Release. *Califf, FDA top officials call for sweeping review of agency opioids policies*. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm484765.htm (accessed January 5, 2017).

FDA. 2017a. *A brief overview of Risk Evaluation and Mitigation Strategies (REMS)*. FDA Basics Webinar. http://www.fda.gov/AboutFDA/Transparency/Basics/ucm325201.htm (accessed January 11, 2017).

FDA. 2017b. *Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting opioid analgesics*. https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm (accessed June 4, 2017).

FDA. 2017c. *Timeline of selected FDA activities & significant events addressing opioid misuse & abuse*. http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm332288.pdf (accessed January 10, 2017).

Frieden, J. 2016. *Remove pain as 5th vital sign, AMA urged*. https://www.medpagetoday.com/meetingcoverage/ama/58486 (accessed May 25, 2017).

Gaither, J.R., J.M. Leventhal, S.A. Ryan, and D.R. Camenga. 2016. National trends in hospitalizations for opioid poisonings among children and adolescents, 1997 to 2012. *JAMA Pediatrics* 170(12):1195-1201.

GAO (U.S. General Accounting Office). 2003. *Prescription drugs. OxyContin abuse and diversion and efforts to address the problem*. http://www.gao.gov/new.items/d04110.pdf (accessed February 21, 2017).

Garcia del Pozo, J., A. Carvajal, J.M. Viloria, A. Velasco, and V. Garcia del Pozo. 2008. Trends in the consumption of opioid analgesics in Spain. Higher increases as fentanyl replaces morphine. *European Journal of Clinical Pharmacology* 64(4):411-415.

Greenwald, G. 2009. *Drug decriminalization in Portugal: Lessons for creating fair and successful drug policies*. https://www.cato.org/publications/white-paper/drug-decriminalization-portugal-lessons-creating-fair-successful-drug-policies (accessed March 17, 2017).

Guerriero, F., and M.C. Reid. 2016. New opioid prescribing guidelines released in the U.S.: What impact will they have in the care of older patients with persistent pain? *Current Medical Research and Opinion* 33(2):275-278.

Haddox, J.D., D. Joranson, R.T. Angarola, A. Brady, D.B. Carr, E.R. Blonsky, K. Burchiel, M. Gitlin, M. Midcap, R. Payne, D. Simon, S. Vasudeyan, and P. Wilson. 1997. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clinical Journal of Pain* 13(1):6-8.

Hauser, W., F. Petzke, L. Radbruch, and T.R. Tolle. 2016. The opioid epidemic and the long-term opioid therapy for chronic noncancer pain revisited: A transatlantic perspective. *Pain Management* 6(3):249-263.

HHS (U.S. Department of Health and Human Services). 2015. *HHS takes strong steps to address opioid-drug related overdose, death and dependence*. https://www.hhs.gov/about/news/2015/03/26/hhs-takes-strong-steps-to-address-opioid-drug-related-overdose-death-and-dependence.html (accessed January 10, 2017).

HHS. 2016a. *Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health*. HHS Publication SMA 16-4984, NSDUH Series H-51. Rockville, MD: Substance Abuse and Mental Health Services Administration.

HHS. 2016b. *National Pain Strategy: A comprehensive population health-level strategy for pain*. Washington, DC: HHS. https://iprcc.nih.gov/docs/HHSNational_Pain_Strategy.pdf (accessed June 27, 2017).

Hoffman, D.E. 2016. Treating pain V. Reducing drug diversion and abuse: Recalibrating the balance in our drug control laws and policies. *Saint Louis University Journal of Health Law & Policy* 1:231-310.

IOM (Institute of Medicine). 2011. *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington, DC: The National Academies Press.

Karanges, E.A., B. Blanch, N.A. Buckley, and S.A. Pearson. 2016. Twenty-five years of prescription opioid use in Australia: A whole-of-population analysis using pharmaceutical claims. *British Journal of Clinical Pharmacology* 82(1):255-267.

Kerr, T., M. Tyndall, K. Li, J. Montaner, and E. Wood. 2005. Safer injection facility use and syringe sharing in injection drug users. *Lancet* 366(9482):316-318.

Lowes, R. 2016. *Drop pain as the fifth vital sign, AAFP says*. http://www.medscape.com/viewarticle/869169 (accessed May 25, 2017).

Manchikanti, L., and A. Singh. 2008. Therapeutic opioids: A ten-year perspective on the complexities and complications of escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 11(2 Suppl.):S63-S88.

Mansbach, R.S., K.A. Schoedel, J.P. Kittrelle, and E.M. Sellers. 2010. The role of adverse events and related safety data in the pre-market evaluation of drug abuse potential. *Drug and Alcohol Dependence* 112(3):173-177.

Marshall, B.D., M.J. Milloy, E. Wood, J.S. Montaner, and T. Kerr. 2011. Reduction in overdose mortality after the opening of North America's first medically supervised safer injecting facility: A retrospective population-based study. *Lancet* 377(9775):1429-1437.

Massachusetts Department of Public Health. 2014. *Findings of the Opioid Task Force and Department of Public Health recommendations on priorities for investments in prevention, intervention, treatment and recovery*. http://www.mass.gov/eohhs/docs/dph/substance-abuse/opioid/report-of-the-opioid-task-force-6-10-14.pdf (accessed February 21, 2017).

Mularksi, R.A., F. White-Chu, D. Overbay, L. Miller, S.M. Asch, and L. Ganzini. 2006. Measuring pain as the 5th vital sign does not improve quality of pain management. *Journal of General Internal Medicine* 21(6):607-612.

Musto, D.F. 1999. *The American disease: Origins of narcotic control*. 3rd ed. New York: Oxford University Press.

Nagelhout, G.E., K. Hummel, M.C.M. de Goeij, H. de Vries, E. Kaner, and P. Lemmens. 2017. How economic recessions and unemployment affect illegal drug use: A systematic realist literature review. *International Journal of Drug Policy* 44:69-83.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2016. *Pain management and prescription opioid-related harms: Exploring the state of the evidence: Proceedings of a workshop—in brief*. Washington, DC: The National Academies Press.

NCHS (National Center on Health Statistics). 2016. *National overdose deaths from select prescription and illicit drugs*. https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates (accessed June 26, 2017).

NIDA (National Institute on Drug Abuse). 2017. *How do opioids work*? https://teens.drugabuse.gov/teachers/mind-over-matter/opioids/how-do-opioids-work (accessed May 25, 2017).

ONDCP (Office of National Drug Control Policy). 2011. *Epidemic: Responding to America's prescription drug abuse crisis*. https://www.ncjrs.gov/pdffiles1/ondcp/rx_abuse_plan.pdf (accessed April 23, 2017).

ONDCP. 2017. *Changing the language of addiction*. https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Memo%20-%20Changing%20Federal%20Terminology%20Regrading%20Substance%20Use%20and%20Substance%20Use%20Disorders.pdf (accessed April 23, 2017).

Pan, G. 2016. *Challenges in assessing real world use and abuse of pain medicines*. PowerPoint presentation. FDA Science Board Meeting. March. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM489209.pdf (accessed January 11, 2017).

Park, T.W., R. Saitz, D. Ganoczy, M.A. Illgen, and A.S. Bohnert. 2015. Benzodiazepine prescribing patterns and deaths from drug overdose among U.S. veterans receiving opioid analgesics: Case-cohort study. *British Medical Journal* 350:h2698.

Pergolizzi, J.V., Jr., R.B. Raffa, and J.A. LeQuang. 2016. The Centers for Disease Control and Prevention opioid guidelines: Potential for unintended consequences and will they be abused? *Journal of Clinical Pharmacy and Therapeutics* 41(6):592-593.

Pokrovnichka, A. 2008. *History of OxyContin: Labeling and Risk Management Program*. PowerPoint presentation. Anesthetic and Life Support Drugs and Drug Safety and Risk Management Advisory Committees, November 13-14. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM248776.pdf (accessed January 11, 2017).

Public Citizen. 2017. *Congressional testimony on OxyContin and the prosecution of Purdue*. https://www.citizen.org/our-work/health-and-safety/congressional-testimony-oxycontin-and-prosecution-purdue (accessed August 2, 2017).

Qaseem, A., T.J. Wilt, R.M. McLean, and M.A. Forciea. 2017. Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine* 10.7326/M16-2367.

Rosenblum, A., L.A. Marsch, H. Joseph, and R.K. Portenoy. 2009. Opioids and the treatment of chronic pain: Controversies, current status, and future directions. *Experimental and Clinical Psychopharmacology* 16(5):405-416.

Rudd, R.A., P. Seth, F. David, and L. Scholl. 2016. Increases in drug and opioid-involved overdose deaths—United States, 2010–2015. *Morbidity and Mortality Weekly Report* 65(50-51):1445-1452.

SAMHSA (Substance Abuse and Mental Health Services Administration). 2015. Treatment Episode Data Set (TEDS) 2003–2013. *National admissions to substance abuse treatment services*. https://www.samhsa.gov/data/sites/default/files/2003_2013_TEDS_National/2003_2013_Treatment_Episode_Data_Set_National.pdf (accessed January 10, 2017).

Senate Committee on Government Operations. 1973. *Reorganization plan no. 2 of 1973, establishing a Drug Enforcement Administration in the Department of Justice*. Washington, DC: U.S. Government Printing Office. https://www.gpo.gov/fdsys/pkg/USCODE-2010-title5/pdf/USCODE-2010-title5-app-reorganiz-other-dup96.pdf (accessed June 11, 2017).

Spillane, J.F. 2004. Debating the Controlled Substances Act. *Drug and Alcohol Dependence* 76(1):17-29.

Spillane, J., and W.B. McAllister. 2003. Keeping the lid on: A century of drug regulation and control. *Drug and Alcohol Dependence* 70(3 Suppl.):S5-S12.

Staffa, J. 2017. *Overview of the prescription opioid epidemic and the FDA activities to address it*. Presentation at DIA/FDA statistics forum, April 24.

UNODC (United Nations Office on Drugs and Crime). 2017. *UNODC statistics*. https://data.unodc.org (accessed May 26, 2017).

VA (U.S. Department of Veterans Affairs) and DoD (U.S. Department of Defense). 2010. *VA/DoD clinical practice guidelines for management of opioid therapy for chronic pain*. https://www.va.gov/painmanagement/docs/cpg_opioidtherapy_summary.pdf (accessed February 21, 2017).

VanZee, A. 2009. The promotion and marketing of OxyContin: Commercial triumph, public health tragedy. *American Journal of Public Health* 99(2):221-227.

Virginia Department of Health. 2016. *The opioid crisis is a public health emergency in Virginia*. http://www.vdh.virginia.gov/home/resources-for-health-care-professionals/the-opioid-addiction-crisis-is-a-public-health-emergency-in-virginia (accessed February 21, 2017).

VonKorff, M., A. Kolodny, R.A. Deyo, and R. Chou. 2011. Long-term opioid therapy reconsidered. *Annals of Internal Medicine* 155(5):325-328.

Voon, P. 2016. *Prevalence, correlates, and regulatory strategies related to pain, opioid misuse, and overdose: The experience in Vancouver, Canada*. Presentation to the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse, Washington, DC. November 4.

Warner, M., L.H. Chen, D.M. Makuc, R.N. Anderson, and A.M. Minino. 2011. *Drug poisoning deaths in the United States, 1980–2008*. https://www.cdc.gov/nchs/products/databriefs/db81.htm (accessed February 21, 2017).

White House. 2016. *National drug control strategy*. https://obamawhitehouse.archives.gov/sites/default/files/ondcp/policy-and-research/2016_ndcs_final_report.pdf (accessed April 23, 2017).

PART I

PAIN MANAGEMENT AND RESEARCH

2

Pain Management and the Intersection of Pain and Opioid Use Disorder

This chapter addresses the scope of the problem of pain in the United States and its association with opioids, and the effectiveness of pharmacologic (both opioid and nonopioid) and nonpharmacologic treatments that may, alone or in combination, help individuals manage pain. The first section summarizes the scope of the problem of pain, focusing in particular on chronic, or persistent, pain, the form most associated with problematic use of opioids. The chapter then presents a detailed discussion of the various pain treatment modalities, reviewing in turn opioid analgesics, nonopioid pharmacologic treatments, interventional pain therapies, and nonpharmacologic treatments. This section is particularly important in helping to contextualize the evidence of effectiveness and limitations for various treatments for pain, given the burden of pain, the risks associated with undertreatment, and the pervasiveness of opioid use and related dose-dependent risks. The next section examines differences in pain experiences and treatment effectiveness among subpopulations, and the final section briefly addresses the intersection between pain and opioid use disorder (OUD) (discussed in greater detail in Chapter 3). A main objective of this chapter is to situate opioids within the broader armamentarium of treatments available for management of pain and to identify potential opportunities for reduced reliance on these medications.

THE SCOPE OF THE PROBLEM OF PAIN

Chronic pain generally is defined as pain lasting 3 or more months or beyond the time of normal tissue healing (Dowell et al., 2016). As described

in the 2011 Institute of Medicine (IOM) report *Relieving Pain in America* (IOM, 2011), pain is a significant public health problem, although estimates of the number of people living with chronic pain in the United States vary widely in population-level surveys (see Croft et al., 2010; Johannes et al., 2010; Nahin, 2015; Portenoy et al., 2004). Using self-reported data from the 2011 National Health Interview Survey's Functioning and Disability Supplement, Nahin (2015) estimates that at the time of the survey, 11.2 percent of the adult U.S. population (25.3 million people) was experiencing daily chronic pain (pain every day for the past 3 months).

The 2011 IOM report appropriately calls attention to the substantial burden of pain in the United States and estimates that "chronic pain alone affects approximately 100 million U.S. adults," a figure that has routinely been quoted in recent years (IOM, 2011, p. 100). The present committee found that it is difficult to formulate a reliable estimate of the prevalence of chronic pain because of differences across surveys in the way pain is defined and measured. The 100 million figure cited in the 2011 IOM report was based on an analysis of data from surveys conducted in 17 developed and developing countries, including the United States, to evaluate differences in the prevalence of common chronic pain conditions by age and sex, as well as the comorbidity of chronic pain conditions with depression and anxiety disorders (Tsang et al., 2008). The age-adjusted prevalence of chronic pain conditions in the previous 12 months for adults in the United States was found to be 43 percent (roughly 100.86 million people based on the total U.S. population aged 18 and over in 2010) (Howden and Meyer, 2011; Tsang et al., 2008). A limitation of that study, in this committee's view, is that the questions asked of survey participants did not distinguish occasional aches and pains from daily continuous or chronic intermittent pain that may interfere with quality of life.[1] As noted by Tsang and colleagues (2008) themselves, one of the limitations of the study is that "the assessment of pain condition did not include severity and duration of pain." Nonetheless, regardless of the exact number of people living with chronic pain in the United States, it clearly affects the lives of millions of Americans.

Chronic pain is associated with multiple comorbidities, including, among others, impaired memory, cognition, and attention; sleep disturbances; reduced physical functioning; and reduced overall quality of life (Dahan et al., 2014; Fine, 2011; IOM, 2011). Chronic noncancer pain also has been found to be associated with work absenteeism (Agaliotis et

[1]Survey participants were asked whether they had ever had "arthritis or rheumatism" in their lifetime. Respondents who replied that they had were asked whether the arthritis or rheumatism had been present in the prior 12 months. Participants also were asked whether they had ever had "chronic back or neck problems" (referred to as back pain), "frequent or severe headaches" (referred to as headaches), and "other chronic pain" in the prior 12 months.

al., 2014). Severe chronic pain at the highest levels is associated with poor health and increased use of medical resources (IOM, 2011), and painful conditions are among the most frequently reported reasons for outpatient visits with physicians in the United States (CDC, 2017). An argument has been made that chronic pain may itself be considered a disease syndrome when it leads to changes in the nervous system over time (IOM, 2011). As discussed later in this chapter, adding to the public health burden of pain are disparities in access to and quality of pain treatment among subpopulations (Anderson et al., 2009; IOM, 2011; Mossey, 2011).

The very real problems of underdiagnosis and undertreatment of pain are valid concerns, but it would be a mistake to infer that greater utilization of opioids would ameliorate these problems. As discussed below, opioids have long been used for the effective management of acute pain (e.g., acute postsurgical and postprocedural pain), but available evidence does not support the long-term use of opioids for management of chronic noncancer pain. On the other hand, evidence indicates that patients taking opioids long-term are at increased risk of OUD and opioid overdose, as well as a number of other adverse outcomes (e.g., cardiovascular events, fractures) (Baldini et al., 2012; Chou et al., 2015; Krashin et al., 2016). Nevertheless, opioids often are used in the management of chronic noncancer pain. As discussed in Chapter 1, for many years physicians prescribed opioids for chronic noncancer pain, sometimes in very high doses, because of the incorrect belief that the risk for the development of substance use disorders and addiction was low (Krashin et al., 2016). Emphasis was appropriately placed on inadequate recognition and treatment of pain. However, these concerns often were not balanced by a similar emphasis on precautions to avoid adverse effects, such as the development of addiction (Kolodny et al., 2015), and the increase in opioid prescribing that began during the 1990s was associated with a parallel increase in opioid-related substance use disorders and opioid-related deaths (Dowell et al., 2016; Kolodny et al., 2015; SAMHSA, 2015). It is estimated that opioid pain relievers (excluding nonmethadone synthetics) directly accounted for more than 17,500 deaths in 2015, up from approximately 6,160 in 1999 (NCHS, 2016). Moreover, these figures do not account for deaths from related conditions (e.g., bloodborne infections associated with OUD; see Chapters 4 and 5 for further detail). There are indications that opioid prescribing is decreasing, but as recently as 2015, tens of millions of opioids were dispensed by U.S. outpatient retail pharmacies (see Figure 1-1 in Chapter 1). The United States consumes the vast majority of opioids worldwide (Hauser et al., 2016).

Acute pain also is relevant to this report. Millions of Americans are diagnosed each year with acute pain conditions (e.g., those associated with surgery, trauma, or acute illness) that typically resolve over days to weeks. Opioids are frequently prescribed to treat these conditions. Opioids may

be effective for managing acute pain when used appropriately, but as with chronic noncancer pain, harms to individuals and society may arise from these uses of opioids (Dowell et al., 2016). See Chapter 5 for discussion of the effectiveness of strategies for addressing these harms.

Little is known about the relationship between or the progression from acute to chronic pain, although preoperative chronic pain is thought to be a risk factor (Gerbershagen et al., 2014). It has been proposed that inadequate management of acute pain may increase an individual's risk for development of chronic pain (Sinatra, 2010). Indeed, some evidence suggests that appropriate treatment of acute pain, particularly persistent postsurgical pain, could decrease the likelihood of the future development of chronic pain (Clarke et al., 2012). Similarly, the use of gabapentin or pregabalin in the immediate preoperative setting has the potential to decrease the need for postsurgical opioids (Tan et al., 2015a). Research is ongoing to identify strategies that can decrease the risk of acute pain developing into persistent pain (McGreevy et al., 2011).

It is important to emphasize that the term "pain management" has not been clearly defined and sometimes is used erroneously to denote solely pharmacologic tools. Yet pain management may involve the use of a number of tools—both pharmacologic and nonpharmacologic—to relieve pain and improve function and quality of life. Before proceeding to a review of these various treatments, it should be noted that, while each may be used on its own, their integration in multimodal strategies that cut across medical disciplines and incorporate a full range of therapeutic options—including cognitive-behavioral, physical/rehabilitation, pharmacologic, and interventional therapies—has been shown to be most effective in the treatment of chronic pain (Koele et al., 2014; Scascighini et al., 2008). In contrast, use of a single pharmacologic modality such as an opioid analgesic, often used for the relief of acute nociceptive pain, is inherently limited in its ability to provide long-term relief and/or reverse ongoing plasticity changes driving chronic pain. Such pain encompasses a complex condition that has defied simple remedies. As noted, persistent pain is classified as chronic if someone has endured it for at least 3 months. Unfortunately, over this time period, the person experiencing the pain may have changed in complex ways. From the neuroscientist's perspective, pathologic plasticity changes in the central and peripheral nervous system have taken hold and have become self-perpetuating, signaling pain and frequently limiting meaningful function. Chapter 3 describes the complex neurobiology related to pain (and reward) processing, identifies promising research areas, and highlights knowledge gaps that could be addressed to help improve the management of chronic pain.

Thus, it must be stressed that a single therapeutic switch to turn off the perception of chronic pain has yet to be found and in fact may not exist.

From the perspective of those suffering chronic pain, any remedy, even one that may simply remit the pain for a few hours or days, may be a welcome relief despite risks or side effects. However, just as chronic pain represents a complex pathophysiologic condition that develops over time, its successful management often requires an equally complex and time-intensive approach. Therefore, combining multiple therapeutic modalities, nonpharmacologic and pharmacologic (nonopioid and opioid), holds promise not only to temper the ongoing pain but also to help return the nervous system and its owner back to a less painful and more functional state. It is significant, then, that many of the nonpharmacologic techniques are reimbursed poorly if at all by third-party payers, creating a disincentive to provide this effective care for patients. See Chapter 5 for further discussion of policies regarding reimbursement of comprehensive pain management.

OPIOID ANALGESICS

Effectiveness and Risks

Opioid analgesics encompass a wide range of medicinal products that typically share the ability to relieve acute severe pain through their action on the μ opioid receptor—the major analgesic opioid receptor expressed throughout the nervous system. Since the isolation of morphine from crude opium by Sertürner in 1803, there has been a progressive increase in the number of opioid analgesics that differ in their chemical composition, route of administration, uptake, distribution, type/rate of elimination, and ability to bind to opioid receptors. Certain of these drugs have ultra-short durations of action uniquely suited to providing analgesia as a component of a balanced surgical anesthetic. Others have very long durations of action resulting either from the intrinsic properties of the opioid molecule or the pharmaceutical formulation; in either case, these opioids are released at a predictable rate into a patient's body. An additional feature of these medications contributing to their clinical utility is the availability of oral, intravenous, transdermal, intranasal, epidural, and intrathecal preparations.

Opioids have long been used successfully to treat acute postsurgical 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). For other types of acute pain, however, such as low back pain, the efficacy of opioids is less clear (Deyo et al., 2015; Friedman et al., 2015). And as noted earlier, while evidence exists to support the use of opioids for the treatment of some acute and subacute pain, evidence to support their use to treat chronic pain is very limited (Chou et al., 2015; Dowell et al., 2016). The few randomized controlled trials (RCTs) demonstrating the efficacy of opioids have had small sample sizes

and rarely have produced data that extend past 3 months, the length of time after which pain is considered to be chronic.

The average reduction in chronic noncancer pain ascribed to opioids has been found to be approximately 30 percent (Kalso et al., 2004), and data on functional improvement are limited. A Danish epidemiological study evaluating the effects of long-term (>6 months) use of opioids in more than 10,000 patients with chronic noncancer pain failed to show improvement on any of the items in the 36-Item Short Form Health Survey (SF-36) used to score health-related quality of life (Eriksen et al., 2006). A meta-analysis of 26 studies examining various opioid drugs (compared with placebo as well as other treatments, including nonsteroidal anti-inflammatory drugs [NSAIDS]) in chronic noncancer pain found that "all patients with CNCP [chronic noncancer pain] do not respond to opioid analgesics, only 30–50% of carefully screened subjects report decrease in pain with opioids; [and] the results of RCTs cannot be generalized to the CNCP population because clinical trials do not include . . . multiple pain complaints . . . or other psychiatric comorbidities" (Sehgal et al., 2013, p. 1211). There is some evidence that return to work is more often delayed than expedited for patients using opioids chronically (VonKorff, 2013). And today, despite the existence of a number of opioid compounds and formulations, there is no evidence that one opioid analgesic is superior to another in its ability to manage either acute or chronic pain, and there is insufficient evidence on appropriate dosing. A study of 1,477 adults prescribed opioids for chronic pain, for example, showed that patients who used lower or intermittent doses of opioids had pain outcomes similar to those of patients who used regular or higher doses (Turner et al., 2016).

With regard to the risks associated with the use of prescription opioids, it has been shown that once patients have been taking opioids longer than 90 days, the risk that they will continue to take them chronically and develop a substance use disorder increases (Krashin et al., 2016). In addition to substance use disorder, morbidity related to opioid therapy for chronic pain includes reduced testosterone, cardiac abnormalities, fractures, and immunosuppression, among other adverse outcomes (Chou et al., 2015). A 2015 systematic review of studies of adults prescribed oral opioids for chronic pain estimates the prevalence of opioid misuse (defined in the study as "opioid use contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm or adverse effects") in the United States to be 21.7–29.3 percent and the prevalence of addiction (defined as continued use despite harm) to be 7.8–11.7 percent (Vowles et al., 2015). In the elderly and other patients with a higher risk of cognitive impairment, opioids may result in further impairment of cognition and executive function (Schiltenwolf et al., 2014). As noted earlier, moreover, there is a risk of death from these drugs due to opioid-induced respiratory depression (Chou et al., 2015).

Of the many long-term consequences of using opioids, tolerance and opioid-induced hyperalgesia (OIH) are commonly cited as reasons for their waning therapeutic effect over time. Strong laboratory evidence demonstrates that these phenomena occur after even short periods of exposure to opioids or after exposure to large doses of the drugs (Angst and Clark, 2006; Trang et al., 2015; Yi and Pryzbylkowski, 2015). Likewise, tolerance and OIH have been demonstrated in people with OUD, and abnormal pain sensitivity in this population is associated with drug craving (Ren et al., 2009). On the other hand, OIH has been observed after short-term exposure to potent, rapidly eliminated opioids such as remifentanil in human volunteers (Angst and Clark, 2006; Eisenach et al., 2015). Correspondingly, patients for whom remifentanil is incorporated into their surgical anesthetic appear to have higher postoperative pain levels or opioid requirements consistent with either tolerance or OIH (de Hoogd et al., 2016; Fletcher and Martinez, 2014). However, the rapidity, severity, and pervasiveness of tolerance and OIH are poorly defined in chronic pain populations, as are possible differences among opioids with respect to causing these adverse consequences. The situation is made more problematic by difficulties in assessing tolerance and OIH in clinical settings. Rapid dose escalation with worsening pain and the spread of painful symptoms have been suggested as indicators of tolerance and OIH, but well-validated clinical methods for quantifying tolerance and OIH in chronic pain patients are lacking (Mao, 2002).

One of the U.S. Food and Drug Administration's (FDA's) required post-marketing studies for extended-release/long-acting (ER/LA) opioid analgesics is an ongoing clinical trial to estimate risk for the development of hyperalgesia following long-term use (at least 1 year) of these drugs to treat chronic pain. This study, which includes an assessment of risk relative to efficacy, is anticipated to be completed in 2019 (see Chapter 6, Annex Table 6-1).

It is important to remember that nonopioid pharmacologic therapies carry their own distinct risks. For example, gastrointestinal bleeding and renal dysfunction are known risks associated with NSAIDs. Likewise, hepatotoxicity and unintended death are risks associated with acetaminophen, and acetaminophen toxicity is thought to contribute to at least some opioid-related mortality (Dunn et al., 2010; McLellan and Turner, 2010). Accordingly, some of the most difficult patients for whom to provide pain relief are those with end-stage liver or kidney disease or with bleeding disorders, many of whom end up taking opioids chronically because of the perceived paucity of effective alternatives.

While all prescription opioids interact with opioid receptors, some more recently developed agents possess additional pharmacologic activity, and even newer agents have been engineered to interact with opioid

receptors in ways that may enhance analgesic benefits while minimizing side effects, such as respiratory depression (Dahan, 2016). Therefore, it is likely that additional opioid drugs with properties perhaps superior in important ways to those of existing drugs will be developed for a wide range of painful conditions. On the other hand, these new drugs are likely to rely at least in part on the activation of the μ opioid receptor, a structure closely linked to important side effects of opioids, including respiratory depression and euphoria. Thus, the propensity of opioid medications to cause overdose or misuse is likely to continue to be cause for concern with these new formulations.

Opioid Prescribing Practices

Beyond differences in analgesic potency (e.g., hydrocodone versus morphine versus hydromorphone), one might ask what dictates prescribing of opioid analgesics for chronic pain. Addressing this question is challenging given the lack of a single integrated source of information on the use of prescription opioids in the United States. This is the case despite calls from both governmental and nongovernmental organizations for improved methods for tracking and accountability of opioid prescribing practices, indications, efficacy, or disposal and the more than decade-long development of the opioid epidemic. Government institutions rely in part on private consulting firms and/or literature generated from industry-sponsored research, or when available, post-marketing data (IOM, 2010). Other information comes from academically directed research focused on specific diagnostic areas, such as opioid use in musculoskeletal disorders (rheumatologic, back pain); treatment of specific disease states, such as sickle cell disease; and dental and emergency department practices. Although a full understanding is constrained by the limited information available, the committee compiled a brief summary of opioid prescribing practices in the United States from these accessible resources.

In 2015, 169 million prescriptions for some of the most common ER/LA and immediate-release (IR) opioid analgesics were dispensed by U.S. outpatient retail pharmacies, down from a high of 206 million in 2011 (see Chapter 1, Figure 1-1). The majority of opioid analgesic prescriptions dispensed during 2005–2015 were for IR opioids, whereas the number of ER/LA opioids dispensed remained nearly constant during this period (~12 percent).

During 2007–2012, self-reported use of opioid analgesics was higher among women (7.2 percent) than men (6.3 percent) and higher among non-Hispanic white adults (7.5 percent) than Hispanic adults (4.9 percent), while there was no significant difference in self-reported use between non-Hispanic white and non-Hispanic black adults (Frenk et al., 2015). From

1999–2002 to 2003–2006, the percentage of adults aged 20 and over who reported that they had used a prescription opioid analgesic in the past 30 days increased from 5.0 to 6.9 percent. From 2003–2006 to 2011–2012, the percentage who used an opioid analgesic remained stable at 6.9 percent. From 1999–2002 to 2011–2012, however, the percentage of users of opioid analgesics who were prescribed an opioid analgesic stronger than morphine increased from 17 to 37 percent (Frenk et al., 2015). Such a shift to more potent formulations may represent an important signal if one is attempting to understand the current ecology of prescription opioid use in the United States. Specifically, a shift from opioid analgesics that are weaker than morphine (codeine, dihydrocodeine, meperidine, pentazocine, propoxyphene, and tramadol) and "morphine-equivalent" (hydrocodone, morphine, and tapentadol) to those stronger than morphine (fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone) may represent an unwarranted change in opioid prescribing practices relative to evidence for the treatment of chronic painful conditions (Frenk et al., 2015). Although information is limited, such a shift to more potent opioids may correlate with reports of increased use of some opioid analgesics, such as oxycodone.

Clinical Contexts in Which Opioids Are Commonly Prescribed

An analysis of IMS Health's national prescription data showed that in 2012, nearly 49 percent of all dispensed opioid prescriptions were accounted for by primary care specialists. Opioid prescribing also varies by provider specialty. In 2012, the rate of opioid prescribing among specialists was highest for specialists in pain medicine (48.6 percent), followed by surgery (36.5 percent) and physical medicine and rehabilitation (35.5 percent). From 2007 to 2012, the greatest increase in the rate of opioid prescribing was among physical medicine and rehabilitation specialists, while the greatest declines were in emergency medicine (–8.9 percent) and dentistry (–5.7 percent) (Levy et al., 2015).

The clinical contexts in which pharmaceutical opioids are used also can be quite diverse. The evaluation of risks and benefits may therefore be different for specific opioids depending on their intended application. A few examples of common clinical contexts in which opioids are used demonstrate some of these differences.

Surgery and Acute Pain

Opioids are used commonly during and following surgery. During a surgical procedure, opioids contribute to the analgesic component of a balanced anesthetic. Often the opioids used are of high potency and short duration of action. In addition to intravenous administration, opioids are

sometimes administered intrathecally or into the epidural space to provide relatively high local concentrations without exposing respiratory centers in the brainstem to the same levels of the drugs.

Postoperatively, opioids are used in the postanesthesia care unit and hospital wards and as predominantly oral medications for a period ranging from days to a month or more during the convalescent period. The rate of discontinuation of opioids after surgery has been studied and is believed to be impacted by ongoing pain, as well as psychological factors and patients' self-perception of their risk for developing OUD (Carroll et al., 2012; Hah et al., 2015). The rate of discontinuation of opioid therapy after surgery is strongly impacted by preoperative use, and is higher for some types of surgery (e.g., joint replacement) than others (Mudumbai et al., 2016; Sun et al., 2016). It remains unclear how intraoperative exposure to opioids contributes to the risk for OUD. Perisurgical exposure to opioids may be an inciting event for the eventual development of OUD in some patients (Sun et al., 2016). Patients with OUD (e.g., individuals on methadone maintenance) are not necessarily excluded from receiving a short course of opioids for acute or acute postoperative pain. Providing excessive amounts of opioids postoperatively is now discouraged, however, and some health care organizations have attempted to limit the amount of postsurgical take-home opioid medication. The effectiveness of such policies is discussed in Chapter 5.

Another commonly encountered acute pain context leading to opioid exposure is the treatment of acute injuries, such as those due to household, sporting, or motor vehicle accidents. In these situations, limited supplies of opioids may be prescribed by emergency departments, urgent care clinics, specialty physicians, and primary care providers. The prescribing of opioids by emergency departments has been especially closely studied, and an increase was found to coincide with an increase in overall opioid prescribing (Maughan et al., 2015). Prescribing in this context can set the stage for a pattern of more chronic use; indeed, observational evidence suggests that long-term opioid use may begin in the emergency department (with 1 in 48 patients prescribed opioids becoming long-term users) (Barnett et al., 2017). Likewise, the use of prescription opioids by former professional athletes is very high, and participants in interscholastic sports may have an elevated risk of opioid use and misuse relative to their nonathlete counterparts (Veliz et al., 2015). Motor vehicle accidents, particularly severe ones, also appear to lead to chronic opioid use in some patients (Zwisler et al., 2015). Opioid prescribing guidelines targeting emergency departments and other acute care settings might contribute to reducing opioid prescribing and increase the use of such measures as urine drug screening prior to prescribing (Chen et al., 2016; del Portal et al., 2016).

Chronic Pain Syndromes

The use of opioids for the management of chronic pain has generated a great deal of attention, and represents the rationale for the prescribing of a large percentage of overall opioid medication consumed each year in the United States. Common types of pain for which these drugs are prescribed include back pain, arthritis, and neuropathic pain (e.g., pain involving tissue injury). Among the complications now associated with the chronic use of opioids for pain are dependence, tolerance, hyperalgesia, addiction, hypogonadism, falls, fractures, sleep-disordered breathing, increased pain after surgery, and poorer surgical outcomes (Baldini et al., 2012; Chou et al., 2015).

Several meta-analyses now available examine the efficacy of opioids for specific pain conditions, such as neuropathic (Gaskell et al., 2016; McNicol et al., 2013) and back (Abdel Shaheed et al., 2016; Chaparro et al., 2014) pain. Additional analyses have included reports on studies involving participants with mixed types of chronic pain (Chou et al., 2014; Pedersen et al., 2014). In general, these meta-analyses suggest that any positive effects of such opioid use have been demonstrated only for relatively short periods of time and that the size of those effects was small. Data are lacking on long-term (>1 year) outcomes such as pain, function, quality of life, and OUD (Chou et al., 2015). Dropout from studies of the use of opioids for chronic pain due to side effects is common, as is discontinuation of the therapy in clinical settings, making it difficult to estimate the benefits of these drugs. Nonetheless, although opioids are commonly prescribed for chronic pain, no widely accepted guidelines suggest their use as first-line analgesic therapy for a chronic pain condition.

Arthritis According to data from the National Health Interview Survey (NHIS), the prevalence of doctor-diagnosed arthritis among adults in the United States during 2013–2015 was 22.7 percent (54.4 million people), with even higher prevalence among individuals with chronic conditions such as heart disease, diabetes, and obesity (Barbour et al., 2017). It is estimated that by 2040, 78 million adults in the United States (26 percent of those aged 18 and older) will have been diagnosed with arthritis (Hootman et al., 2016). Adults with arthritis made up more than half (53 percent) of adults taking prescribed opioids in 2013 (Hootman et al., 2016). Given the widespread use of opioids for noncancer pain and the fact that individuals with musculoskeletal disorders, including arthritis, represent the largest population using prescription opioids, understanding the factors driving opioid use among these individuals could shed light on the broader landscape of prescribing practices.

In a retrospective cohort study evaluating prescription data on patients with rheumatoid arthritis (RA) (n = 501), which after osteoarthritis is one of the more common forms of arthritis, and comparable non-RA subjects (n = 532) during 2005–2014, total and chronic opioid use[2] in 2014 was found to be substantially higher in RA than in non-RA participants (40 versus 24 percent and 12 versus 4 percent, respectively). Opioid use had increased by 19 percent per year in both the RA and non-RA cohorts over the study period (95 percent confidence interval [CI] 1.15, 1.25), with an odds ratio of 3.35 to start first chronic use of opioids within the 10-year study period (Zamora-Legoff et al., 2016). Curiously, factors measuring disease severity for RA were not associated with an increased risk of chronic opioid use, posing the unanswered question of what, if any, pathophysiologic and/or functional factor(s) influence the decision to escalate to more potent and/or long-term opioid therapy (Zamora-Legoff et al., 2016).

Fibromyalgia Ten to 20 percent of patients with RA have fibromyalgia, which often involves widespread musculoskeletal pain. A review of available treatments for the chronic pain of fibromyalgia revealed no evidence from clinical trials that opioids are effective for the treatment of this pain (Goldenberg, 2016). In fact, observational studies found that patients with fibromyalgia receiving opioids had poorer outcomes than those receiving nonopioid therapies, and current guidelines recommend against the use of opioids for treating this pain. Yet despite the lack of efficacy and evidence to the contrary, real-world studies revealed that among patients with fibromyalgia who had been newly prescribed amitriptyline, duloxetine, pregabalin, or gabapentin, opioid use was greater than 50 percent during their baseline period (Kim et al., 2013).

Back pain Back pain is one of the main reasons people visit a primary care or family practice physician, and also predominates in other clinical contexts, such as in the care of veterans. In a study of veterans treated in a regional health care network for chronic noncancer pain, for example, factors associated with use of high-dose opioids (≥180 milligrams morphine-equivalent dose), after controlling for demographic factors and facility, included low back pain, neuropathy, and nicotine dependence. Within the high-dose group, approximately equal percentages of patients had received oxycodone IR (48 percent) and/or morphine ER (52 percent) (Morasco et al., 2010). Although the long-term efficacy of opioids in the management of back pain is unknown, the clinical benefits of shorter-term opioid

[2]Chronic opioid use was defined as opioid prescriptions for 60 days or more within a 6-month period and use of one or more of the following opioids: transdermal fentanyl, methadone, and oxycodone ER (Zamora-Legoff et al., 2016).

therapy to treat this condition appear to be relatively moderate compared with the many well-documented adverse effects (Deyo et al., 2015). In their review, Deyo and colleagues (2015) note that for seven short-term trials (≤12-week follow-up) examining the use of strong opioids for chronic low back pain, there was moderate evidence of pain reduction and functional improvement compared with placebo. Nevertheless, opioids continue to be used widely in an attempt to manage back pain for longer periods of time. For example, in a large study of a managed care plan (Kaiser Permanente Northwest health care system in Portland, Oregon) examining the pattern of opioid use 6 months before and after an index visit for back pain, 61 percent of the 26,014 eligible patients had received a course of opioid therapy, and 19 percent had become long-term (≥120 days or >90 days with 10 or more fills) opioid users. Among the long-term users, 59 percent had received short-acting (SA) opioids, and 39 percent had received both SA and LA opioids. Psychological and behavioral difficulties appeared to drive long-term opioid use in persons with back pain (Deyo et al., 2011).

Musculoskeletal Conditions and Fractures, Sprains, and Contusions

Tracking of opioid prescriptions currently is not linked to such details as medical indication, whether the patient's pain is acute or chronic, or other pertinent details of medical history. Rather, the primary tracking factors are the 9th and 10th revisions of the *International Classification of Diseases* (ICD) (Pan, 2016). On this basis, diseases of the musculoskeletal system and connective tissues (ICD-9 codes 710–739) are among the conditions most commonly associated with the use of opioids (FDA, 2016; Pan, 2016). According to office-based physician reports, in 2015 nearly 54 percent of diagnoses of chronic conditions associated with use of hydrocodone/acetaminophen were for diseases of the musculoskeletal system and connective tissues (which include arthritis and back pain). Among acute conditions, injuries (fractures, sprains, and contusions [ICD-9 codes 800–999]) were the conditions most commonly associated with the use of hydrocodone/acetaminophen (42 percent), followed by diseases of the musculoskeletal system and connective tissues (17 percent) (FDA, 2016). Cumulative ICD data for the period January 2007–November 2011 indicate that the shares of musculoskeletal system and connective tissue diagnoses associated with the use of different types of opioids were as follows: morphine ER (68 percent), morphine IR (56 percent), oxycodone IR (41 percent), hydrocodone combination (25 percent), and oxycodone combination (20 percent) (Pan, 2016). The shares of individuals with fractures, sprains, and contusions using various types of opioids were considerably different, with oxycodone combination (26 percent) and hydrocodone combination (19 percent) dominating, followed by oxycodone IR (8 percent), morphine ER (3 percent),

and morphine IR (4 percent) (Pan, 2016). Based on these data, it appears that oxycodone IR and morphine IR and ER, as opposed to combination products, have been used more frequently to treat chronic pain associated with musculoskeletal and connective tissue disorders.

Cancer-Related Pain and End-of-Life Care

The aggressive use of opioids has long been accepted and strongly promoted for the treatment of pain in patients with cancer or those in end-of-life and palliative care. Foundational work in this area suggested that in most patients, control of pain due to active cancers could be achieved using oral analgesics, including opioids. Such data led to the development of the World Health Organization "Analgesic Ladder," which outlines the use of progressively stronger analgesics as necessary to control pain in these patients (WHO, 1986). The pain, oncology, and palliative care literatures are replete with studies of various IR and LA opioids used to control cancer pain, generally with positive results. It was within the contexts of cancer and palliative care that the concept of "breakthrough" pain treatment gained popularity. The emergence of this concept has in turn supported the development of fast-acting high-potency opioid preparations such as transmucosal and intranasal products. Overall, the aggressive use of opioids for control of pain in cancer and palliative care patients is common and strongly supported by both the available literature and the medical community (Hadley et al., 2013; Schmidt-Hansen et al., 2015; Wiffen et al., 2016; Zeppetella and Davies, 2013).

However, the use of opioids in these patients is not without caveats. For example, nausea, constipation, sedation, and other side effects are common after the administration of opioids in patients with cancer pain, just as they are in those suffering from other pain conditions. Accidental overdose also can occur. Moreover, studies examining the results of urine drug screens from patients with cancer and in palliative care have provided significant evidence of opioid misuse and diversion (Barclay et al., 2014; Childers et al., 2015), while many cancer pain and palliative care clinics lack formal policies addressing drug misuse and diversion (Tan et al., 2015b). Thus, improperly stored or monitored medications prescribed to cancer or palliative care patients may make their way into the community.

An additional problem increasingly being recognized relates to chronic pain in cancer survivors. In addition to common noncancer-related causes, chronic pain in cancer survivors can result from the sequelae of the disease itself or such treatments as surgery, radiation, and chemotherapy. Opioid use in cancer survivors is common (Carmona-Bayonas et al., 2016), although data with which to quantify its frequency are scarce. Guidelines have been issued suggesting that providers use approaches similar to those

employed for noncancer paints when making decisions about ongoing opioid prescribing (Kurita and Sjogren, 2015; Paice et al., 2016).

Dentistry

It has been estimated that dentists prescribe 12 percent of all IR opioids (hydrocodone, oxycodone), second only to family physicians (Denisco et al., 2011), although their rates of prescribing may have declined in recent years (Levy et al., 2015). Dentists prescribe opioids mainly for the short term to treat acute postsurgical pain. Third molar extraction, for example, is probably the most common surgical procedure performed in healthy adults. It is estimated that 3.5 million third molar extractions are performed by oral and maxillofacial surgery specialists annually (and this number does not include the extractions performed by general dentists). One study found ibuprofen to be the peripherally acting postsurgical drug of choice among 73.5 percent of oral surgeons; however, 85 percent of them almost always prescribed a centrally acting opioid alone or in combination with another analgesic agent. Hydrocodone is among the opioids most commonly prescribed by oral surgeons; one study found that the combination usually was with acetaminophen, and 20 tablets on average were prescribed (Moore et al., 2006a,b). Based on these data, at least 3.5 million people with an average age of 20 (the average age for third molar extraction) may be exposed to opioids related to dental treatment (Denisco et al., 2011).

Opioids also may be prescribed for dental pain in emergency departments. One study found that 45 percent of emergency department visits for a nontraumatic dental condition ended with an opioid prescription (Okunseri et al., 2014). It is important to note that nontraumatic acute dental pain can be treated with a relatively simple dental procedure in a dental office; however, few emergency departments are equipped, staffed, or designed to provide dental care.

Leftover opioids prescribed by dentists may be a concern if they are shared with friends or family members to help with apparent symptoms of pain, or for other reasons (O'Neil and Hannah, 2010). Therefore, it is recommended that opioids be prescribed only for several days following an oral surgical procedure. Although literature on the duration of pain following oral surgery is scarce, 2–3 days of treatment is often thought to be sufficient (Biron et al., 1996). Moreover, extended severe pain after oral surgery may indicate infection or some other complication, and thus a visit to the dentist is a better option than prolonged treatment with opioids or other pain medications.

Therapy with opioids following third molar extraction or other oral surgery procedures may be indicated as it does provide adequate pain relief (Weiland et al., 2015). However, treatment with peripherally acting anal-

gesic agents, such as ibuprofen and naproxen, has been shown to provide good pain relief as well (Moore et al., 2015) and can be as effective as opioids for many patients who undergo impacted tooth extraction (Hersh et al., 1993). Nonopioid analgesic agents such as NSAIDs may be advisable as the first line of therapy for the routine management of acute postoperative dental-related pain for patients who have no contraindications for their use (Becker, 2010; Donaldson and Goodchild, 2010).

Mandatory checking of data from prescription drug monitoring programs (which are discussed in more detail in Chapter 5) was shown to be effective in changing the prescribing pattern for pain medications among dentists in a dental urgent care clinic in New York State (Rasubala et al., 2015). Before prescribing opioids, it may be beneficial for dentists (as well as other providers; see below) to screen patients for substance misuse as well as substance misuse risk factors. General dentists often have long-term relationships with their patients and therefore are well positioned to perform this screening. Oral surgeons or specialists, who often see patients only for a specific procedure, may consult the referring dentist or physician for this purpose (Denisco et al., 2011).

Decision Making About Opioid Prescribing

The list of factors contributing to the decision of whether to prescribe opioids includes not only the provider's desire to reduce a patient's suffering but also the expectations of the patient regarding pain control. Concern has been raised that increased attention to the issues of acute and chronic pain has led to the expectation that patients should experience little or no pain once a provider has been informed of the problem. The prescription of medication represents a rapid method of addressing a pain complaint, certainly accomplished more easily than providing a course of physical therapy, psychological counseling, spinal injection, or many other available approaches to the treatment of pain. For that reason, analgesics including powerful opioid pain relievers are an attractive option. On the other hand, emphasis is increasing on setting reasonable expectations and establishing mutually agreed-upon goals for the control of chronic pain, with an emphasis on communication and safety (Dowell et al., 2016).

Regrettably, providers may feel pressured to provide opioids for fear of poor evaluations of their performance. Measures instituted over the past decade or so that may contribute to this pressure include the designation of pain as the "fifth vital sign" (Lanser and Gessell, 2001) and the increasing attention to patient feedback on surveys regarding pain control as part of their care. Importantly, in 2016 the Centers for Medicare & Medicaid Services issued a proposed rule to remove posthospitalization patient survey questions about pain management from scores that are tied to Medicare

payments in an effort to reduce unnecessary opioid prescribing.[3] However, rankings of patient satisfaction remain important to hospitals and providers as the rankings can affect their business, and providers' pay may be impacted by patient evaluations as well. The precise impact of pain control on patient satisfaction is somewhat unclear, although some have suggested that communication and compassion may be more important than pain control itself in influencing a patient's survey response (Lee, 2016). Further discussion on the related topics of clinical practice guidelines and industry promotion is included in Chapters 5 and 6, respectively.

Discussions between providers and patients about the use of nonopioid alternatives may be difficult. In some instances, providers may find it easier to write an opioid prescription than to have a discussion with the patient about the balance of risks and benefits of using an opioid versus alternative therapies. This may be the case in particular with patients who have come to believe that opioids are the best treatment for their chronic pain and who feel that alternative forms of treatment will not work as well. As discussed in Chapter 5, educating providers and patients about alternative forms of treatment may be one means of reducing reliance on the use of prescription opioids to manage chronic pain.

Assessment and Mitigation of Risk When Prescribing Opioids

As discussed in Chapter 5, growing recognition of important areas of overlap between opioid therapy for pain and opioid misuse has led to multiple forms of response, including statements, policies, and guidelines issued by federal agencies, state governments, advocacy groups, professional societies, academic panels, and others. Yet while the need for a more cautious approach to opioid prescribing has generally been acknowledged, there has been no overarching effort to coordinate responses among concerned groups. In addition, a tension exists between efforts to curtail prescribing and the interests of at least some groups of patients in maintaining access to opioids.

Many of the recommendations commonly discussed in considering opioids for the management of chronic noncancer pain are encapsulated in the so-called universal precautions of pain medicine (Gourlay et al., 2005). These 10 steps (see Box 2-1) were not proposed for use exclusively when managing opioids, although opioid management is an important area for their application.

Beyond these overarching principles of responsible opioid management are efforts to construct risk assessment tools. Generally, the goal has been to assemble and validate reasonably brief questionnaires useful in clinical

[3] 81 C.F.R. 45603.

BOX 2-1
Universal Precautions in the Use of Pain Medicine for Treatment of Chronic Pain

1. Make a Diagnosis with Appropriate Differential
2. Psychological Assessment Including Risk of Addictive Disorders
3. Informed Consent
4. Treatment Agreement
5. Pre- and Post-Intervention Assessment of Pain Level and Function
6. Appropriate Trial of Opioid Therapy +/– Adjunctive Medication
7. Reassessment of Pain Score and Level of Function
8. Regularly Assess the "Four As" of Pain Medicine: Analgesia, Activity, Adverse Effects, and Aberrant Behavior
9. Periodically Review Pain Diagnosis and Comorbid Conditions, Including Addictive Disorders
10. Documentation

SOURCE: Excerpted from Gourlay et al., 2005.

situations that would provide prescribers with information concerning the likelihood of development of opioid misuse should opioids be provided for the management of pain. Several such tools have been developed. Those used commonly include the Screener and Opioid Assessment for Patients with Pain (SOAPP and SOAPP-Revised) (Butler et al., 2004, 2009); the Diagnosis, Intractability, Risk, and Efficacy (DIRE) inventory (Webster and Webster, 2005); and the Opioid Risk Tool (ORT) (Belgrade et al., 2006). Each has been studied, and some information directly comparing their properties is available (Moore et al., 2009). Reviews of the utility of these screening tools suggest some predictive value, yet significant caveats exist (Chou et al., 2009b). For example, the predictive power of these tools is limited, they differ in their definitions of misuse or aberrant behavior, and the body of data validating them is fairly small. See further discussion on the evidence of effectiveness of these tools in Chapter 3.

Opioid Tapering

In addition to initiation of opioids, providers face questions about how to manage patients who are already taking the drugs, some of whom have been maintained chronically on them for months to years. Over the past decades, millions of Americans have been exposed to and many are now maintained chronically on opioid pain medications. The short- and longer-

term risks of opioid use are more serious than previously estimated, and as discussed above, the likely benefits of chronic opioid use for pain are lower for many patients than previously believed. As a result, a large group of "legacy" chronic pain patients are receiving opioids at doses or under circumstances that are inappropriate in light of current knowledge. Information useful in understanding how best to manage this group of patients is lacking in many clinical settings.

The U.S. Centers for Disease Control and Prevention's (CDC's) Guideline for Prescribing Opioids for Chronic Pain (see Chapter 5) recommends that patients who have been on high dosages of opioids "be offered the opportunity to re-evaluate their continued use of opioids at high dosages in light of recent evidence regarding the association of opioid dosage and overdose risk" and that providers review the risks and benefits of continued opioid therapy with these patients (Dowell et al., 2016, p. 1638). The guideline further recommends consideration of opioid tapering when there is no evidence of improvement in pain or function, particularly when the opioid dose has reached more than 50 morphine milligram equivalents (MME) with or without added benzodiazepines or signs of harm (Dowell et al., 2016). Implicit here is the importance of assessment and reassessment of patients on chronic opioids. If the patient's pain and function have not improved significantly with the initiation or increase in the dose of opioids, providers might reconsider continuing use given the risk of adverse effects. Evidence suggests that tapering of opioids prior to elective surgery may decrease the risk of developing chronic pain after surgery, thereby reducing postsurgery analgesic requirements (Chapman et al., 2011). A slow taper is likely better tolerated, particularly in patients taking opioids chronically. The CDC guideline calls for as slow as a 10 percent reduction per month in combination with support from the patient's clinician and psychological and other specialists as needed (Dowell et al., 2016). A study of a small sample of patients in a primary care setting found that patients considered the risk of increased pain and of withdrawal symptoms from the tapering of opioids to be greater than the risk of overdose from continuing to use the drug. Discussions of tapering with patients may be more successful if these fears are addressed as part of the conversation (Frank et al., 2016).

Practice Tools to Reduce Potentially Harmful Opioid Use in the Course of Pain Treatment

Patient–Provider Agreements

The use of patient–provider agreements (PPAs), also referred to as opioid treatment agreements (OTAs) or pain contracts, has been reported as a possible tool in the clinical management of chronic pain (Fishman et al.,

2002a,b). The precise components of PPAs may vary among practices, but in general they serve to document the understanding between patient and clinician about the treatment plan and its goals. PPAs provide an opportunity to discuss with patients the risks and benefits of opioid therapy. The agreement may describe the roles and responsibilities of the patient and the provider and the grounds for discontinuation or continuation of the opioid treatment based on the risk-benefit ratio (Gourlay et al., 2005; Quill, 1983). Addiction, misuse, significant nonadherence to the agreement, or risk to the public may be the major reasons for discontinuation of treatment.

Despite the potential of such agreements, it is clear that the ability of providers to recognize nonadherence to treatment plans is limited (Osterberg and Blaschke, 2005). The ability to apply the contract may also be limited because patients do not have the choice of whether to agree to it. Moreover, while data on effectiveness are limited, one study reports that the use of PPAs may be relatively low (aside from high-risk patients) and that patients may not always realize when they have signed one, which could limit their utility (Penko et al., 2012). One study showed that more than 60 percent of patients adhered to an OTA with a median follow-up of 22.5 months; 7 percent of OTAs were canceled because of substance misuse and noncompliance (Hariharan et al., 2007). Ongoing ethical debate surrounding PPAs is important to acknowledge. Despite their potential, universal utilization of PPAs is resisted on a variety of grounds, including limited health literacy and concerns about increasing disparities and further stigmatizing pain patients (Payne et al., 2010). Indeed, use of PPAs does not guarantee better care: "[unscrupulous physicians] practicing in 'pill mills' regularly require their patients to sign pain contracts" (Payne et al., 2010, p. 11). Overall, while there is no consensus regarding the use of PPAs, they are being used to varying degrees in chronic pain treatment and may facilitate monitoring of adherence to treatment plans. More research could clarify their effective use and outcomes to help improve adherence and monitoring, as well as reduce the potential for unintended negative consequences.

Consultation with and Referral to Pain Specialists

Primary care providers, including those in emergency medicine settings, often are the first point of medical contact for patients with pain. Given the limited number of pain specialists, primary care providers play an essential role in pain management and in overcoming the challenge of undertreatment of pain (IOM, 2011). Yet there are occasions when these providers can benefit from consultation with or referral of patients to pain specialists—providers who have had specialty training in the diagnosis and treatment of painful conditions (often from the fields of anesthesiology, neurology, physical medicine and rehabilitation, psychology, or psychiatry).

Partnership with pain specialists may help primary care providers maximize pain relief and function for patients while minimizing the risk of use of opioids and other treatments. Working in tandem with a pain specialist may help all involved define shared goals in the patient's pain treatment plan. Establishing expectations at the outset is helpful for both patient and physician;[4] setting realistic expectations at the beginning of treatment can affect outcomes and patient satisfaction. Some pain specialists have had specialized training in psychiatry and/or addiction medicine, which can enable them to evaluate whether opioids are appropriate for the individual patient and to treat patients with substance use disorders. There are models for coordination with primary care to treat pain in high-risk patients in the context of a patient-centered medical home (Cheatle et al., 2012).

Pain specialists also may be consulted prior to surgery for recommendations regarding chronic use of opioids as patients' tolerance for the drugs may adversely affect their postoperative experience. Pain specialists may offer recommendations on maximizing nonopioid therapy prior to surgery and on employing regional anesthetic techniques that may assist in minimizing the use of opioids intra- and postoperatively (Huxtable et al., 2011; McGreevey et al., 2011). Pain specialists that work in the context of multidisciplinary pain centers are able to individualize patient care and treat patients holistically. (The section on clinical research in Chapter 3 includes discussion of improving pain management in the primary care setting despite a relative lack of access to pain specialists, while the discussion of Project ECHO in Chapter 4 describes a model for providing high-quality care through expert teleconsultation with community providers.)

Summary

Opioids are widely prescribed in a variety of settings for treatment of both acute and chronic pain, frequently including back pain, pain due to arthritis and other musculoskeletal conditions, and dental pain. However, data are lacking on the longer-term benefits of opioids in the management of chronic noncancer pain. Moreover, studies do show an increased risk for a number of adverse outcomes from long-term use of opioids, including OUD, overdose, and other adverse effects. Moreover, no widely accepted guidelines recommend the use of opioids as a first-line therapy for management of chronic noncancer pain. Despite the lack of evidence

[4]A retrospective review of 248 patients for whom treatment expectations and anticipated level of pain relief were documented in the initial intake record found that the expectation in back pain patients was at least 58 percent pain relief. Fibromyalgia patients anticipated 54 percent pain relief from their office visit, along with reduction of other distressing symptoms, while those with migraine expected complete relief without associated side effects (O'Brien et al., 2010).

supporting the practice, however, providers continue to prescribe opioids for extended periods.

NONOPIOID PHARMACOLOGIC TREATMENTS

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs are commonly used to treat acute pain following trauma or interventional procedures, as well as pain due to some chronic inflammatory musculoskeletal conditions, such as arthritis. These drugs inhibit the cyclooxygenase (COX) enzymes that catalyze the transformation of arachidonic acid to prostaglandins (PGs)—evanescent, locally acting lipid mediators with diverse biological effects. PGs include PGE_2 and PGI_2, which have been shown to mediate pain and inflammation. COXs are of two types: COX-1, which tends to be ubiquitously expressed and accounts for the greater part of hemostatic and gut barrier integrity; and COX-2, which is readily upregulated by cytokines and mitogens and largely accounts for PG formation in pain, inflammation, and cancer. Older NSAIDs, such as ibuprofen and naproxen, inhibit both COX-1 and COX-2 at therapeutic doses. The development of NSAIDs specifically for inhibition of COX-2, such as rofecoxib and celecoxib, was prompted by serious adverse gastrointestinal (GI) effects of those older agents, attributed to inhibition of platelet COX-1-dependent thromboxane A_2 formation (predisposing to bleeding) and disruption of barrier function due to inhibition of COX-1-dependent formation of PGE_2 and PGI_2 by gastroduodenal epithelium. However, a reduction in the serious adverse GI effects of these earlier drugs was accompanied by an increase in cardiovascular adverse effects, such as myocardial infarction, stroke, and heart failure, resulting from suppression of the cardioprotective properties of COX-2-derived PGI_2 and PGE_2 in the cardiovascular system (Grosser et al., 2010).

Aspirin, also an NSAID, relieves pain at high (>325 mg) doses that inhibit COX-1 and COX-2. As with other nonspecific NSAIDs, however, such efficacy is accompanied by adverse GI effects. Aspirin is by far more commonly consumed at low (<100 mg/day) doses for cardioprotection, and although the incidence of serious adverse GI effects is roughly doubled with these lower doses, such events are much less common than at higher analgesic doses. Aspirin differs from other NSAIDs in that it covalently modifies COX (the other drugs are competitive active site inhibitors), requiring de novo synthesis of the enzyme for recovery of PG formation from aspirin exposure. In the case of the anucleate platelet, which contains only COX-1, this requires the production of new platelets. Chronic administration of low-dose aspirin suppresses platelet COX-1-derived production of thromboxane A_2, a vasoconstrictor and platelet agonist, and this mechanism is

sufficient to explain the efficacy of low-dose aspirin in the secondary prevention of heart attack and stroke (Fitzgerald and FitzGerald, 2013). The place of low-dose aspirin in primary prevention is currently unclear; the number of heart attacks prevented and serious adverse GI effects caused are roughly in balance.

APAP (Paracetamol), or acetaminophen, is another NSAID, inhibiting both COX-1 and COX-2 by ~50 percent at the most commonly used daily dose of 1,000 mg (Catella-Lawson et al., 2001). At this dose, it is effective in relief of mild pain but is commonly used as an antipyretic. A Cochrane review found that ibuprofen in combination with acetaminophen provided better analgesia than either drug alone at the same dose, and with a smaller chance of an adverse event (Derry et al., 2013a). However, it is unclear whether this finding reflects a distinct mechanism of action of acetaminophen or merely more efficient COX inhibition by the combination.

Studies in mice suggest that the antipyretic property of APAP derives from suppression of PGE_2-dependent activation of the E prostanoid receptor 3 (EP3) (Ushikubi et al., 1998). This COX/PGE/EP3 pathway is activated by the receptor activator of nuclear factor kappa-B ligand (RANKL) acting on its tumor necrosis factor (TNF) receptor-related RANK receptor in astrocytes (Hanada et al., 2009). While GI complications of APAP are uncommon, indirect higher doses (>4,000 mg/day) may have an adverse GI effect profile similar to that of other nonspecific COX inhibitors. Many effects beyond COX inhibition have been attributed to APAP, but the importance of their contribution to either its efficacy or its adverse effect profile is unclear. The biggest concern with APAP is liver toxicity; overdose may cause fatal acute liver failure (Fontana, 2008). This effect may also be mechanism-based as hepatotoxicity complicates treatment with diclofenac, an older NSAID that turns out to be a quite specific inhibitor of COX-2. The genetic basis for predisposition to hepatotoxicity from lumiracoxib, a diclofenac analog specifically designed to inhibit COX-2, has been established (Singer et al., 2010).

Combination therapy, including APAP and other NSAIDs, was found to be superior to the combination of the opioid hydrocodone and APAP, with fewer side effects, for pain from dental extractions (Moore and Hersh, 2013). And a systematic review comparing oral NSAIDS with opioids for treatment of pain due to knee osteoarthritis over at least 8 weeks' duration found similar pain relief for both analgesics (Smith et al., 2016b).

Antidepressants

Antidepressants—including tricyclic antidepressants (TCAs), combined serotonin-noradrenalin reuptake inhibitors (SNRIs), and selective serotonin reuptake inhibitors (SSRIs)—are one of the oldest pharmacological treat-

ments for chronic pain. Studies have found specific antidepressants (or classes of antidepressants) to be effective for the treatment of various types of pain. For example, amitriptyline improves pain for postherpetic neuralgia (Graff-Radford et al., 2000) and for fibromyalgia (Moore et al., 2012), while duloxetine can improve pain for diabetic peripheral neuropathy (Lunn et al., 2014) and osteoarthritis knee pain (Wang et al., 2015). TCAs and SNRIs are recommended as a first choice (along with gabapentinoids) for postherpetic neuralgia, painful neuropathies, and central pain (Dworkin et al., 2010). SSRIs generally are better tolerated by patients relative to other antidepressants, but the evidence on their efficacy for treating chronic pain is inconclusive (Patetsos and Horjales-Araujo, 2016).

Although depression is common among patients with chronic pain (Fishbain et al., 1997; Iacovides and Siamouli, 2008), the analgesic effect of antidepressants is separate from their effect on depression. Pain relief occurs at lower doses than doses with an antidepression effect (Hameroff et al., 1984; Langohr et al., 1982; Magni, 1991), and has been noted in both depressed and nondepressed patients (Couch and Hassanein, 1976; Jenkins et al., 2012; Lance and Curran, 1964; Max et al., 1987).

The mechanism of action of antidepressants on pain is not fully understood. Antidepressants act mainly by reducing noradrenalin and serotonin reuptake and enhancing the descending inhibition (Gillman, 2007). While both norepinephrine and serotonin have an effect on mood and pain (Sindrup and Jensen, 1999), catecholamine blockade appears to be more important in pain reduction. Indirect mechanisms of action may include (1) enhancement of the effects of endogenous opioids by increasing either their production or expression of opioid receptors (Hamon et al., 1987; Sacerdote et al., 1987), (2) antagonism of *N*-methyl-D-aspartate (NMDA) receptors (Luccarini et al., 2004), (3) blockade of sodium and/or calcium channels (Gerner et al., 2003; Wang et al., 2015), (4) blockade of histamine or cholinergic receptors (Abdel-Salam et al., 2004; Butler et al., 1985), and (5) increased expression of γ-aminobutyric acid (GABA) type B receptors in the spinal cord (McCarson et al., 2006). It is important to note that attenuation of chronic pain by antidepressants is not immediate; the clinical effect usually is noted only after days or weeks of treatment.

Common side effects of antidepressants include dry mouth, blurred vision, constipation, difficulty in passing urine, weight gain, and drowsiness. The SSRIs are generally better tolerated than other antidepressants, but their side effects can include nausea, tremor, hyperarousal, and drowsiness (Goodman et al., 2001). Adverse effects may be less likely with gradual dose escalation. Combination therapy with gabapentinoids, opioids, and topical agents is sometimes considered in refractory cases (Gilron et al., 2009, 2013).

Anticonvulsants

Anticonvulsant medications, principally gabapentin (and, more recently, pregabalin), have come to serve as first-line therapies in the treatment of chronic neuropathic painful conditions (with the exception of trigeminal neuralgia) (Wiffen et al., 2017), as well as acute perioperative pain (Nir et al., 2016). Gabapentin, an anticonvulsant initially introduced for the treatment of partial complex seizures, is approved in the United States for postherpetic neuralgia (PHN). With the expiration of the exclusivity patent on gabapentin, pregabalin was introduced and obtained FDA approval for the treatment of PHN, as well as diabetic polyneuropathy and fibromyalgia. Independently, gabapentin also has been found effective in the treatment of fibromyalgia, although further research is needed (Cooper et al., 2017). Expert opinion in the form of guideline recommendations has emerged as well, in many cases being updated by societies dedicated to the evidence-based management of neuropathic pain, such as the Neuropathic Pain Special Interest Group (NeuPSIG) (Dworkin et al., 2007, 2010; Sardar et al., 2016). Regrettably, these drugs have an emerging potential for misuse, particularly in individuals with OUD (Evoy et al., 2017; Havens, 2016).

Mechanistically, the goal of these agents is to suppress the sensation of peripheral neuropathic pain, described as arising from both unmyelinated C-type (slowly conducting) nerve fibers, associated with sensations of dull, aching, burning, and poorly localized pain, and thinly myelinated A-delta nerve fibers, which are more rapidly conducting and signal sensations of sharp, stabbing, and often well-localized pain. Central nervous system (CNS)/spinal-glial pathways underlie a combination of signs (hypoesthesia, hyper/hypoalgesia, heat/cold hyperalgesia, allodynia) and symptoms (paraesthesias, sensation of burning and/or shooting pain) that, together with the appropriate clinical context, increase the diagnosis of neuropathic pain (Haanpää et al., 2009).

Unlike opioids, gabapentinoids (gabapentin, pregabalin) act primarily to reduce hyperalgesic states under conditions of inflammation and nerve injury rather than changing pain thresholds under nonpathological conditions (Werner et al., 2001). Therefore, gabapentinoids modulate the pain pathway under pathophysiologic conditions. Under hyperalgesic conditions, gabapentin and pregabalin act supraspinally to enhance the descending inhibitory noradrenergic system onto the dorsal horn of the spinal cord (Hayashida et al., 2007; Tanabe et al., 2008). In addition, it has been proposed that gabapentin and pregabalin act at the level of the spinal cord through binding to alpha$_2$-δ_1 subunits of a voltage-gated calcium channel (VGCC) expressed in presynaptic terminals of primary afferent nociceptors (Li et al., 2006). As discussed earlier in the chapter, the use of gabapentin

or pregabalin in the immediate preoperative setting has the potential to decrease the need for postsurgical opioids (Tan et al., 2015a).

Analgesic response rates for peripheral neuropathic painful conditions tend to average approximately 30 percent and rarely if ever exceed 50 percent. Therefore, despite their "effectiveness" in the treatment of PHN, diabetic polyneuropathy, and fibromyalgia, gabapentin and pregabalin have not been proven effective in the treatment of postamputation/phantom limb pain. Nevertheless, they may still offer a benefit to those patients who have failed other analgesic therapy. More recently, gabapentin and pregabalin have been emerging in a widening range of applications initially considered "off-label," including as single or part of multimodal therapies for perioperative pain management (Chaparro et al., 2013), opioid-sparing strategies and reduction of the risk of opioid-induced hyperalgesia (Stoicea et al., 2015), and neuropathic pain originating from cancer or its treatment (Vadalouca et al., 2012). However, as noted above, misuse of gabapentinoids is of growing concern and the risk for misuse of these drugs may be higher in individuals with a history of opioid misuse (Evoy et al., 2017; Havens, 2016).

Capsaicin Creams and Patches

Persons suffering from chronic neuropathic pain often encounter difficulty with their pharmacotherapy and are unable to tolerate the side effects of such agents as anticonvulsants, antidepressants, and other centrally acting therapies. Moreover, such therapies may be ineffective. Long before the advent of clinical trials, physicians successfully used native plant derivatives to provide pain relief. Among these, medicinal plant derivatives from hot chilies in South America were used as far back as 4000 BC. Capsaicin, the pungent principal ingredient in hot chili peppers, is now recognized as the primary therapeutic agent acting on the capsaicin receptor TRPV1 in many of these medicinal plants (Schumacher, 2010). Acting predominantly on C-type primary afferent nociceptors, capsaicin has long been appreciated as inducing pain following its initial application, but paradoxically, having a topical analgesic effect with repeated application. A series of overlapping capsaicin-induced effects that include desensitization, nociceptor dysfunction, neuropeptide depletion (Cao et al., 1998; Yaksh et al., 1979), and nociceptive terminal destruction (Robbins et al., 1998; Simone et al., 1998) are now understood as underlying the analgesic action of topically applied capsaicin.

Topical creams or patches containing capsaicin can sometimes be effective for certain dermatomally restricted neuropathic conditions. However, several aspects of topical capsaicin treatment appear to limit its overall effectiveness and application in clinical practice: the area of pain has a

restricted pattern of distribution (dermatomal or nondermatomal); repeated capsaicin application (up to four to five times daily) is required to establish and maintain an adequate degree of analgesia; and topical application may cause initial or ongoing pain/irritation. In response to these limitations, the capsaicin content in these preparations tends to be "low-dose" (0.025 or 0.075 percent). When such low-dose capsaicin preparations have been studied or compared with so-called first-line neuropathic pain treatments using a grading system requiring multiple RCTs, they typically have not provided robust neuropathic pain relief and showed poor to moderate efficacy in the treatment of either musculoskeletal or neuropathic symptoms (Attal et al., 2006; Mason et al., 2004).

PHN is one of the most prevalent painful conditions associated with neuropathy that clinicians may encounter. It is driven in the United States by some 800,000 annual cases of primary herpes zoster infection (Schmader, 2002). A Cochrane review examined six studies of topical capsaicin involving 2,073 patients conducted through December 2012, which included RCTs and controlled trials of at least 6 weeks' duration. Four studies of a combined 1,272 participants with PHN showed estimated numbers needed to treat (NNT) to attain "much improved or very much improved pain" of 8.8 and 7.0, respectively (Derry et al., 2013b).

In one study, high-dose (5 to 10 percent) capsaicin, initially under regional anesthesia and later following topical local anesthetic pretreatment, was used in an attempt to circumvent the limitations of repeated low-dose capsaicin application and resulted in a wide range of posttreatment pain relief (Robbins et al., 1998). The strongest evidence exists for the use of high-dose capsaicin for the management of painful PHN. As with other therapeutic options for the treatment of painful neuropathic conditions, however, there appear to be responders and nonresponders to capsaicin among patients experiencing PHN and a range of other neuropathic conditions. Overall, the quantified magnitude of the analgesic effect of capsaicin is typically modest (10 to 30 percent), although one study showed that among participants followed for 12 months, 10 percent experienced complete resolution of painful symptoms from PHN and other peripheral neuropathic conditions (Mou et al., 2013). Beyond PHN, other painful neuropathic conditions sensitive to the analgesic effects of topical capsaicin (with decreasing levels of evidence) include HIV-associated painful neuropathy (Derry et al., 2013b), painful diabetic neuropathy, and postsurgical neuropathic pain.

Local Anesthetics/Sodium Channel Blockers

The use of local anesthetics for the relief of acute and chronic pain has typically relied on the restricted deposition of the anesthetic within sub-

cutaneous tissues, adjacent to target nerves and/or spinal epidural routes. The analgesic action is based on the ability to block voltage-gated sodium channel (VGSC)-mediated sodium influx into neuronal cells in response to local membrane depolarization. Ideally, the goal is to achieve analgesia through the blockade of sodium currents in small-diameter (nociceptive) neurons of C and Aδ fiber type that are carried by members of the tetrodotoxin (TTX)-resistant sodium channel family (predominantly Nav1.8 and Nav1.9) that are differentially expressed in small-diameter/pain-sensing neurons (Devor et al., 1992; Persaud and Strichartz, 2002). Since increased VGSC subtype expression on primary afferent neurons (nociceptors) is now linked to inflammatory and neuropathic pain, the blockade by local anesthetics represents a plausible mechanistic approach to treatment of chronic pain (Waxman et al., 1999). Accordingly, efforts are under way to develop a new generation of local anesthetics/sodium channel blockers that selectively block sodium channel subtypes in sensory neurons, with the goal of obtaining an analgesic effect while sparing normal touch or motor function (Kort et al., 2008).

However, widespread administration of local anesthetics is limited by toxicity to the CNS and the cardiac conduction system. Selective, continuous infusion of low-dose local anesthetics adjacent to the nerve trunks, such as the brachial plexus or peripheral nerves, as well as through the epidural route, offers advantages over other modes of postoperative analgesia (Guay, 2006). In many cases, these techniques have been extended to cancer and noncancer chronic pain treatments.

Alternatively, continuous systemic infusion of the local anesthetic lidocaine has shown promise in the treatment of a wide range of chronic painful conditions that have not responded to more established analgesic approaches in both adults and pediatric patients (Gibbons et al., 2016; Kandil et al., 2017). Although studies are still emerging, intravenous lidocaine infusion may help reduce intensity of pain and improve activity levels in a selected group of chronic pain patients. Lidocaine infusion also has been used safely and successfully in patients suffering from advanced cancer pain, both in the hospital setting without telemetric monitoring and in palliative care units, hospices, or even patients' homes, given suitable nursing supervision (Peixoto and Hawley, 2015). The outcomes of lidocaine infusion in perioperative settings are mixed, with focused clinical applications, such as following complex spine surgery, showing promise (Farag et al., 2013). On the other hand, broader application across the spectrum of perioperative pain care may yield less than expected outcomes as there is only low to moderate evidence that lidocaine infusion compared with placebo has a large impact on pain scores, especially in the early postoperative phase (Kranke et al., 2015). Questions that need to be addressed before lidocaine

can be used as a mainstream treatment include precise dosing regimen, infusion duration, and patient selection criteria (Kandil et al., 2017).

Lidocaine (topical) patches (5 percent), represent yet another route of delivery of local anesthetics for the treatment of acute and chronic pain, having been shown to be efficacious for PHN and diabetic neuropathy (Mick and Correa-Illanes, 2012). The efficacy of broader use of lidocaine patches in the treatment of other neuropathic pain ailments is undetermined (Finnerup et al., 2015), and there is as yet no evidence for the effectiveness of lidocaine patches in the relief of postoperative pain (Bai et al., 2015; Mooney et al., 2014).

Alpha 2 (α_2) Adrenoreceptor Agonists

Although practitioners may be familiar with the antihypertensive and sedative properties of α_2 adrenoreceptor agonists (clonidine, dexmedetomidine), substantial evidence indicates that they function as analgesic agents, having a synergistic effect with opioids and efficacy in opioid-tolerant patients. Anecdotal case reports suggest that α_2 adrenoreceptor agonists may offer an alternative analgesic strategy for patients that have failed classic opioid management for painful conditions (Pirbudak et al., 2014).

Two complementary mechanisms couple α_2 adrenoreceptor agonists to analgesic action: activation of descending spinal inhibition and direct activation of presynaptic α_2 receptors on sensory afferent terminals in the dorsal horn (Buerkle and Yaksh, 1998; Sanders and Maze, 2007). Agonists such as clonidine can directly produce spinal analgesia, and intrathecal administration augments spinal levels of norepinephrine and acetylcholine, both of which may play a role in the consequent spinal analgesia (Hassenbusch et al., 2002; Klimscha et al., 1997). Accordingly, epidural/spinal clonidine has been approved for infusion in the treatment of cancer/neuropathic pain that is refractory to opioid analgesics (Hassenbusch et al., 2002). As there is no apparent cross-tolerance between clonidine and opioid analgesics at a spinal site of action, their ability to synergize with morphine under nerve injury and neuropathic conditions has emerged as a critical translational finding (Ossipov et al., 1997).

Such α_2 adrenoreceptor agonists have also been found to be useful in perioperative analgesia for thoracic paravertebral blocks (PVBs) in patients undergoing modified radical mastectomy and for other perineural infusions (Mohamed et al., 2014). In addition, their systemic use in the perioperative period has been found to reduce opioid requirements and improve analgesia, although with common adverse effects such as bradycardia and arterial hypotension (Blaudszun et al., 2012).

The use of systemic clonidine and dexmedetomidine for the treatment of chronic pain has been described, but well-controlled studies are lack-

ing. More commonly, these agents have found a role in opioid-dependent patients and are FDA-approved for the treatment of opioid withdrawal symptoms in the detoxification of opioid dependence. More recently, these agents have appeared in detoxification protocols in the setting of hyperalgesia (Monterubbianesi et al., 2012). Beyond the continuous intrathecal administration of clonidine for intractable pain conditions, the clinical utility of systemic α_2 adrenoreceptor agonists in chronic pain or hyperalgesia remains unresolved (Blaudszun et al., 2012).

NMDA Antagonists (Ketamine)

The analgesic action of ketamine is a consequence of its noncompetitive blockade of the NMDA receptor expressed both in the brain (supraspinally) and in the dorsal horn of the spinal cord. Ketamine's effects are dose dependent and may be broadly categorized as "anesthetic" (high dose), "analgesic" (medium dose), and "opioid-sparing"/antihyperalgesic (low dose). One key principle underlying the action of the low- to medium-dose effects involves blockade of NMDA-mediated neurotransmission under conditions of tissue injury (inflammation/nerve injury).

Following nociceptor activation, excitatory amino acids (glutamate) are released from the central terminals of primary afferent nociceptors onto spinal neurons expressing NMDA receptors. Under persistent nociceptive pain and activation of C-type nociceptors and in turn, activation of ionotropic NMDA receptors, changes occur in neuronal plasticity at the nociceptive processing center of the spinal cord—the dorsal horn (Li et al., 1999). This increase in excitability of dorsal horn spinal cord neurons, which has been described as "central sensitization" (Li et al., 1999; Woolf and Mannion, 1999), encompasses several features, including the spreading of pain sensitivity beyond the original site of injury (secondary hyperalgesia), as well as mechanical allodynia. Blockade of NMDA receptor function in the dorsal horn has been shown selectively to attenuate the pain, hyperalgesia, and allodynia associated with ongoing tissue injury. Importantly, the action of an NMDA antagonist such as ketamine at the dorsal horn can block sensitization but spare the normal signaling of acute pain detection (Yaksh et al., 1999).

The notion that opioid-induced tolerance and hyperalgesia may share a common mechanism with central sensitization has been proposed. Although the exact mechanism of opioid tolerance is not known, it is believed to include the involvement of NMDA receptors, nitric oxide pathway, and μ opioid receptors. Escalating doses of opioids given in an attempt to manage the pain of progressive malignant and nonmalignant diseases in adults and children can drive further pain and hyperalgesia. Under these difficult clinical conditions, low-dose ketamine has been

shown to offer improvement in both pain control and opioid dose reduction that are often greater than 50 percent (Eilers et al., 2001; Loftus et al., 2010). Use of low-dose ketamine is intended to reverse or prevent central sensitization, opioid tolerance, and hyperalgesia while improving pain control (Aggarwal et al., 2013). More recently, the role of low-dose ketamine was investigated in the treatment of complex chronic painful conditions in a study at an outpatient chronic pain clinic, with some promising outcomes (Kosharskyy et al., 2013). Such positive findings are tempered by the variable and dose-dependent profile of ketamine-related adverse effects (psychomimetic), which can limit its clinical application. The development of GRIN2B-directed or other more selective NMDA receptor agents may avoid some of ketamine's troublesome side effects (Niesters and Dahan, 2012; Preskorn et al., 2008).

Modest reductions in pain and short-term opioid requirements have been observed with the use of perioperative ketamine infusions (Barreveld et al., 2013; Cenzig et al., 2014; Elia and Tramer, 2005; Souzdalnitski et al., 2014; Zakine et al., 2008), but complete avoidance of opioids and other analgesics is generally not achieved. Limited additional evidence (Loftus et al., 2010) suggests that ketamine may reduce the persistence of postoperative pain.

Cannabinoids

Cannabis and its subcompounds, cannabinoids, have been used for medical and recreational purposes for hundreds of years. The use of cannabis as a recreational drug is illegal in most countries. Recently, however, some countries around the world and several U.S. states have legalized its use for chronically ill patients. Various studies have shown a positive effect of cannabinoids on chronic pain (Whiting et al., 2015), but potential cognitive effects and possible dose-dependent long-term risk for mental illness remain a concern, especially for patients with chronic pain that will require long-term therapy.

More than 100 cannabinoids have been identified in nature or chemically synthesized (ElSohly and Gul, 2014). The best-known cannabinoid is tetrahydrocannabinol (THC), known mainly for its psychosedative effects. Two cannabinoid receptors (CBs) have been cloned. CB1 is present in the brain, the spinal cord, and the peripheral nervous system, as well as in a number of neuronal tissues, including the liver, skeletal muscle, and the gastrointestinal tract; most of its analgesic effect is mediated by the CB1 receptor. CB2 is found mainly in immune cells in the peripheral nervous system or microglia in the CNS and to a lesser extent in the peripheral nervous system, primarily after injury and inflammatory response (Atwood and Mackie, 2010; Howlett, 2002). Several endocannabinoids have been iden-

tified, anandamide and 2-arachidonoylglycerol (2-AG) probably being the best studied. They are synthesized mainly by neurons but also by immune cells (Bisogno et al., 1997; De Petrocellis et al., 2000).

The endogenous action of cannabinoids is not limited to the cannabinoid receptors; it may be associated with calcitonin gene-related peptide (CGRP), transient receptor potential vanilloid (TRPV), and NMDA receptors as well (Mitrirattanakul et al., 2006). In animal studies, the combination of opioids with cannabinoids has shown notable synergistic effects (Cichewicz, 2004). Interestingly, some NSAIDs inhibit anandamide degradation (Duggan et al., 2011). For medical use, cannabinoids can be smoked; inhaled; mixed with food or drinks; or administered orally, sublingually, or even topically. They can be taken in herbal form, extracted naturally from the plant, or manufactured synthetically.

Recent systematic reviews and meta-analyses have found evidence to support the use of cannabinoids for the treatment of such chronic pain conditions as neuropathic pain, cancer-related pain, fibromyalgia, and HIV-associated neuropathy (Lynch and Ware, 2015; Whiting et al., 2015). A recent National Academies of Sciences, Engineering, and Medicine report on the health effects of cannabis and cannabinoids cites substantial evidence that cannabis is an effective treatment for chronic pain in adults and effects improvements for some pain patients with chemotherapy-induced nausea and vomiting. The report also notes a lack of evidence regarding the efficacy, dose, routes of administration, and side effects of cannabis products in the United States (NASEM, 2017). Low- to moderate-quality evidence has been found regarding the ability of cannabinoids to effect improvements in appetite reduction and weight loss in HIV/AIDS patients, sleep outcomes in individuals with certain illness-related sleep disorders, or symptoms of Tourette syndrome. While further research is needed, some studies also have shown that cannabinoids are associated with an increased risk of short-term adverse events such as cognitive and psychiatric effects, nervous systems disorders, dry mouth, and drowsiness (Lynch and Ware, 2015; Whiting et al., 2015).

The precise magnitude and consequences of the risk associated with therapeutic cannabinoid use are presently unknown. However, psychoactivity, memory deficiencies, impaired coordination and performance, and long-term risk for mental illness are the major issues in the development of cannabinoid-based analgesics (Karila et al., 2014; Semple et al., 2005). Alternative approaches to overcome the undesired effects of cannabinoids can include the development of endocannabinoid degradation inhibitors (Lomazzo et al., 2015) and cannabinoids that affect only peripheral receptors (Richardson et al., 1998). More research is necessary to determine the efficacy and safety of cannabinoid-related therapy for chronic pain patients

and whether adjunctive therapies with existing analgesics may enhance its therapeutic effect while reducing unwanted side effects.

Naltrexone

Naltrexone is an oral opioid antagonist that is FDA-approved for the treatment of OUD. Some evidence, currently limited to a few case reports, indicates that greatly reduced doses of naltrexone (one-tenth normal) may have analgesic properties for limited chronic pain conditions, such as fibromyalgia and complex regional pain syndrome (CRPS). Although the mechanism of action for analgesia associated with low-dose naltrexone is unclear, it is thought to involve an anti-inflammatory effect through the blocking of toll-like receptor 4 (TLR4) on microglial cells, inhibiting microglial activation. Activated microglia are thought to play a major role in the development of neuropathic pain (Chopra and Cooper, 2013; Tsuda, 2016; Younger et al., 2014). Experimental animal models also demonstrate reversal of neuropathic pain by naltrexone via TLR4 antagonism (Hutchinson et al., 2008). In a small randomized, double-blind, placebo-controlled, crossover design study, 31 women with fibromyalgia were given low-dose naltrexone or placebo. Those taking 4.5 mg of naltrexone daily reported modest pain reduction and improved satisfaction and mood (Younger et al., 2013). Chopra and Cooper (2013) report two cases of long-standing CRPS whose signs and symptoms were significantly improved with 4.5 mg daily low-dose naltrexone. More research, particularly replication of these limited reports, could help ascertain the potential role of low-dose naltrexone in the treatment of chronic pain.

Summary

A number of pharmacologic treatments can be used to manage pain. While each nonopioid alternative has its own indications and risks, some 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, carry lower risk of adverse outcomes. Nonopioids such as cannabinoids and ketamine, which have shown promise for relief of some forms of pain in some pain management settings, also have potential adverse side effects. In cases of opioid tolerance, α_2 androreceptor agonists can provide improved analgesia and help reduce signs and symptoms of opioid withdrawal. Subanesthetic doses of NMDA receptor antagonists can be highly effective in blocking/reversing the pain amplification and hyperalgesic states, although dose-dependent side effects, such as altered perceptions and vivid dreams, limit their widespread application.

INTERVENTIONAL PAIN THERAPIES

Interventional pain management involves the use of invasive techniques, such as joint injections, nerve blocks, spinal cord stimulation, and other procedures, to reduce pain. Such techniques are best performed in the context of a multimodal treatment regimen, including physical therapy to maximize functional restoration. There has been a significant increase in the volume of certain interventional procedures over the past 10 years, much of it focused on low back and neck pain with or without radiation to the hip and other lower extremities (Chou et al., 2009a; Friedly et al., 2007). Low back pain is the most common cause of chronic pain in adults in the United States, followed by severe headache or migraine and then neck pain (Freburger et al., 2009; HHS, 2016; Rubin, 2007).

Types of Interventional Pain Therapies

Epidural steroid injections are the most commonly performed interventional pain therapies (Manchikanti et al., 2012), increasing in number each year. This increase, however, has not been matched by similar reductions in disability or improvements in health status among those with low back and leg pain, and may have contributed to the rise in health care costs (Chou et al., 2009a). The injections are commonly given to relieve radicular pain or sciatica associated with disc protrusions. An analysis of all types (cervical, thoracic, and lumbar) and routes (caudal, interlaminar, and transforaminal) of epidural injections using Medicare data from 2000 to 2011 showed an overall procedural increase of 130 percent/100,000 Medicare beneficiaries (representing an increase of 7.5 percent per year), with only an 18 percent increase in new Medicare beneficiaries for the same time period (an increase of 1.5 percent per year). The highest increases were seen for lumbosacral transforaminal injections, at 665 percent/100,000 Medicare beneficiaries, an increase of 20.3 percent per year over the study period (Manchikanti et al., 2013). Epidural steroid injections came under increased scrutiny after reports of serious neurologic events related to contaminated compounded glucocorticoids, in addition to other catastrophic injuries related to the injection itself. Injuries related to the performance of cervical epidurals have garnered significant attention. Guidelines for preventing associated neurologic complications were published in 2015 (Rathmell et al., 2015).

Other interventional pain therapies for axial low back pain include such techniques as trigger-point injections for myofascial pain of the low back, injections involving either the lumbar facet or sacroiliac joints, and denervation of the nerves that supply those joints. Lumbar facet (or zygapophyseal) joints are richly innervated and a source of axial low back pain. The medial branch of the dorsal rami of the spinal nerves innervates

both the facet joints and the overlying multifidus muscle, the interspinous ligament, and surrounding muscle, as well as the periosteum (Cohen and Raja, 2007). Evidence to support the use of intra-articular facet joint injections for long-term pain relief is limited (Chou et al., 2009a). The medial branches are first anesthetized using local anesthetic as a diagnostic tool to confirm the location of the pain. If pain is relieved, the medial branches may be lesioned using radiofrequency (RF) denervation to provide pain relief for an average of 10.5 months (after which the nerves regenerate). The RF may then be repeated for prolonged relief (Schofferman and Kine, 2004). Another type of lesioning, cooled RF, has been used in treating sacroiliac joint pain.

Spinal cord stimulation (SCS) has expanded in scope in recent years, from being utilized mainly for neuropathic pain related to painful postlaminectomy pain syndrome or failed back surgery syndrome to being applied for other neuropathic, sympathetic, vascular, and even visceral pain syndromes (Deer et al., 2014). The therapy involves placing an electrical lead in the epidural space that is connected to a programmable generator to relieve pain. A trial stimulator is first placed percutaneously under image guidance and left in place for up to 1 week, followed by implantation if the trial provides significant pain relief. Traditional SCS has been successful in treating extremity pain, but other areas and types of pain have been difficult to treat. Newer models of SCS utilize higher-frequency stimulation of 10,000 Hz (compared with 40 to 60 Hz) to improve relief of intractable axial low back pain. A comparison study found that the higher-frequency SCS provided superior pain relief (Kapural et al., 2016), and also was not associated with the stimulation-induced paresthesias that can lead to trial failures with traditional SCS (Kapural et al., 2016). Other new forms of SCS include burst stimulation, which uses bursts of five spikes at 40 Hz (De Ridder et al., 2010, 2013), and targeting of SCS at the dorsal root ganglion rather than the central spine (Deer et al., 2014). SCS has the advantage of being reversible and adjustable, and of being capable of providing years of pain relief (Deer et al., 2014). There is evidence for its cost-effectiveness in the relief of pain due to failed back surgery syndrome, CRPS, painful peripheral artery disease, and refractory angina (Kumar and Rizvi, 2013).

Interventional therapies also are offered for pain relief from migraine and other forms of severe headache. Botulinum toxin, a protease exotoxin derived from *Clostridium botulinum*, may be used for chronic migraine when other therapies have failed (Persaud et al., 2013). Other forms of headache, particularly occipital headache, cervicogenic headache, and headache originating from the upper cervical spine, may be amenable to targeted spinal intervention, such as occipital nerve blocks and cervical medial branch RF denervation.

Careful patient selection is critical to the success of interventional therapies. It is recommended that before such interventions are considered, a targeted history and assessment be performed to rule out the presence of potentially harmful conditions (e.g., malignancy, vascular abnormalities, spinal cord compression, fracture, or infection) and to assess for potential side effects (e.g., adrenal suppression from cumulative steroid use) (Leary and Swislocki, 2013). Complications of interventional pain management are multifactorial and are related to issues including performance of the procedure, patient anatomy, and comorbidities. The use of S.A.F.E. (Safety, Appropriateness, Fiscal neutrality, and Effectiveness) principles has been proposed as a foundation for interventional pain treatment algorithms (Krames et al., 2009). This approach has been used in advocating for early intervention for some pain syndromes (e.g., complex regional pain syndrome) for which the timing of interventional therapies may affect outcomes, and their early application may be cost-effective in the long run despite initial costs (Poree et al., 2013).

Summary

Further research is needed to better understand the effectiveness of a variety of interventional techniques for painful conditions, as well as optimal patient selection to improve health outcomes. However, these treatments may provide effective pain relief for many patients with some forms of pain (e.g., low back and neck pain) in the context of a multidisciplinary approach.

NONPHARMACOLOGIC TREATMENTS

Acupuncture

The use of acupuncture for the treatment of pain has become widespread in recent decades. Acupuncture is a key component of traditional Chinese medicine that involves insertion of needles through the skin to acupuncture points. Pressure, heat, electrical current, laser light, and other means also may be used to stimulate these points. Investigations have demonstrated that the nervous system, neurotransmitters, and other endogenous substances respond to the needling stimulation to induce analgesia (Foster and Sweeney, 1987). It has been shown that acupuncture analgesia is mediated by opioids produced in the periaqueductal gray and can be reversed by naloxone, an opioid antagonist (Cheng and Pomeranz, 1980). Recent studies also suggest activation of cannabinoid receptors as a possible mechanism of action (Gondim et al., 2012).

Systematic reviews evaluating the effect of acupuncture in treating

pain have revealed mixed results. Some reviews have found minimal or no effect (Lee et al., 2008; Madsen et al., 2009), while others have found acupuncture to be superior to sham acupuncture and placebo (Berman et al., 1999; White et al., 2007), and still others have concluded that data are insufficient to support a recommendation (Furlan et al., 2005; Paley et al., 2015; Smith et al., 2016a; van Tulder et al., 1999). Recent reviews and meta-analyses examining the effect of acupuncture on musculoskeletal pain (neck and back pain, osteoarthritis, chronic headache and shoulder pain, fibromyalgia) have found that overall, acupuncture is superior to sham and no acupuncture, but with relatively modest differences between true and sham acupuncture (Vickers et al., 2012; Yuan et al., 2016). Although it has been suggested that acupuncture is an effective treatment for pain, additional factors, such as potent placebo and context effects, may play a role in its observed effect as well (Linde et al., 2010a,b; Vickers et al., 2012). It also has been suggested that acupuncture may have value in the treatment of chronic and tension headaches (Linde et al., 2009b; Vickers et al., 2012), as well as in prophylactic treatment for migraine (Linde et al., 2009a). Additional RCTs are needed to determine the effect of acupuncture on neuropathic and postsurgical pain.

Manual Therapies

Manual therapies, including massage and chiropractic and osteopathic manipulation (such as spinal manipulative therapy), are commonly recommended for the treatment of musculoskeletal pain. However, high-quality evidence about these therapies is sparse, and there is little evidence that these therapies are as effective or more so than standard treatments. Cochrane reviews have been conducted on the evidence for these therapies in low back pain. For massage, the quality of the evidence was found to be "low" or "very low," and the authors "have very little confidence that massage is an effective treatment for low-back pain" (Furlan et al., 2015). Evidence on combined chiropractic interventions shows a slight improvement in pain in the short and medium terms, but there is no evidence showing that chiropractic interventions have a clinically meaningful advantage over other treatments (Walker et al., 2011). Spinal manipulative therapy has not been shown to be different from other common interventions (Rubinstein et al., 2011).

A 2014 systematic review of massage therapy for fibromyalgia pain found that massage therapy of at least 5 weeks' duration resulted in significant improvement in pain, anxiety, and depression. However, the authors note that larger-scale and longer-term RCTs are needed to confirm these findings (Li et al., 2014).

Physical Therapy and Exercise

Physical therapy and exercise often are included in the treatment plan offered to patients suffering from musculoskeletal pain conditions such as fibromyalgia, arthritis, and back and neck pain. In addition to its direct effect on pain, exercise may improve overall physical and mental health (Iacovides and Siamouli, 2008). The exact mechanisms by which physical therapy and exercise affect pain are unknown. It is believed, however, that activation of the CNS pain modulation pathways (Lannersten and Kosek, 2010) and the release of beta-endorphins play a major role in the palliative effect (Bement and Sluka, 2005; Stagg et al., 2011). Other suggested mechanisms include activation of such neurotransmitters as norepinephrine and serotonin (Dietrich and McDaniel, 2004), interactions with the cardiovascular system (Lovick, 1993), and involvement of the adenosinergic system (Martins et al., 2013). Despite the lack of strict guidelines or protocols for physical activity that may help patients with chronic pain, it appears that various types of physical activity can alleviate pain, including aerobic exercise, strength and flexibility training, walking, and manual therapy. Exercises such as yoga, tai chi, and qi gong have received particular attention for the treatment of pain because of the potential effect of the "mind–body" component of these practices. Systematic reviews have shown that these practices may be effective (Bai et al., 2015; Cramer et al., 2013; Kong et al., 2016), but further high-quality research is needed. Exercise has been shown to be effective for treatment of many types and locations of pain, including fibromyalgia (Busch et al., 2013; Carson et al., 2010; Hauser et al., 2010), back pain (Chang et al., 2016; Hayden et al., 2005; O'Connor et al., 2015; van Middelkoop et al., 2010), osteoarthritis (Fransen et al., 2014; Jansen et al., 2011), whiplash-associated pain (Stewart et al., 2007), and potentially even neuropathic pain (Dobson et al., 2014).

However, there are a number of barriers to the successful use of exercise therapy for pain management. These barriers include patient factors, such as lack of knowledge about exercise, fears of worsening existing pain, depression, excessive deconditioning, and a lack of self-efficacy. Patients also may lack access to a safe place to exercise, time to exercise, and support from family or the workplace. Finally, there are health care delivery barriers, including the system's overly rigid focus on the biomedical model for pain, a lack of attention to or education about the value of exercise, a lack of supervision to ensure patient safety and comfort (Kroll, 2015), and a lack of insurance coverage of the costs of exercise and physical therapy.

Although it appears that recommending physical activity and exercise is warranted for patients suffering from chronic pain, further research is needed to evaluate the optimal treatment and intensity to recommend, and to explore the benefit of combining physical activity with other non-

pharmacologic therapies and pharmacologic treatment for pain reduction. In particular, there is some evidence that multidisciplinary rehabilitation, which includes physical treatments such as exercise as well as psychosocial interventions, may improve pain and function (Kamper et al., 2015; Lee et al., 2014), but further research is needed.

Cognitive-Behavioral Therapy (CBT)

CBT has been shown to be effective in managing chronic pain, either on its own or together with other pain management tools, such as medication. Over the past half century, evidence has accrued that the experience of pain is not based solely on sensory or neurologic states but is influenced by cognitive and affective processes (Ehde et al., 2014). A person's thoughts and beliefs about pain can affect a number of pain-related issues, including the intensity of pain, anxiety and depression, physical disability, activity limitations, and catastrophizing (Ehde et al., 2014). Altering these thoughts and beliefs through CBT can change a person's experience of and adaptation to pain, decreasing its intensity and improving day-to-day functioning and the ability to cope with the pain (Knoerl et al., 2016). CBT usually is delivered through multiple sessions of individual or group therapy in which a variety of strategies are conveyed to participants, including practicing relaxation techniques, reframing negative thoughts, scheduling activity to maximize functionality, and improving sleep patterns (Knoerl et al., 2016).

Numerous studies have demonstrated the efficacy of CBT (e.g., Ehde et al., 2014; Morley et al., 1999; Williams et al., 2012). A 2012 Cochrane review (Williams et al., 2012), for example, found that CBT, compared with treatment as usual at posttreatment, had a small but significant effect on pain intensity and disability and a moderate effect on catastrophizing and anxiety and depression (Knoerl et al., 2016). CBT is currently "the prevailing psychological treatment for individuals with chronic pain conditions such as low back pain, headaches, arthritis, orofacial pain, and fibromyalgia" (Ehde et al., 2014). However, the studies of CBT that have been performed have varied in the method of its delivery, the specific strategies used, and which outcome variables were studied, making it difficult to evaluate whether and to what extent CBT is efficacious for achieving specific pain-related outcomes (Knoerl et al., 2016). Knoerl and colleagues (2016) sought to remedy this evidence gap with an integrative review of 35 studies on CBT and chronic pain. They found that CBT was effective at reducing pain intensity in 43 percent of these trials (only 8 of 35 studies used pain intensity as a primary outcome, although it was measured in all studies); for a wider group of pain-related variables, including physical functioning, anxiety, depression, and quality of life, CBT was effective in

86 percent of trials. The authors note that CBT has been understudied in military veterans and patients with chronic pain related to cancer treatment.

Barriers to the provision of CBT include limited access to providers, inadequate insurance coverage, lack of knowledge about CBT among health care providers, and patients' perception of stigma associated with CBT (Ehde et al., 2014). A 2016 study (Bee et al., 2016) of the acceptability of CBT among chronic pain patients found that preintervention patients viewed CBT as less relevant to their condition than other interventions (e.g., exercise). Some patients believed that the suggestion of using a psychological approach for a predominantly physical problem implied that the pain was not valid or was the result of "an underlying character weakness" (Bee et al., 2016). However, patients who received the CBT intervention reported high satisfaction, finding that it helped them shift toward proactive pain management (Bee et al., 2016).

In addition to CBT, there are other psychosocial interventions for chronic pain, such as acceptance and commitment therapy (ACT), in which patients are encouraged to change their responses to pain rather than seek a reduction in the pain itself. Studies on ACT have shown promise, but further research is needed (Vowels et al., 2014; Wetherell et al., 2011).

Mindfulness Meditation

Mindfulness is defined as purposefully paying attention in the present moment, nonjudgmentally (Kabat-Zinn, 2003). Operationalized, it means "(a) regulated, sustained attention to the moment-to-moment quality and character of sensory, emotional and cognitive events, (b) the recognition of such events as momentary, fleeting and changeable (past and future representations of those events being considered cognitive abstractions), and (c) a consequent lack of emotional or cognitive appraisal and/or reactions to these events" (Zeidan et al., 2012). One such intervention, mindfulness-based stress reduction (Kabat-Zinn, 2003), the most studied mindfulness intervention, trains individuals in acquiring and practicing these skills, including for the management of various forms of chronic pain. Although of mixed quality, a large number of studies have found mindfulness interventions to have beneficial effects for patients with pain.

A meta-analysis of 38 RCTs of various forms of mindfulness meditation intervention for chronic pain management found that mindfulness improved pain, reduced symptoms of depression, and improved quality of life compared with treatment as usual, support groups, education, stress management, and waitlist controls (Hilton et al., 2017). Evidence is strongest for the efficacy of mindfulness in reducing symptoms of depression and improving mental health–related quality of life, for which the quality of evidence is

rated high and moderate, respectively. While small, statistically significant effects on pain are promising, these findings are tempered by the low quality of the evidence (e.g., lack of intent-to-treat analysis, low follow-up rate, small samples, inadequately powered studies). Effects on reducing analgesic use were mixed, with some studies showing reductions and others not. The authors conclude that more well-designed RCTs are needed to develop an evidence base on the effectiveness of mindfulness interventions (Hilton et al., 2017).

Beyond demonstrating efficacy, it is important to understand the hypothesized mechanisms underlying the use of mindfulness interventions as therapy for pain management. An understanding of the neuronal and molecular basis of changes in the brain that accompany mindfulness meditation is also nascent (Tang et al., 2015). Nonetheless, emerging evidence is providing useful information on how mindfulness meditation may cause neuroplastic changes in the structure and function of the brain regions involved in regulation of attention, emotion, and self-awareness, which are also factors involved in the cognitive modulation of pain (Zeidan et al., 2012). Accumulating evidence indicates that it can attenuate the subjective experience of pain, and that it shares as well as has distinct neural substrates engaged by cognitive factors known to modulate pain (Hilton et al., 2017).

One question has been whether the analgesic effects of mindfulness meditation are different from those of placebo. Zeidan and colleagues (2015) directly explored this question in healthy volunteers. They conducted an RCT involving four conditions (mindfulness meditation, sham mindfulness meditation, placebo conditioning, and book-listening control). Intervention efficacy was assessed using psychophysical evaluation of experimental pain and functional neuroimaging. The authors found that mindfulness meditation produced significantly greater reductions in pain intensity and unpleasantness relative to the other conditions. Importantly, their findings indicate that mindfulness meditation employs distinct neural mechanisms—specifically, higher-order brain regions, including orbitofrontal and cingulate cortices. They suggest that these findings may foster greater acceptance of meditation as an adjunct pain therapy.

Taken together, this emerging body of work suggests that the practice of mindfulness meditation for pain management may be promising. There is a need for further research with rigorous designs and larger samples that include patients with chronic pain to provide high-quality tests of the efficacy of this therapy. In addition, studies are needed to connect findings from studies of the neuronal and molecular bases of changes in the brain that accompany mindfulness meditation with behavioral measures.

Placebo Analgesia

Placebo is a dummy treatment, such as a pharmacologically inert preparation ("sugar pill") or sham procedure. The difference in treatment effect between a group that has received no treatment and one that has received placebo is considered the "placebo effect." Pain is one of the areas in which placebo has been most studied.

It has been shown in research and clinical settings that the expectation of pain relief can induce a strong analgesic effect. Placebo analgesic response is the result of this phenomenon. Consistent placebo analgesic effect has been demonstrated in dental pain, postthoracotomy pain, low back pain, irritable bowel syndrome, neuropathic pain, and experimental pain (Enck et al., 2008; Finniss et al., 2010; Kaptchuk and Miller, 2015; Price et al., 2008). The response to placebo is heterogeneous, being affected by individual differences in conditioning (Colloca and Benedetti, 2006; Kantor et al., 1966), expectations (Morton et al., 2010), optimism (Morton et al., 2009), and suggestibility (De Pascalis et al., 2002), as well as the nature of the placebo provided (Kong et al., 2013) and other factors. The placebo effect was found to be as strong as that of 7.5 mg of morphine following third molar extraction (Levine et al., 1981), and open administration of medication has been shown to be more effective than hidden administration (Colloca et al., 2004). Moreover, patients who are told that they are receiving a very potent pain killer have been found to require less of the same opioid than patients who are not (Pollo et al., 2001). And patients provided with a treatment that they believe is good for them benefit more from that treatment (Kalauokalani, 2001).

The "nocebo effect" is the term used to describe an undesirable outcome, such as an increase in pain, due to negative expectations (or conditioning). The nocebo effect is longer-lasting and probably greater than the placebo effect (Colloca et al., 2008). Patients in placebo groups often report side effects similar to those of the active drug if they were exposed to the possible side effects described in the consent form (Barsky et al., 2002).

Placebo cannot be considered sham or no treatment. The effect of any treatment for pain may be a combination of its effect and the placebo effect (Beecher, 1955; Howick et al., 2013).

The placebo effect is associated with activity in the prefrontal cortex, insular cortex, thalamus, forebrain structures, and spinal cord. An opioid antagonist (naloxone) can reverse placebo analgesia (Levine et al., 1978), suggesting involvement of the endogenous opioid system and probably the descending pain modulatory system. It also has been suggested that the endocannabinoid system is involved in placebo's analgesic effect (Benedetti and Amanzio, 2011). Better understanding of the placebo effect could lead

to the development of independent treatment protocols or methods that would augment the effect of existing treatments.

Focus on Self-Management

An important recommendation of the 2011 IOM report *Relieving Pain in America* was that health care provider organizations promote and enable self-management of pain as the starting point of pain management (IOM, 2011). Self-management can be defined as "the ability to manage the symptoms, treatment, physical and psychosocial consequences and life-style changes inherent in living with a chronic condition" (Barlow et al., 2002). In the context of chronic pain, self-management may involve acceptance of the painful condition, exercise, pacing, relaxation, and other positive steps toward higher levels of functioning if not immediate reduction in pain intensity. Such approaches tend to deemphasize the role of medications such as opioids. Although significant barriers to pain self-management exist, such as lack of family support, limited resources, and depression (Bair et al., 2009), research on chronic pain self-management and the implementation of self-management programs is expanding. Examples of self-management programs for chronic pain include those designed for low back pain (Slater et al., 2012), knee pain (Button et al., 2015), arthritis (Vermaak et al., 2015), and other forms of chronic pain. It may be hoped that the reliance on opioids as a first-line management strategy by both patients and medical providers will diminish as self-management programs become more common.

Summary

Nonpharmacologic interventions for pain treatment, including acupuncture, physical therapy and exercise, CBT, and mindfulness meditation, represent powerful tools in the management of chronic pain. Many are components of successful self-management. While further research is needed to better understand the mechanism of action and the appropriate dosage and delivery for some nonpharmacologic approaches, they may provide effective pain relief for many patients in place of or in combination with pharmacologic approaches.

DIFFERENCES IN PAIN EXPERIENCES AND TREATMENT EFFECTIVENESS AMONG SUBPOPULATIONS

Part of the committee's charge was to review the available evidence on differences in the experience of pain and the effectiveness of treatments across subpopulations. This section briefly reviews research findings on

this issue among selected subpopulations in the United States, including findings pertinent to prescription opioids. A review of the effectiveness of all of the available treatments for pain for subpopulations is beyond the scope of this study. For additional discussion of disparities in pain among subpopulations, the reader is encouraged to see the report *Relieving Pain in America* (IOM, 2011). The discussion here does not address individual (e.g., genetic) differences in susceptibility to pain, which are touched on in Chapter 3.

Sex

Research indicates that women are more likely than men to experience chronic pain and report higher sensitivity to pain (Bartley and Fillingim, 2013). Findings have been mixed regarding severity of pain, with women reporting greater severity than men in some studies but no sex differences in severity being found in other studies (Bartley and Fillingim, 2013). Certain chronic pain conditions, such as fibromyalgia, migraine and headache, irritable bowel syndrome, temporomandibular disorders, and interstitial cystitis, are diagnosed more commonly in women than in men (Bartley and Fillingim, 2013). The reasons for differences in the experience of pain by sex are not entirely understood, may be multifactorial, and may depend on the type of pain and/or condition. Possible explanations include differences in genotype and endogenous opioid functioning, sex hormones, psychosocial processes, and stereotypical gender roles that may make men less expressive about pain (Bartley and Fillingim, 2013; Fillingim et al., 2009). Provider beliefs also may play a role in differential rates of diagnosis of painful conditions between men and women.

With respect to prescription opioids, the sex of a patient can impact both the efficacy of an opioid and the likelihood that an opioid-related adverse event will be experienced. In acute administration settings, opioids have been observed to cause more respiratory depression, nausea, and pruritus in female compared with male patients (Angst et al., 2012; Riley et al., 2010). The chronic use of opioids also can alter sex hormones in men and women, leading to impotence in men and menstrual irregularities in women (Rhodin et al., 2010). A review of 18 studies showed lower opioid consumption postoperatively among women than men, but this finding has not been consistent, may depend on the type of procedure performed, and may reflect increased prevalence or reduced tolerance of side effects from opioids in women rather than less need for pain relief (Miaskowski et al., 2000). A meta-analysis found no sex-specific effects for μ opioid analgesia across 25 clinical studies of μ opioids and greater analgesic effects for women when analyses were restricted to patient-controlled analgesia (Niesters et al., 2010).

Race and Ethnicity

Research consistently shows differences in pain experiences among racial and ethnic groups (Hoffman et al., 2016; IOM, 2011). African American patients have been found to be less likely than whites to be prescribed pain medications for both cancer and noncancer pain (Anderson et al., 2009; Goyal et al., 2015; Todd et al., 2000). African Americans also report greater pain than whites for several painful conditions (IOM, 2011). Some experimental data show that African Americans have a lower pain threshold than whites, but these differences are small and may be clinically insignificant. A recent review of research on the pain experiences of Hispanic Americans found that this population reports fewer pain conditions and significantly lower rates of chronic pain compared with non-Hispanic whites in national surveys. However, Hispanic Americans report experiencing more severe pain and higher sensitivity to pain (Hollingshead et al., 2016).

The impact of race and ethnicity on opioid prescribing in particular has been evaluated in several studies. Some research indicates that blacks are less likely than non-Hispanic whites to receive an opioid for chronic noncancer pain (Cintron and Morrison, 2006; Dickason et al., 2016; Ringwalt et al., 2014, 2015), and this disparity appears to be more common in some specialty settings than in others (Ringwalt et al., 2014). These observations are consistent with reports showing that pain in minority versus white patients tends to be underestimated by health care providers (Cintron and Morrison, 2006). Evidence does not strongly suggest that patients of different races/ethnicities are more or less likely to display aberrant behaviors in prescription opioid use (Ives et al., 2006; Vijayaraghavan et al., 2012), although providers may be more likely to believe that a black or Hispanic versus a white patient is misusing prescription opioids (Becker et al., 2011; Vijayaraghavan et al., 2011).

Lower socioeconomic status also is a risk factor for pain and its undertreatment. This association may be due to poorer overall health, employment-related factors (e.g., a higher proportion of individuals employed in occupations with a higher risk of injury), lower access to quality pain care, and other factors. Some of the observed disparity in treatment for pain by race and ethnicity likely is explained by socioeconomic status, as racial and ethnic minority populations are disproportionately low-income or poor (IOM, 2011).

Age

Age is positively associated with increased risk for the development of conditions, such as osteoarthritis and other musculoskeletal conditions,

and chronic diseases, such as diabetes, that can be painful. Yet while some studies show a continual increase in pain prevalence with age, others show a decrease with age, an increase up to ages 75–85 followed by a decrease, or no differences by age (Abdulla et al., 2013). Experimental and clinical studies have found that the elderly are more vulnerable than younger individuals to severe and persistent pain and have reduced ability to tolerate severe pain. In addition, older people are more likely to have comorbidities that complicate diagnosis and treatment of painful conditions (IOM, 2011). Other factors that may influence the severity of pain in the elderly are complex manifestations of pain, underreporting of or reduced ability to report pain, and higher rates of treatment side effects (IOM, 2011).

The aging process can affect the safety of opioid prescribing as a result of alterations in drug metabolism, elimination, and sensitivity. In addition, the presence of comorbid conditions and the use of potentially interacting medications to treat those conditions may increase with age. Concern exists, for example, about the use of opioids for noncancer pain in older adults because of the risks of sedation, overdose, and falls. These risks have prompted recommendations for lower starting doses, slower titration, and avoidance of use of other sedating drugs such as benzodiazepines (Kahan et al., 2011). The use of methadone in the elderly raises particular concern as this is a potent opioid with variable pharmacokinetics and a propensity for drug–drug interactions, and may also cause cardiac dysrhythmias (van Ojik et al., 2012).

Geography

Many rural communities in the United States have limited access to providers with training in pain management (Eaton et al., 2014; IOM, 2011). At the same time, residents of rural areas tend to be older and more likely to have painful chronic health conditions relative to those in urban areas (Eaton et al., 2014; Jukkala et al., 2008). As discussed in Chapter 4, states with large rural populations have experienced disproportionate morbidity and mortality from nonmedical use of prescription opioids (Keyes et al., 2014). Telemedicine/Internet-based technologies are one approach that has been used to bridge geographic distance to improve the quality of pain care in communities with limited access to providers with expertise in pain management (Currie et al., 2015; Eaton et al., 2014).

History of Substance Use Disorder

It is common for patients with histories of substance use disorders to also have chronic pain. Among patients receiving methadone maintenance treatment, for example, more than 40 percent have chronic pain (Dunn et

al., 2015; Voon et al., 2015). In addition, patients maintained on methadone and buprenorphine have measurably lower pain thresholds and tolerances than nonopioid-receiving controls (Compton et al., 2001, 2012). Likewise, it is common when looking cross-sectionally at populations of patients managed with opioids to identify a significant percentage with substance use disorders. The percentage of such patients in a treatment population is dependent on such risk factors as younger age and higher overall opioid dosage (Palmer et al., 2015). This complexity is addressed further in Chapter 3, where research on the intersection of pain and OUD is discussed, and knowledge gaps are identified.

A history of substance use disorder is a risk factor for aberrant opioid use among those being treated for pain (Chou et al., 2009b). Opioid risk assessment tools often take this characteristic into account, and such risk assessment is advocated in the CDC Guideline for Prescribing Opioids for Chronic Pain (Dowell et al., 2016).

Summary

In summary, differences have been observed among subpopulations in the types and severity of pain experienced and in access to and receipt of quality pain care depending on such factors as sex, age, race and ethnicity, location of residence, and history of substance use disorder. Moreover, while further research is needed, different subpopulations of patients may have different levels of analgesic response to opioids, experience side effects of differing severity, and display drug misuse at different rates.

THE INTERSECTION BETWEEN PAIN AND OPIOID USE DISORDER

Pain and reward are considered opponent processes but are processed within overlapping brain structures. Rewarding stimuli can decrease pain sensitivity (Leknes and Tracey, 2008), whereas pain can impair reward processing, leading to an anhedonic state (Elman et al., 2013). Few studies have examined the disruption of this circuitry caused by pain and whether the dopaminergic system contributes to the aversive component of ongoing persistent pain (Navratilova et al., 2012, 2015). Furthermore, how the presence of pain modifies the reinforcing properties of natural rewards or opioids is not known. The mesolimbic pathway is a critical brain circuit altered in opioid addiction, making it an ideal system in which to investigate the mechanistic basis for opioid misuse in the presence of pain (Cui et al., 2014; Fields and Margolis, 2015). Opioid-induced release of dopamine in the nucleus accumbens contributes to opioids' misuse potential, whereas an allostatic shift in reward signaling leads to the pathological state of addic-

tion (Koob, 2008). μ opioid receptor agonists are positively reinforcing and are used extensively as a first-line treatment for clinical pain. Furthermore, recent research (Blanco et al., 2016) shows that persistent pain may lead individuals to use prescription opioids in patterns different from what their prescribing physician initially intended, resulting in opioid misuse or OUD. The neurobiology of the reward pathway and of the intersection of pain and OUD is described in more in detail in Chapter 3.

REFERENCES

Abdel-Salam, O.M.E., A.R. Baiuomy, and M.S. Arbid. 2004. Studies on the anti-inflammatory effect of fluoxetine in the rat. *Pharmacological Research* 49(2):119-131.

Abdel Shaheed, C., C.G. Maher, K.A. Williams, R. Day, and A.J. McLachlan. 2016. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: A systematic review and meta-analysis. *JAMA Internal Medicine* 176(7):958-968.

Abdulla, A., N. Adamns, M. Bone, A.M. Elliott, J. Gaffin, D. Jones, R. Knaggs, D. Martin, L. Sampson, and P. Schoefield. 2013. Guidance on the management of pain in older people. *Age and Ageing* 42(Suppl. 1):1-67.

Agaliotis, M., M.G. Mackey, S. Jan, and M. Fransen. 2014. Burden of reduced work productivity among people with chronic knee pain: A systematic review. *Occupational and Environmental Medicine* 71(9):651-659.

Aggarwal, A., O. Zekry, and S. Gibson. 2013. *Long term effectiveness of subanesthetic inpatient intravenous ketamine infusion therapy in the management of chronic non-cancer pain*. Presented at 33rd Annual Scientific Meeting of the Australian Pain Society, Canberra, ACT Australia. March 19.

Anderson, K.O., C.R. Green, and R. Payne. 2009. Racial and ethnic disparities in pain: Causes and consequences of unequal care. *The Journal of Pain* 10(12):1187-1204.

Angst, M.S., and J.D Clark. 2006. Opioid-induced hyperalgesia: A qualitative systematic review. *Anesthesiology* 104(3):570-587.

Angst, M.S., L.C. Lazzeroni, N.G. Phillips, D.R. Drover, M. Tingle, A. Ray, G.E. Swan, and J.D. Clark. 2012. Aversive and reinforcing opioid effects: A pharmacogenomic twin study. *Anesthesiology* 117(1):22-37.

Attal, N., G. Cruccu, M. Haanpaa, P. Hansson, T.S. Jensen, T. Nurmikko, C. Sampaio, S. Sindrup, and P. Wiffen. 2006. EFNS guidelines on pharmacological treatment of neuropathic pain. *European Journal of Neurology* 13(11):1153-1169.

Atwood, B.K., and K. Mackie. 2010. CB2: A cannabinoid receptor with an identity crisis. *British Journal of Pharmacology* 160(3):467-479.

Bai, Y., T. Miller, M. Tan, L.S. Law, and T.J. Gan. 2015. Lidocaine patch for acute pain management: A meta-analysis of prospective controlled trials. *Current Medical Research and Opinion* 31(3):575-581.

Bair, M.J., M.S. Matthias, K.A. Nyland, M.A. Huffman, D.L. Stubbs, K. Kroenke, and T.M. Damush. 2009. Barriers and facilitators to chronic pain self-management: A qualitative study of primary care patients with comorbid musculoskeletal pain and depression. *Pain Medicine* 10(7):1280-1290.

Baldini, A., M. Von Korff, and E.H. Lin. 2012. A review of potential adverse effects of long-term opioid therapy: A practitioner's guide. *Primary Care Companion for CNS Disorders* 14(3).

Barbour, K.E., C.G. Helmick, M. Boring, and T.J. Brady. 2017. Vital Signs: Prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation—United States, 2013-2015. *Morbidity and Mortality Weekly Report* 66(9):246-253.

Barclay, J.S., J.E. Owens, and L.J. Blackhall. 2014. Screening for substance abuse risk in cancer patients using the Opioid Risk Tool and urine drug screen. *Supportive Care in Cancer* 22(7):1883-1888.

Barlow, J., J. Sheasby, A. Turner, and J. Hainsworth. 2002. Self-management approaches for people with chronic conditions: A review. *Patient Education and Counseling* 48(2):177-187.

Barnett, M.L., A.R. Olenski, and A.B. Jena. 2017. Opioid-prescribing patterns of emergency physicians and risk of long-term use. *New England Journal of Medicine* 376(7):663-673.

Barreveld, A.M., D.J. Correll, X. Liu, B. Max, J.A. McGowan, L. Shovel, A.D. Wasan, and S.S. Nedeljkovic. 2013. Ketamine decreases postoperative pain scores in patients taking opioids for chronic pain: Results of a prospective, randomized, double-blind study. *Pain Medicine* 14(6):925-934.

Barsky, A.J., R. Saintfort, M.P. Rogers, and J.F. Borus. 2002. Nonspecific medication side effects and the nocebo phenomenon. *Journal of the American Medical Association* 287(5):622-627.

Bartley, E.J., and R.B. Fillingim. 2013. Sex differences in pain: A brief review of clinical and experimental findings. *British Journal of Anaesthesia* 111(1):52-58.

Becker, D.E. 2010. Pain management: Part 1: Managing acute and postoperative dental pain. *Anesthesia Progress* 57(2):67-78.

Becker, W.C., J.L. Starrels, M. Heo, X. Li, M.G. Weiner, and B.J. Turner. 2011. Racial differences in primary care opioid risk reduction strategies. *Annals of Family Medicine* 9(3):219-225.

Bee, P., J. McBeth, G.J. MacFarlane, and K. Lovell. 2016. Managing chronic widespread pain in primary care: A qualitative study of patient perspectives and implications for treatment delivery. *BMC Musculoskeletal Disorders* 17(1):354.

Beecher, H.K. 1955. The powerful placebo. *Journal of the American Medical Association* 159(17):1602-1606.

Belgrade, M.J., C.D. Schamber, and B.R. Lindgren. 2006. The DIRE score: Predicting outcomes of opioid prescribing for chronic pain. *The Journal of Pain* 7(9):671-681.

Bement, M.K., and K.A. Sluka. 2005. Low-intensity exercise reverses chronic muscle pain in the rat in a naloxone-dependent manner. *Archives of Physical Medicine and Rehabilitation* 86(9):1736-1740.

Benedetti, F., and M. Amanzio. 2011. The placebo response: How words and rituals change the patient's brain. *Patient Education and Counseling* 84(3):413-419.

Berman, B.M., J. Ezzo, V. Hadhazy, and J.P. Swyers. 1999. Is acupuncture effective in the treatment of fibromyalgia? *Journal of Family Practice* 48(3):213-218.

Biron, R.T., E.V. Hersh, H.D. Barber, and R.J. Seckinger. 1996. A pilot investigation: Postsurgical analgesic consumption by dental implant patients. *Dentistry* 16(3):12-13.

Bisogno, T., M. Ventriglia, A. Milone, M. Mosca, G. Cimino, and V. Di Marzo. 1997. Occurrence and metabolism of anandamide and related acyl-ethanolamides in ovaries of the sea urchin paracentrotus lividus. *Biochimica Biophysica Acta* 1345(3):338-348.

Blanco, C., M.M. Wall, M. Okuda, S. Wang, M. Iza, and M. Olfson. 2016. Pain as a predictor of opioid use disorder in a nationally-representative sample. *American Journal of Psychiatry* 173(12):1189-1195.

Blaudszun, G., K. Lysakowski, N. Elia, and M.R. Tramer. 2012. Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: Systematic review and meta-analysis of randomized controlled trials. *Anesthesiology* 116(6):1312-1322.

Buerkle, H., and T.L. Yaksh. 1998. Pharmacological evidence for different alpha 2-adrenergic receptor sites mediating analgesia and sedation in the rat. *British Journal of Anaesthesia* 81(2):208-215.

Busch, A.J., S.C. Webber, R.S. Richards, J. Bidonde, C.L. Schachter, L.A. Schafer, A. Danyliw, A. Sawant, V. Dal Bello-Haas, T. Rader, and T.J. Overand. 2013. Resistance exercise training for fibromyalgia. *Cochrane Database of Systematic Reviews* 12:CD010884.

Butler, S.H., Weil-Fugazza, J., F. Godefroy, and J.M. Besson. 1985. Reduction of arthritis and pain behaviour following chronic administration of amitriptyline or imipramine in rats with adjuvant-induced arthritis. *Pain* 23(2):159-175.

Butler, S.F., S.H. Budman, K. Fernandez, and R.N. Jamison. 2004. Validation of a screener and opioid assessment measure for patients with chronic pain. *Pain* 112(1-2):65-75.

Butler, S.F., S.H. Budman, K.D. Fernandez, G.J. Fanciullo, and R.N. Jamison. 2009. Cross-validation of a screener to predict opioid misuse in chronic pain patients (SOAPP-R). *Journal of Addiction Medicine* 3(2):66-73.

Button, K., P.E. Roos, I. Spasic, P. Adamson, and R.W. van Deursen. 2015. The clinical effectiveness of self-care interventions with an exercise component to manage knee conditions: A systematic review. *Knee* 22(5):360-371.

Cao, Y.Q., P.W. Mantyh, E.J. Carlson, A.M. Gillespie, C.J. Epstein, and A.I. Basbaum. 1998. Primary afferent tachykinins are required to experience moderate to intense pain. *Nature* 392(6674):390-394.

Carmona-Bayonas, A., P. Jiménez-Fonseca, E. Castañón, A. Ramchandani-Vaswani, R. Sánchez-Bayona, A. Custodio, D. Calvo-Temprano, and J.A. Virizuela. 2016. Chronic opioid therapy in long-term cancer survivors. *Clinical & Translational Oncology* 19(2): 236-250.

Carroll, I., C.K. Wang, B.M. Wang, M.J. Gillespie, R. McCue, J.W. Younger, J. Trafton, K. Humphreys, S.B. Goodman, F. Dirbas, R.I. Whyte, J.S. Donington, W.B. Cannon, and S.C. Mackey. 2012. A pilot cohort study of the determinants of longitudinal opioid use after surgery. *Anesthesia and Analgesia* 115(3):694-702.

Carson, J.W., K.M. Carson, K.D. Jones, R.M. Bennett, C.L. Wright, and S.D. Mist. 2010. A pilot randomized controlled trial of the yoga of awareness program in the management of fibromyalgia. *Pain* 151(2):530-539.

Catella-Lawson, F., M.P. Reilly, S.C. Kapoor, A.J. Cucchiara, S. DeMarco, B. Tournier, S.N. Vyas, and G.A. FitzGerald. 2001. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *New England Journal of Medicine* 345(25):1809-1817.

CDC (U.S. Centers for Disease Control and Prevention). 2017. *Ambulatory care use and physician office visits.* https://www.cdc.gov/nchs/fastats/physician-visits.htm (accessed April 17, 2017).

Cengiz, P., G. Gokcinar, I. Karabeyoglu, H. Topcu, G.S. Cicek, and N. Gogus. 2014. Intraoperative low-dose ketamine infusion reduces acute postoperative pain following total knee replacement surgery: A prospective, randomized double-blind placebo-controlled trial. *Journal of the College of Physicians and Surgeons—Pakistan* 24(5):299-303.

Chang, D.G., J.A. Holt, M. Sklar, and E.J. Groessl. 2016. Yoga as a treatment for chronic low back pain: A systematic review of the literature. *Journal of Orthopedics & Rheumatology* 3(1):1-8.

Chaparro, L.E., S.A. Smith, R.A. Moore, P.J. Wiffen, and I. Gilron. 2013. Pharmacotherapy for the prevention of chronic pain after surgery in adults. *Cochrane Database of Systematic Reviews* 7:CD008307.

Chaparro, L.E., A.D. Furlan, A. Deshpande, A. Mailis-Gagnon, S. Atlas, and D.C. Turk. 2014. Opioids compared with placebo or other treatments for chronic low back pain: An update of the Cochrane Review. *Spine (Philadelphia, PA 1976)* 39(7):556-563.

Chapman, C.R., J. Davis, G.W. Donaldson, and D. Winchester. 2011. Postoperative pain trajectories in chronic pain patients undergoing surgery. The effects of chronic opioid pharmacotherapy on acute pain. *The Journal of Pain* 12(12):1240-1246.

Cheatle, M.D., J.W. Klocek, and A.T. McClellan. 2012. Managing pain and high risk patients within the patient centered medical home. *Translational Behavior Medicine* 2(1):47-56.

Chen, J.H., J. Hom, I. Richman, S.M. Asch, T. Podchiyska, and N.A. Johansen. 2016. Effect of opioid prescribing guidelines in primary care. *Medicine (Baltimore)* 95(35):e4760.

Cheng, R.S., and B.H. Pomeranz. 1980. Electroacupuncture analgesia is mediated by stereospecific opiate receptors and is reversed by antagonists of type I receptors. *Life Sciences* 26(8):631-638.

Childers, J.W., L.A. King, and R.M. Arnold. 2015. Chronic pain and risk factors for opioid misuse in a palliative care clinic. *American Journal of Hospice & Palliative Care* 32(6):654-659.

Chopra, P., and M.S. Cooper. 2013. Treatment of complex regional pain syndrome (CRPS) using low dose naltrexone (LDN). *Journal of Neuroimmune Pharmacology* 8(3):470-476.

Chou, R., S.J. Atlas, S.P. Stanos, and R. Rosenquist. 2009a. Nonsurgical interventional therapies for low back pain: A review of the evidence for an American Pain Society clinical practice guideline. *Spine (Philadelphia, PA 1976)* 34(10):1078-1093.

Chou, R., G.J. Fanciullo, P.G. Fine, C. Miaskoski, S.D. Passik, and R.K. Portenoy. 2009b. Opioids for chronic noncancer pain: Prediction and identification of aberrant drug-related behaviors: A review of the evidence for an American Pain Society and American Academy of Pain Medicine clinical practice guideline. *The Journal of Pain* 10(2):131-146.

Chou, R., R. Deyo, B. Devine, R.Hansen, S. Sullivan, J.G. Jarvik, I. Blazina, T. Dana, C. Bougatsos, and J. Turner. 2014. The effectiveness and risks of long-term opioid treatment of chronic pain. Report no. 14-E005-EF. Rockville, MD: Agency for Healthcare Research and Quality.

Chou, R., J.A. Turner, E.B. Devine, R.N. Hansen, S.D. Sullivan, I. Blazina, T. Dana, C. Bougatsos, and R.A. Deyo. 2015. The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of Internal Medicine* 162(4):276-286.

Cichewicz, D.L. 2004. Synergistic interactions between cannabinoid and opioid analgesics. *Life Sciences* 74(11):1317-1324.

Cintron, A., and R.S. Morrison. 2006. Pain and ethnicity in the United States: A systematic review. *Journal of Palliative Medicine* 9(6):1454-1473.

Clarke, H., R.P. Bonin, B.A. Orser, M. Englesakis, D.N. Wijeysundera, and J. Katz. 2012. The prevention of chronic postsurgical pain using gabapentin and pregabalin: A combined systematic review and meta-analysis. *Pain Medicine* 115(2):428-442.

Cohen, S., and S.N. Raja. 2007. Pathogenesis, diagnosis, and treatment of lumbar zygapophysial (facet) joint pain. *Anesthesiology* 106(3):591-614.

Colloca, L., and F. Benedetti. 2006. How prior experience shapes placebo analgesia. *Pain* 124(1-2):126-133.

Colloca, L., L. Lopiano, M. Lanotte, and F. Benedetti. 2004. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *The Lancet Neurology* 3(11):679-684.

Colloca, L., M. Sigaudo, and F. Benedetti. 2008. The role of learning in nocebo and placebo effects. *Pain* 136(1-2):211-218.

Compton, P., V.C. Charuvastra, and W. Ling. 2001. Pain intolerance in opioid-maintained former opiate addicts: Effect of long-acting maintenance agent. *Drug and Alcohol Dependence* 63(2):139-146.

Compton, P., C.P. Canamar, M. Hillhouse, and W. Ling. 2012. Hyperalgesia in heroin dependent patients and the effects of opioid substitution therapy. *The Journal of Pain* 13(4): 401-409.

Cooper, T.E., S. Derry, P.J. Wiffen, and R.A. Moore. 2017. Gabapentin for fibromyalgia pain in adults. *Cochrane Database of Systematic Reviews* 1:CD012188.

Couch, J.R., and R.S. Hassanein. 1976. Migraine and depression: Effect of amitriptyline prophylaxis. *Transactions of the American Neurological Association* 101:234-237.

Cramer, H., R. Lauche, H. Haller, and G. Dobos. 2013. A systematic review and meta-analysis of yoga for low back pain. *Clinical Journal of Pain* 29(5):450-460.

Croft, P., F. M. Blyth, and D. van der Windt (Eds.). 2010. *Chronic pain epidemiology: From aetiology to public health*. New York: Oxford University Press.

Cui, Y., S. B. Ostlund, A.S. James, C.S. Park, W. Ge, K.W. Roberts, N. Mittal, N.P. Murphy, C. Cepeda, B.L. Kieffer, M.S. Levine, J.D. Jentsch, W.M. Walwyn, Y.E. Sun, C.J. Evans, N.T. Maidment, and Y.X. Yang. 2014. Targeted expression of mu-opioid receptors in a subset of striatal direct-pathway neurons restores opiate reward. *Nature Neuroscience* 17(2):254-261.

Currie, M., L.J. Philip, and A. Roberts. 2015. Attitudes towards the use and acceptance of eHealth technologies: A case study of older adults living with chronic pain and implications for rural healthcare. *BMC Health Services Research* 15:162.

Dahan, A. 2016. Potent opioid analgesia without respiratory depression: Could it be possible? *Anesthesiology* 125(5):841-843.

Dahan, A., M. van Velzen, and M. Niesters. 2014. Comorbidities and the complexities of chronic pain. *Anesthesiology* 121(4):675-677.

de Hoogd, S., S.J. Ahlers, E.P. van Dongen, E.M. van de Garde, B.T.A. Hamilton-Ter, A. Dahan, D. Tibboel, and C.A. Knibbe. 2016. Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? An update of the literature. *Clinical Journal of Pain* 32(8):726-735.

De Pascalis, V., C. Chiaradia, and E. Carotenuto. 2002. The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. *Pain* 96(3):393-402.

De Petrocellis, L., D. Melck, T. Bisogno, and V. Di Marzo. 2000. Endocannabinoids and fatty acid amides in cancer, inflammation and related disorders. *Chemistry and Physics of Lipids* 108(1-2):191-209.

De Ridder, D., S. Vanneste, M. Plazier, E. van der Loo, and T. Menovsky. 2010. Burst spinal cord stimulation: Toward paresthesia-free pain suppression. *Neurosurgery* 66(5):986-990.

De Ridder, D., M. Plazier, N. Kamerling, T. Menovsky, and S. Vanneste. 2013. Burst spinal cord stimulation for limb and back pain. *World Neurosurgery* 80(5):642-649.

Deer, T., M. Mekhail, D. Provenzano, J. Pope, E. Krames, M. Leong, R.M. Levy, D. Abejon, E. Buchser, A. Burton, A. Buvanendran, K. Dandido, D. Caraway, M. Cousins, M. DeJongste, S. Diwan, S. Eldabe, K. Gatzinsky, R.D. Foreman, S. Hayek, P. Kim, T. Kinfe, D.Kloth, K. Kuman, S. Rizvi, S.P. Lad, L. Liem, B. Linderoth, S. Mackey, G. McDowell, P. McRoberts, L. Poree, J. Prager, L. Raso, R. Rauck, M. Russo, B. Simpson, K. Slavin, P. Staats, M.H. Stanton-Hicks, P. Verrills, J. Wellington, K. Williams, and R. North. 2014. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: The Neuromodulation Appropriateness Consensus Committee. *Neuromodulation* 17(6):515-550.

del Portal, D.A., M.E. Healy, W.A. Satz, and R.M. McNamara. 2016. Impact of an opioid prescribing guideline in the acute care setting. *Journal of Emergency Medicine* 50(1):21-27.

Denisco, R.C., G.A. Kenna, M.G. O'Neil, R.J. Kulich, P.A. Moore, W.T. Kane, N.R. Mehta, E.V. Hersh, and N.P. Katz. 2011. Prevention of prescription opioid abuse: The role of the dentist. *Journal of the American Dental Association* 142(7):800-810.

Derry, C.J., S. Derry, and R.A. Moore. 2013a. Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain. *Cochrane Database of Systematic Reviews* 6:CD010210.

Derry, S., A. Sven-Rice, P. Cole, T. Tan, and R.A. Moore. 2013b. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2:CD007393.

Devor, M., P.D. Wall, and N. Catalan. 1992. Systemic lidocaine silences ectopic neuroma and DRG discharge without blocking nerve conduction. *Pain* 48(2):261-268.

Deyo, R.A., D.H. Smith, E.S. Johnson, M. Donovan, C.J. Tillotson, X. Yang, A.F. Petrik, and S.K. Dobscha. 2011. *Journal of the American Board of Family Medicine* 24(6):717-727.

Deyo, R.A., M. VonKorff, and D. Duhrkoop. 2015. Opioids for low back pain. *British Medical Journal* 350:g6380.

Dickason, R.M., V. Chauhan, A. Mor, E. Ibler, S. Kuehnle, D. Mahoney, E. Armbrecht, and P. Dalawari. 2016. Racial differences in opiate administration for pain relief at an academic emergency department. *Western Journal of Emergency Medicine* 16(3):372-380.

Dietrich, A., and W.F. McDaniel. 2004. Endocannabinoids and exercise. *British Journal of Sports Medicine* 38(5):536-541.

Dobson, J.L., J. McMillan, and L. Li. 2014. Benefits of exercise intervention in reducing neuropathic pain. *Frontiers in Cellular Neuroscience* 8:102.

Donaldson, M., and J.H. Goodchild. 2010. Appropriate analgesic prescribing for the general dentist. *General Dentistry* 58(4):291-297.

Dowell, D., T.M. Haegerich, and R. Chou. 2016. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *Morbidity and Mortality Weekly Report* 65(1):1-49.

Duggan, K.C., D.J. Hermanson, J. Musee, J.J. Prusakiewicz, J.L. Scheib, B.D. Carter, S. Banerjee, J.A. Oates, and L.J. Marnett. 2011. (R)-profens are substrate-selective inhibitors of endocannabinoid oxygenation by COX-2. *Nature Chemical Biology* 7(11):803-809.

Dunn, K.M., K.W. Saunders, C.M. Rutter, C.J. Banta-Green, J.O. Merrill, M.D. Sullivan, C.M. Weisner, M.J. Silverberg, C.I. Campbell, B.M. Psaty, and M. VonKorff. 2010. Opioid prescriptions for chronic pain and overdose: A cohort study. *Annals of Internal Medicine* 152(2):85-92.

Dunn, K.E., D.A. Tompkins, M. Fingerhood, and E.C. Strain. 2015. Characterizing pain and associated coping strategies in methadone and buprenorphine-maintained patients. *Drug and Alcohol Dependence* 157:143-149.

Dworkin, R.H., A.B. O'Connor, M. Backonja, J.T. Farrar, N.B. Finnerup, T.S. Jensen, E.A. Kalso, J.D. Loeser, C. Miaskowski, T.J. Nurmikko, R.K. Portenoy, A.S.C. Rice, B.R. Stacey, R. Treede, D.C. Turk, and M.W. Wallace. 2007. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 132(3):237-251.

Dworkin, R.H., A.B. O'Connor, J. Audette, R. Baron, G.K. Gourlay, M.L. Haanpaa, J.L. Kent, E.J. Krane, A.A. Lebel, R.M. Levy, S.C. Mackey, J. Mayer, C. Miaskowski, S.N. Raja, A.S.C. Rice, K.E. Schmader, B. Stacey, S. Stanos, R. Treede, D.C. Turk, G.A. Walco, and C.D. Wells. 2010. Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. *Mayo Clinic Proceedings* 85(Suppl 3):S3-S14.

Eaton, L.H., D.B. Gordon, S. Wyant, B.R. Theodore, A.R. Meins, T. Rue, C. Towle, D. Tauben, and A.Z. Doorenbos. 2014. Development and implementation of a telehealth-enhanced intervention for pain and symptom management. *Contemporary Clinical Trials* 38(2):213-220.

Ehde, D.M., T.M. Dillworth, and J.A. Turner. 2014. Cognitive-behavioral therapy for individuals with chronic pain: Efficacy, innovations, and directions for research. *American Psychologist* 69(2):153-166.

Eilers, H., L.A. Philip, P.E. Bickler, W.R. McKay, and M.A. Schumacher. 2001. The reversal of fentanyl-induced tolerance by administration of "small-dose" ketamine. *Anesthesia and Analgesia* 93(1):213-214.

Eisenach, J.C., C. Tong, and R.S. Curry. 2015. Failure of intrathecal ketorolac to reduce remifentanil-induced postinfusion hyperalgesia in humans. *Pain* 156(1):81-87.

Elia, N., and M.R. Tramer. 2005. Ketamine and postoperative pain—A quantitative systematic review of randomised trials. *Pain* 106(6):1856-1861.

Elman, I., D. Borsook, and N.D. Volkow. 2013. Pain and suicidality: Insights from reward and addiction neuroscience. *Progress in Neurobiology* 109:1-27.

ElSohly, M.A., and W. Gul. 2014. *Handbook of cannabis (Chapter 2)*. Oxford, UK: Oxford University Press.

Enck, P., F. Benedetti, and M. Schedlowski. 2008. New insights into the placebo and nocebo responses. *Neuron* 59(2):195-206.

Eriksen, J., P. Sjogren, E. Bruera, O. Ekholm, and N.K. Rasmussen. 2006. Critical issues on opioids in chronic non-cancer pain: An epidemiological study. *Pain* 125(1-2):172-179.

Evoy, K.E., M.D. Morrison, and S.R. Saklad. 2017. Abuse and misuse of pregabalin and gabapentin. *Drugs* 77(4):403-426.

Farag, E., M. Ghobrial, D.I. Sessler, J.E. Dalton, J. Liu, J.H. Lee, S. Zaky, E. Benzel, W. Bingaman, and A. Kurz. 2013. Effect of perioperative intravenous lidocaine administration on pain, opioid consumption, and quality of life after complex spine surgery. *Anesthesiology* 119(4):932-940.

FDA (U.S. Food and Drug Administration). 2016. *FDA briefing document. Joint meeting of Anesthetic and Analgesic Drug Products Advisory Committee and Drug Safety and Risk Management Advisory Committee*. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM498784.pdf (accessed February 2, 2017).

Fields, H.L., and E.B. Margolis. 2015. Understanding opioid reward. *Trends in Neurosciences* 38(4):217-225.

Fillingim, R.B., C.D. King, M.C. Ribeiro-Dasilva, B. Rahim-Williams, and J.L. Riley III. 2009. Sex, gender, and pain: A review of recent clinical and experimental findings. *The Journal of Pain* 10(5):447-485.

Fine, P.G. 2011. Long-term consequences of chronic pain: Mounting evidence for pain as a neurological disease and parallels with other chronic disease states. *Pain Medicine* 12(7):996-1004.

Finnerup, N.B., N. Attal, S. Haroutounian, E. McNicol, R. Baron, R.H. Dworkin, I. Gilron, M. Haanpaa, P. Hansson, T.S. Jensen, P.R. Kamerman, K. Lund, A. Moore, S.N. Raja, A.S. Rice, M. Rowbotham, E. Sena, P. Siddall, B.H. Smith, and M. Wallace. 2015. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurology* 14(2):162-173.

Finniss, D.G., T.J. Kaptchuk, F. Miller, and F. Benedetti. 2010. Biological, clinical, and ethical advances of placebo effects. *Lancet* 375(9715):686-695.

Fishbain, D.A., R. Cutler, H.L. Rosomoff, and R.S. Rosomoff. 1997. Chronic pain-associated depression: Antecedent or consequence of chronic pain? A review. *The Clinical Journal of Pain* 13(2):116-137.

Fishman, S.M., P.G. Kreis, and R.N. Jamison. 2002a. The opioid contract. *The Clinical Journal of Pain* 18(4 Suppl.):S70-S75.

Fishman, S.M., G. Mahajan, S.W. Jung, and B.L. Wilsey. 2002b. The trilateral opioid contract. Bridging the pain clinic and the primary care physician through the opioid contract. *Journal of Pain Symptom Management* 24(3):335-344.

Fitzgerald, D.J., and G.A. FitzGerald. 2013. Historical lessons in translational medicine: Cyclooxygenase inhibition and P2Y12 antagonism. *Circulation Research* 112(1):174-194.

Fletcher, D., and V. Martinez. 2014. Opioid-induced hyperalgesia in patients after surgery: A systematic review and a meta-analysis. *British Journal of Anaesthesia* 112(6):991-1004.

Fontana, R.J. 2008. Acute liver failure including acetaminophen overdose. *Medical Clinics of North America* 92(4):761-794.

Foster, J.M., and B.P. Sweeney. 1987. The mechanisms of acupuncture analgesia. *British Journal of Hospital Medicine* 38(4):308-312.

Frank, J.W., C. Levy, D.D. Matlock, S.L. Calcaterra, S.R. Mueller, S. Koester, and I.A. Binswanger. 2016. Patients' perspectives on tapering of chronic opioid therapy: A qualitative study. *Pain Medicine* 17(10):1838-1847.

Fransen, M., S. McConnell, G. Hernandez-Molina, and S. Reichenbach. 2014. Exercise for osteoarthritis of the hip. *Cochrane Database of Systematic Reviews* 4:CD007912.

Freburger, J.K., G.M. Holmes, R.P. Agans, A.M. Jackman, J.D. Darter, A.S. Wallace, L.D. Castel, W.D. Kalseek, and T.S. Carey. 2009. The rising prevalence of chronic low back pain. *Archives of Internal Medicine* 169(3):251-258.

Frenk, S.M., K.S. Porter, and L.J. Paulozzi. 2015. *Prescription opioid analgesic use among adults: United States, 1999–2012*. NCHS Data Brief No. 189. https://www.cdc.gov/nchs/data/dataBriefs/db189.pdf (accessed September 13, 2017).

Friedly, J., L. Chan, and R. Deyo. 2007. Increases in lumbosacral injections in the Medicare population. *Spine* 32(16):1754-1760.

Friedman, B.W., A.A. Dym, M. Davitt, L. Holden, C. Solorzano, D. Esses, P.E. Bijur, and J. Gallagher. 2015. Naproxen with cyclobenzaprine, oxycodone/acetaminophen, or placebo for treating acute low back pain: A randomized clinical trial. *Journal of the American Medical Association* 314(15):1572-1580.

Furlan, A.D., M. van Tulder, D. Cherkin, H. Tsukayama, L. Lao, B. Koes, and B. Berman. 2005. Acupuncture and dry-needling for low back pain: An updated systematic review within the framework of the Cochrane collaboration. *Spine (Philadelphia, PA 1976)* 30(8):944-963.

Furlan, A.D., L.E. Chaparro, E. Irvin, A. Mailis-Gagnon. 2011. A comparison between enriched and non-enriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain. *Pain Research and Management* 16(5):337-351.

Furlan, A.D., M. Giraldo, A. Baskwill, E. Irvin, and M. Imamura. 2015. Massage for low-back pain. *Cochrane Database of Systematic Reviews* (9):CD001929.

Gaskell, H., S. Derry, C. Stannard, and R.A. Moore. 2016. Oxycodone for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 7:CD010692.

Gerbershagen, H.J., E. Pogatzki-Zahn, S. Aduckathil, L.M. Peelen, T.H. Kappen, A.J. van Wijck, C.J. Kalkman, and W. Meissner. 2014. Procedure-specific risk factor analysis for the development of severe postoperative pain. *Anesthesiology* 120(5):1237-1245.

Gerner, P., A.E. Haderer, M. Mujtaba, Y. Sudoh, S. Narang, S. Abdi, V. Srinivasa, C. Pertl, and G.K. Wang. 2003. Assessment of differential blockade by amitriptyline and its n-methyl derivative in different species by different routes. *Anesthesiology* 98(6):1484-1490.

Gibbons, K., A. DeMonbrun, E.J. Beckman, P. Keefer, D. Wagner, M. Stewart, D. Saul, S. Hakel, M. Liu, and M. Niedner. 2016. Continuous lidocaine infusions to manage opioid-refractory pain in a series of cancer patients in a pediatric hospital. *Pediatric Blood & Cancer* 63(7):1168-1174.

Gillman, P.K. 2007. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. *British Journal of Pharmacology* 151(6):737-748.

Gilron, I., J.M. Bailey, D. Tu, R.R. Holden, A.C. Jackson, and R.L. Houlden. 2009. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: A double-blind, randomised controlled crossover trial. *Lancet* 374(9697):1252-1261.

Gilron, I., T.S. Jensen, and A.H. Dickenson. 2013. Combination pharmacotherapy for management of chronic pain: From bench to bedside. *The Lancet Neurology* 12(11):1084-1095.

Goldenberg, D.L. 2016. Is there evidence for any truly effective therapy in fibromyalgia? *Pain Management* 6(4):325-329.

Gondim, D.V., J.C.B. Araujo, A.L. Cavalcante, A. Havt, J. da Siva Quetz, G.A. de Castro Brito, R. de Albuquerque Ribeiro, and M. Lima Vale. 2012. CB1 and CB2 contribute to antinociceptive and anti-inflammatory effects of electroacupuncture on experimental arthritis of the rat temporomandibular joint. *Canadian Journal of Physiology and Pharmacology* 90(11):1479-1489.

Goodman, L.S., J.G. Hardman, L.E. Limbird, and A.G. Gilman. 2001. *Goodman & Gilman's: The pharmacological basis of therapeutics*. New York: McGraw-Hill.

Gourlay, D.L., H.A. Heit, and A. Almahrezi. 2005. Universal precautions in pain medicine: A rational approach to the treatment of chronic pain. *Pain Medicine* 6(2):107-112.

Goyal, M.K., N. Kuppermann, S.D. Cleary, S.J. Teach, and J.M. Chamberlain. 2015. Racial disparities in pain management of children with appendicitis in emergency departments. *JAMA Pediatrics* 169(11):996-1002.

Graff-Radford, S.B., L.R. Shaw, and B.N. Naliboff. 2000. Amitriptyline and fluphenazine in the treatment of postherpetic neuralgia. *The Clinical Journal of Pain* 16(3):188-192.

Grosser, T., Y. Yu, and G.A. FitzGerald. 2010. Emotion recollected in tranquility: Lessons learned from the COX-2 saga. *Annual Review of Medicine* 61:17-33.

Guay, J. 2006. The benefits of adding epidural analgesia to general anesthesia: A metaanalysis. *Journal of Anesthesia* 20(4):335-340.

Haanpää, M.L., M.M. Backonja, M.I. Bennett, D. Bouhassira, G. Cruccu, P.T. Hansson, T.S. Jensen, T. Kauppila, A.S. Rice, B.H. Smith, R.D. Treede, and R. Baron. 2009. Assessment of neuropathic pain in primary care. *American Journal of Medicine* 122(10 Suppl.):S13-S21.

Hadley, G., S. Derry, R.A. Moore, and P.J. Wiffen. 2013. Transdermal fentanyl for cancer pain. *Cochrane Database of Systematic Reviews* 10:CD010270.

Hah, J.M., Y. Sharifzadeh, B.M. Wang, M.J. Gillespie, S.B. Goodman, S.C. Mackey, and I.R. Carroll. 2015. Factors associated with opioid use in a cohort of patients presenting for surgery. *Pain Research and Treatment* 2015:829696.

Hameroff, S.R., J.L. Weiss, J.C. Lerman, R.C. Cork, K.S. Watts, B.R. Crago, C.P. Neuman, J.R. Womble, and T.P. Davis. 1984. Doxepin's effects on chronic pain and depression: A controlled study. *Journal of Clinical Psychiatry* 45(3 Pt. 2):47-53.

Hamon, M., H. Gozlan, S. Bourgoin, J.J. Benoliel, A. Mauborgne, H. Taquet, F. Cesselin, and J.A. Mico. 1987. Opioid receptors and neuropeptides in the CNS in rats treated chronically with amoxapine or amitriptyline. *Neuropharmacology* 26(6):531-539.

Hanada, R., A. Leibbrandt, T. Hanada, S. Kitaoka, T. Furuyashiki, H. Fujihara, J. Trichereau, M. Paolino, F. Qadri, R. Plehm, S. Klaere, V. Komnenovic, H. Mimata, H. Yoshimatsu, N. Takahashi, A. von Haeseler, M. Bader, S.S. Kilic, Y. Ueta, C Pifl, S. Narumiya, and J.M. Penninger. 2009. Central control of fever and female body temperature by RANKL/RANK. *Nature* 462(7272):505-509.

Hariharan, J., G.C. Lamb, and J.M. Neuner. 2007. Long-term opioid contract use for chronic pain management in primary care practice. A five year experience. *Journal of General Internal Medicine* 22(4):485-490.

Hassenbusch, S.J., S. Gunes, S. Wachsman, and K.D. Willis. 2002. Intrathecal clonidine in the treatment of intractable pain: A phase I/II study. *Pain Medicine* 3(2):85-91.

Hauser, W., P. Klose, J. Langhorst, B. Moradi, M. Steinbach, M. Schiltenwolf, and A. Busch. 2010. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: A systematic review and meta-analysis of randomised controlled trials. *Arthritis Research & Therapy* 12(3):R79.

Hauser, W., F. Petzke, L. Radbruch, and T.R. Tolle. 2016. The opioid epidemic and the long-term opioid therapy for chronic noncancer pain revisited: A transatlantic perspective. *Pain Management* 6(3):249-263.

Havens, J. 2016. Prescription Drug Abuse in Rural Appalachia: Ushering in the Next Decade of the Epidemic. Presentation to the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse, Washington, DC. September 22.

Hayashida, K., S. DeGoes, R. Curry, and J.C. Eisenach. 2007. Gabapentin activates spinal noradrenergic activity in rats and humans and reduces hypersensitivity after surgery. *Anesthesiology* 106(3):557-562.

Hayden, J.A., M.W. van Tulder, A. Malmivaara, and B.W. Koes. 2005. Exercise therapy for treatment of non-specific low back pain. *Cochrane Database of Systematic Reviews* 3:CD000335.

Hersh, E.V., S. Cooper, N. Betts, D. Wedell, K. MacAfee, P. Quinn, C. Lamp, G. Gaston, S. Bergman, and E. Henry. 1993. Single dose and multidose analgesic study of ibuprofen and meclofenamate sodium after third molar surgery. *Oral Surgery, Oral Medicine, and Oral Pathology* 76(6):680-687.

HHS (U.S. Department of Health and Human Services). 2016. *Health, United States, 2015: With special feature on racial and ethnic health disparities*. Hyattsville, MD: CDC, National Center for Health Statistics. https://www.cdc.gov/nchs/data/hus/hus15.pdf (accessed April 23, 2017).

Hilton, L., S. Hempel, B.A. Ewing, E. Apaydin, L. Xenadis, S. Newberry, B. Colaiaco, A. Ruelaz Maheer, R.M. Shanman, M.E. Sorbero, and M.A. Maglione. 2017. Mindfulness meditation for chronic pain: Systematic review and meta-analysis. *Annals of Behavioral Medicine* 51(2):199-213.

Hoffman, K.M., S. Trawalter, J.R. Axt, and M.N. Oliver. 2016. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proceedings of the National Academy of Sciences of the United States of America* 113(16):4296-4301.

Hollingshead, N.A., L. Ashburn-Nardo, J.C. Stewart, and A.T. Hirsh. 2016. The pain experience of Hispanic Americans: A critical literature review and conceptual model. *The Journal of Pain* 17(5):513-528.

Hootman, J.M., C.G. Helmick, K.E. Barbour, K.A. Theis, and M.A. Boring. 2016. Updated projected prevalence of self-reported doctor-diagnosed arthritis and arthritis-attributable activity limitation among U.S. adults, 2015-2040. *Arthritis & Rheumatology* 68(7):1582-1587.

Howden, L.M., and J.A. Meyer. 2011. *Age and sex composition, 2010. 2010 Census Briefs*. https://www.census.gov/prod/cen2010/briefs/c2010br-03.pdf (accessed April 17, 2017).

Howick, J., F.L. Bishop, C. Heneghan, J. Wolstenholme, S. Stevens, F.D. Hobbs, and G. Lewith. 2013. Placebo use in the United Kingdom: Results from a national survey of primary care practitioners. *PLoS One* 8(3):e58247.

Howlett, A.C. 2002. The cannabinoid receptors. *Prostaglandins & Other Lipid Mediators* 68-69:619-631.

Hutchinson, M.R., Y. Zhang, K. Brown, B.D. Coats, M. Shridhar, P.W. Sholar, S.J. Patel, N.Y. Crysdale, J.A. Harrison, S.F. Maier, K.C. Rice, and L.R. Watkins. 2008. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: Involvement of toll-like receptor 4 (TLR4). *European Journal of Neuroscience* 28(1):20-29.

Huxtable, C.A., L.J. Roberts, A. Somogyi, and P.E. Macintyre. 2011. Acute pain management in opioid-tolerant patients: A growing challenge. *Anaesthesia and Intensive Care* 39(5):804-823.

Iacovides, A., and M. Siamouli. 2008. Comorbid mental and somatic disorders: An epidemiological perspective. *Current Opinion in Psychiatry* 21(4):417-421.

IOM (Institute of Medicine). 2010. *Clinical data as the basic staple of health learning: Creating and protecting a public good: Workshop summary*. Washington, DC: The National Academies Press.

IOM. 2011. *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington, DC: The National Academies Press.

Ives, T.J., P.R. Chelminski, C.A. Hammett-Stabler, R.M. Malone, J.S. Perhac, N.M. Potisek, B.B. Shilliday, D.A. DeWalt, and M.P. Pignone. 2006. Predictors of opioid misuse in patients with chronic pain: A prospective cohort study. *BMC Health Services Research* 6:46.

Jansen, M.J., W. Viechtbauer, A.F. Lenssen, E.J. Hendriks, and R.A. de Bie. 2011. Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: A systematic review. *Journal of Physiotherapy* 57(1):11-20.

Jenkins, R.W., K. McDonald, and C.S. Greenberg. 2012. Numb chin syndrome in acute myeloid leukemia. *The American Journal of the Medical Sciences* 344(3):237-240.

Johannes, C., T.K. Le, X. Zhou, J.A. Johnson, and R.H. Dworkin. 2010. The prevalence of chronic pain in United States adults: Results of an Internet-based survey. *The Journal of Pain* 11(11):1230-1239.

Jukkala, A.M., S.J. Henly, and L.L. Lindeke. 2008. Rural perceptions of continuing professional education. *Journal of Continuing Education in Nursing* 39(12):555-563.

Kabat-Zinn, J. 2003. Mindfulness-based interventions in context: Past, present, and future. *Clinical Psychology Science and Practice* 10(2):144-156.

Kahan, M., L. Wilson, A. Mailis-Gagnon, and A. Srivastava. 2011. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: Clinical summary for family physicians. Part 2: Special populations. *Canadian Family Physician* 57(11):1269-1276, e419-e428.

Kalauokalani, D., D.C. Cherkin, K.J. Sherman, T.D. Koepsell, and R.A. Deyo. 2001. Lessons from a trial of acupuncture and massage for low back pain: Patient expectations and treatment effects. *Spine (Philadelphia, PA 1976)* 26(13):1418-1424.

Kalso, E., J.E. Edwards, R.A. Moore, and H.J. McQuay. 2004. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain* 112(3):372-380.

Kamper, S.J., A.T. Apeldoorn, A. Chiarotto, R.J. Smeets, R.W. Ostelo, J. Guzman, and M.W. van Tulder. 2015. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. *British Medical Journal* 350:h444.

Kandil, E., E. Melikman, and B. Adinoff. 2017. Lidocaine infusion: A promising therapeutic approach for chronic pain. *Journal of Anesthesia & Clinical Research* 8(1):pii:697.

Kantor, T.G., A. Sunshine, F. Laska, M. Meisner, and M. Hopper. 1966. Oral analgesic studies: Pentazocine hydrochloride, codeine, aspirin, and placebo and their influence on response to placebo. *Clinical Pharmacology and Therapeutics* 7(4):447-454.

Kaptchuk, T.J., and F.G. Miller. 2015. Placebo effects in medicine. *New England Journal of Medicine* 373(1):8-9.

Kapural, L., C. Yu, M.W. Doust, B.E. Gliner, R. Vallejo, B.T. Stitzman, K. Amirdelfan, D.M. Morgan, T.L. Yearwood, R. Bundschu, T. Yang, R. Benyamin, and A.H. Burgher. 2016. Comparison of 10-kHz high-frequency and traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: 24-month results from a multicenter, randomized, controlled pivotal trial. *Neurosurgery* 79(5):1-10.

Karila, L., P. Roux, B. Rolland, A. Benyamina, M. Reynaud, H.J. Aubin, and C. Lancon. 2014. Acute and long-term effects of cannabis use: A review. *Current Pharmaceutical Design* 20(25):4112-4118.

Keyes, K.M., M. Cerda, J.E. Brady, J.R. Havens, and S. Galea. 2014. Understanding the rural-urban differences in nonmedical prescription opioid use and abuse in the United States. *American Journal of Public Health* 104(2):e52-e59.

Kim, S.C., J.E. Landon, and D.H. Solomon. 2013. Clinical characteristics and medication uses among fibromyalgia patients newly prescribed amitriptyline, duloxetine, gabapentin, or pregabalin. *Arthritis Care & Research* 65(11):1813-1819.

Klimscha, W., C. Tong, and J.C. Eisenach. 1997. Intrathecal alpha 2-adrenergic agonists stimulate acetylcholine and norepinephrine release from the spinal cord dorsal horn in sheep. An in vivo microdialysis study. *Anesthesiology* 87(1):110-116.

Knoerl, R., E.M. Lavoie Smith, and J. Weisberg. 2016. Chronic pain and cognitive behavioral therapy: An integrative review. *Western Journal of Nursing Research* 38(5):596-628.

Koele, R., G. Volker, F. van Vree, M. van Gestel, A. Koke, and T. Vliet Vlieland. 2014. Multidisciplinary rehabilitation for chronic widespread musculoskeletal pain: Results from daily practice. *Musculoskeletal Care* 12(4):210-220.

Kolodny, A., D. T. Courtwright, C. S. Hwang, P. Kreiner, J. L. Eadie, T.W. Clark, and G.C. Alexander. 2015. The prescription opioid and heroin crisis: A public health approach to an epidemic of addiction. *Annual Review of Public Health* 36:559-574.

Kong, J., R. Spaeth, A. Cook, I. Kirsch, B. Claggett, M. Vangel, R.L. Gollub, J.W. Smoller, and T.J. Kaptchuk. 2013. Are all placebo effects equal? Placebo pills, sham acupuncture, cue conditioning and their association. *PLoS One* 8(7):e67485.

Kong, L.J., R. Lauche, P. Klose, J.H. Bu, X.C. Yang, C.Q. Guo, G. Dobos, and Y.W. Cheng. 2016. Tai chi for chronic pain conditions: A systematic review and meta-analysis of randomized controlled trials. *Scientific Reports* 6:25325.

Koob, G.F. 2008. A role for brain stress systems in addiction. *Neuron* 59(1):11-34.

Kort, M.E., I. Drizin, R.J. Gregg, M.J. Scanio, L. Shi, M.F. Gross, R.N. Atkinson, M.S. Johnson, G.J. Pacofsky, J.B. Thomas, W.A. Carroll, M.J. Krambis, D. Liu, CC. Shieh, X. Zhang, G. Hernandez, J.P. Mikusa, C. Zhong, S. Joshi, P. Honore, R. Roeloffs, K.C. Marsh, B.P. Murray, J. Liu, S. Werness, C.R. Faltynek, D.S. Krafte, M.F. Jarvis, M.L. Chapman, and B.E. Marron. 2008. Discovery and biological evaluation of 5-aryl-2-furfuramides, potent and selective blockers of the Nav1.8 sodium channel with efficacy in models of neuropathic and inflammatory pain. *Journal of Medicinal Chemistry* 51(3):407-416.

Kosharskyy, B., W. Almonte, N. Shaparin, M. Pappagallo, and H. Smith. 2013. Intravenous infusions in chronic pain management. *Pain Physician* 16(3):231-249.

Krames, E., L.R. Poree, R. Deer, and R. Levy. 2009. Rethinking algorithms of pain care: The use of S.A.F.E. Principles. *Pain Medicine* 10(1):1-5.

Kranke, P., J. Jokinen, N.L. Pace, A. Schnabel, M.W. Hollmann, K. Hahnenkamp, L.H. Eberhart, D.M. Poepping, and S. Weibel. 2015. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. *Cochrane Database of Systematic Reviews* 7:CD009642.

Krashin, D., N. Murinova, and M. Sullivan. 2016. Challenges to treatment of chronic pain and addiction during the "opioid crisis." *Current Pain and Headache Reports* 20(12):65.

Kroll, H.R. 2015. Exercise therapy for chronic pain. *Physical Medicine and Rehabilitation Clinics of North America* 26(2):263-281.

Kumar, K., and S. Rizvi. 2013. Cost-effectiveness of spinal cord stimulation therapy in management of chronic pain. *Pain Medicine* 14(11):1631-1649.

Kurita, G.P., and P. Sjogren. 2015. Pain management in cancer survivorship. *Acta Oncologica (Stockholm, Sweden)* 54(5):629-634.

Lance, J.W., and D.A. Curran. 1964. Treatment of chronic tension headache. *Lancet* 1(7345):1236-1239.

Langohr, H.D., M. Stohr, and F. Petruch. 1982. An open and double-blind cross-over study on the efficacy of clomipramine (Anafranil) in patients with painful mono- and polyneuropathies. *European Neurology* 21(5):309-317.

Lannersten, L., and E. Kosek. 2010. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. *Pain* 151(1):77-86.

Lanser, P., and S. Gesell. 2001. Pain management: The fifth vital sign. *Healthcare Benchmarks* 8(6):68-70.

Leary, J., and A. Swislocki. 2013. Hypothalamic-pituitary-adrenal suppression and iatrogenic Cushing's Syndrome as a complication of epidural steroid injections. *Case Reports in Endocrinology* 2013(4):617042.

Lee, C., C. Crawford, and S. Swann. 2014. Active Self-Care Therapies for Pain (PACT) Working Group. Multimodal, integrative therapies for the self-management of chronic pain symptoms. *Pain Medicine* 15(Suppl. 1):S76-S85.

Lee, M.S., B.C. Shin, and E. Ernst. 2008. Acupuncture for rheumatoid arthritis: A systematic review. *Rheumatology (Oxford)* 47(12):1747-1753.

Lee, T.H. 2016. Zero pain is not the goal. *Journal of the American Medical Association* 315(15):1575-1577.

Leknes, S., and I. Tracey. 2008. A common neurobiology for pain and pleasure. *Nature Reviews Neuroscience* 9(4):314-320.

Levine, J.D., N.C. Gordon, and H.L. Fields. 1978. The mechanism of placebo analgesia. *Lancet* 2(8091):654-657.

Levine, J.D., N.C. Gordon, R. Smith, and H.L. Fields. 1981. Analgesic responses to morphine and placebo in individuals with postoperative pain. *Pain* 10(3):379-389.

Levy, B., L. Paulozzi, K.A. Mack, and C.M. Jones. 2015. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007-2012. *American Journal of Preventive Medicine* 49(3):409-413.

Li, C.Y., X.L. Zhang, E.A. Matthews, K.W. Li, A. Kurwa, A. Boroujerdi, J. Gross, M.S. Gold, A.H. Dickenson, G. Feng, and Z.D. Lou. 2006. Calcium channel alpha2delta1 subunit mediates spinal hyperexcitability in pain modulation. *Pain* 125(1-2):20-34.

Li, J., D.A. Simone, and A.A. Larson. 1999. Windup leads to characteristics of central sensitization. *Pain* 79(1):75-82.

Li, Y.H,. F.Y. Wang, C.Q. Feng, X.F. Yang, and Y.H. Sun. 2014. Massage therapy for fibromyalgia: A systematic review and meta-analysis of randomized controlled trials. *PLoS One* 9(2):e89304.

Linde, K., G. Allais, B. Brinkhaus, E. Manheimer, A. Vickers, and A.R. White. 2009a. Acupuncture for migraine prophylaxis. *Cochrane Database of Systematic Reviews* 1:CD001218.

Linde, K., G. Allais, B. Brinkhaus, E. Manheimer, A. Vickers, and A.R. White. 2009b. Acupuncture for tension-type headache. *Cochrane Database of Systematic Reviews* 1:CD007587.

Linde, K., K. Niemann, and K. Meissner. 2010a. Are sham acupuncture interventions more effective than (other) placebos? A re-analysis of data from the Cochrane review on placebo effects. *Forschende Komplementarmedizin* 17(5):259-264.

Linde, K., K. Niemann, and K. Meissner. 2010b. How large are the nonspecific effects of acupuncture? A meta-analysis of randomized controlled trials. *BMC Medicine* 8:75.

Loftus, R.W., M.P. Yeager, J.A. Clark, J.R. Brown, W.A. Abdu, D.K. Sengupta, and M.L. Beach. 2010. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. *Anesthesiology* 113(3):639-646.

Lomazzo, E., L. Bindila, F. Remmers, R. Lerner, C. Schwitter, U. Hoheisel, and B. Lutz. 2015. Therapeutic potential of inhibitors of endocannabinoid degradation for the treatment of stress-related hyperalgesia in an animal model of chronic pain. *Neuropsychopharmacology* 40(2):488-501.

Lovick, T.A. 1993. Integrated activity of cardiovascular and pain regulatory systems: Role in adaptive behavioural responses. *Progress in Neurobiology* 40(5):631-644.

Luccarini, P., L. Perrier, C. Degoulange, A.M. Gaydier, and R. Dallel. 2004. Synergistic antinociceptive effect of amitriptyline and morphine in the rat orofacial formalin test. *Anesthesiology* 100(3):690-696.

Lunn, M.P., R.A. Hughes, and P.J. Wiffen. 2014. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database of Systematic Reviews* 1:CD007115.

Lynch, M.E., and M.A. Ware. 2015. Cannabinoids for the treatment of chronic non-cancer pain: An updated systematic review of randomized controlled trials. *Journal of Neuroimmune Pharmacology* 10(2):293-301.

Madsen, M.V., P.C. Gotzsche, and A. Hrobjartsson. 2009. Acupuncture treatment for pain: Systematic review of randomised clinical trials with acupuncture, placebo acupuncture, and no acupuncture groups. *British Medical Journal* 338:a3115.

Magni, G. 1991. The use of antidepressants in the treatment of chronic pain. A review of the current evidence. *Drugs* 42(5):730-748.

Manchikanti, L., R.M. Buenaventura, K.N. Manchikanti, X. Ruan, S. Gupta, H.S. Smith, P.J. Christo, and S.P. Ward. 2012. Effectiveness of therapeutic lumbar transforaminal epidural steroid injections in managing lumbar spinal pain. *Pain Physician* 15(3):E199-E245.

Manchikanti, L., V. Pampati, F.J.E. Falco, and J.A. Hirsch. 2013. Assessment of the growth of epidural injections in the Medicare population from 2000 to 2011. *Pain Physician* 16(4):E349-E364.

Mao, J. 2002. Opioid-induced abnormal pain sensitivity: Implications in clinical opioid therapy. *Pain* 100(3):213-217.

Martins, D.F., L. Mazzardo-Martins, F. Soldi, J. Stramosk, A.P. Piovezan, and A.R. Santos. 2013. High-intensity swimming exercise reduces neuropathic pain in an animal model of complex regional pain syndrome type I: Evidence for a role of the adenosinergic system. *Neuroscience* 234:69-76.

Mason, L., R.A. Moore, S. Derry, J.E. Edwards, and H.J. McQuay. 2004. Systematic review of topical capsaicin for the treatment of chronic pain. *British Medical Journal* 328(7446):991.

Maughan, B.C., M.A. Bachhuber, N. Mitra, J.L. Starrels. 2015. Prescription monitoring programs and emergency department visits involving opioids, 2004–2011. *Drug and Alcohol Dependence* 156:282-288.

Max, M.B., M. Culnane, S.C. Schafer, R.H. Gracely, D.J. Walther, B. Smoller, and R. Dubner. 1987. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology* 37(4):589-596.

McCarson, K.E., V. Duric, S.A. Reisman, M. Winter, and S.J. Enna. 2006. GABA(B) receptor function and subunit expression in the rat spinal cord as indicators of stress and the antinociceptive response to antidepressants. *Brain Research* 1068(1):109-117.

McGreevy, K., M.M. Bottros, and S.N. Raja. 2011. Preventing chronic pain following acute pain: Risk factors, preventive strategies, and their efficacy. *European Journal of Pain Supplement* 5(2):365-372.

McLellan, A.T., and B. Turner. 2010. Chronic noncancer pain management and opioid overdose: Time to change prescribing practices. *Annals of Internal Medicine* 152(2):123-124.

McNicol, E.D., A. Midbari, and E. Eisenberg. 2013. Opioids for neuropathic pain. *Cochrane Database of Systematic Reviews* 8:CD006146.

Miaskowski, C., R.W. Gear, and J.D. Levine. 2000. Sex-related differences in analgesic responses. In *Sex, gender, and pain*, edited by R.B. Fillingim. Seattle, WA: IASP Press.

Mick, G., and G. Correa-Illanes. 2012. Topical management with the 5% lidocaine medicated plaster—A review. *Current Medical Research and Opinion* 28(6):937-951.

Mitrirattanakul, S., N. Ramakul, A.V. Guerrero, Y. Matsuka, T. Ono, H. Iwase, K. Mackie, K.F. Faull, and I. Spigelman. 2006. Site-specific increases in peripheral cannabinoid receptors and their endogenous ligands in a model of neuropathic pain. *Pain* 126(1-3):102-114.

Mohamed, S.A., K.M. Fares, A.A. Mohamed, and N.H. Alieldin. 2014. Dexmedetomidine as an adjunctive analgesic with bupivacaine in paravertebral analgesia for breast cancer surgery. *Pain Physician* 17(5):E589-E598.

Monterubbianesi, M.C., J. Capuccini, I. Ferioli, D. Tassinari, D. Sarti, and W. Raffaeli. 2012. High opioid dosage rapid detoxification of cancer patient in palliative care with the Raffaeli model. *Journal of Opioid Management* 8(5):292-298.

Mooney, J.J., P.S. Pagel, and A. Kundu. 2014. Safety, tolerability, and short-term efficacy of intravenous lidocaine infusions for the treatment of chronic pain in adolescents and young adults: A preliminary report. *Pain Medicine* 15(5):820-825.

Moore, P.A., and E.V. Hersh. 2013. Combining ibuprofen and acetaminophen for acute pain management after third-molar extractions: Translating clinical research to dental practice. *Journal of the American Dental Association* 144(8):898-908.

Moore, P.A., H.S. Nahouraii, J.G. Zovko, and S.R. Wisniewski. 2006a. Dental therapeutic practice patterns in the U.S. I. Anesthesia and sedation. *General Dentistry* 54(2):92-98.

Moore, P.A., H.S. Nahouraii, J.G. Zovko, and S.R. Wisniewski. 2006b. Dental therapeutic practice patterns in the U.S. II. Analgesics, corticosteroids, and antibiotics. *General Dentistry* 54(3):201-207.

Moore, R.A., S. Derry, D. Aldington, P. Cole, and P.J. Wiffen. 2012. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database of Systematic Reviews* 12:CD008242.

Moore, R.A., P.J. Wiffen, S. Derry, T. Maguire, Y.M. Roy, and L. Tyrrell. 2015. Non-prescription (OTC) oral analgesics for acute pain: An overview of Cochrane reviews. *Cochrane Database of Systematic Reviews* 11:CD010794.

Moraso, B.J., J.P. Duckart, T.P. Carr, R.A. Deyo, and S.K. Dobscha. 2010. Clinical characteristics of veterans prescribed high doses of opioid medications for chronic non-cancer pain. *Pain* 151(3):625-632.

Morley, S., C. Eccleston, and A. Williams. 1999. Systematic review and meta-analysis of randomized controlled trials of cognitive behaviour therapy and behaviour therapy for chronic pain in adults, excluding headache. *Pain* 80(1999):1-13.

Morton, D.L., A. Watson, W. El-Deredy, and A.K. Jones. 2009. Reproducibility of placebo analgesia: Effect of dispositional optimism. *Pain* 146(1-2):194-198.

Morton, D.L., W. El-Deredy, A. Watson, and A.K. Jones. 2010. Placebo analgesia as a case of a cognitive style driven by prior expectation. *Brain Research* 1359:137-141.

Mossey, J.M. 2011. Defining racial and ethnic disparities in pain management. *Clinical Orthopaedics and Related Research* 469(7):1859-1870.

Mou, J.F. Paillard, B. Turnbull, J. Trudeau, M. Stoker, and N.P. Katz. 2013. Efficacy of Qutenza® (capsaicin) 8% patch for neuropathic pain: A meta-analysis of the Qutenza Clinical Trials Database. *Pain* 154(9):1632-1639.

Mudumbai, S.C., E.M. Oliva, E.T. Lewis, J. Trafton, D. Posner, E.R. Mariano, R.S. Stafford, T. Wagner, and J.D. Clark. 2016. Time-to-cessation of postoperative opioids: A population-level analysis of the Veterans Affairs Health Care System. *Pain Medicine* 17(9):1732-1743.

Nahin, R.L. 2015. Estimates of pain prevalence in severity in adults: United States, 2012. *The Journal of Pain* 16(8):769-780.

NASEM (National Academies of Sciences, Engineering, and Medicine). 2017. *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. Washington, DC: The National Academies Press.

Navratilova, E., J.Y. Xie, A. Okun, C. Qu, N. Eyde, S. Ci, M.H. Ossipov, T. King, H.L. Fields, and F. Porreca. 2012. Pain relief produces negative reinforcement through activation of mesolimbic reward-valuation circuitry. *Proceedings of the National Academy of Sciences of the United States of America* 109(50):20709-20713.

Navratilova, E., J.Y. Xie, D. Meske, C. Qu, K. Morimura, A. Okun, N. Arakawa, M. Ossipov, H.L. Fields, and F. Porreca. 2015. Endogenous opioid activity in the anterior cingulate cortex is required for relief of pain. *Journal of Neuroscience* 35(18):7264-7271.

NCHS (National Center on Health Statistics). 2016. *National overdose deaths from select prescription and illicit drugs*. CDC WONDER.

Niesters, M., and A. Dahan. 2012. Pharmacokinetic and pharmacodynamic considerations for NMDA receptor antagonists in the treatment of chronic neuropathic pain. *Expert Opinion in Drug Metabolism & Toxicology* 8(11):1409-1417.

Niesters, M., A. Dahan, B. Kest, J. Zacny, T. Stijnen, L. Aarts, and E. Sarton. 2010. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. *Pain* 151(1):61-68.

Nir, R.R., H. Nahman-Averbuch, R. Moont, E. Sprecher, and D. Yarnitsky. 2016. Preoperative preemptive drug administration for acute postoperative pain: A systematic review and meta-analysis. *European Journal of Pain* 20(7):1025-1043.

O'Brien, E.M., R.M. Staud, A.D. Hassinger, R.C. McCulloch, J.G. Craggs, J.W. Atchison, D.D. Price, and M.E. Robinson. 2010. Patient-centered perspective on treatment outcomes in chronic pain. *Pain Medicine* 11(1):6-15.

O'Connor, S.R., M.A. Tully, B. Ryan, C.M. Bleakley, G.D. Baxter, J.M. Bradley, and S.M. McDonough. 2015. Walking exercise for chronic musculoskeletal pain: Systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation* 96(4):724-734.

Okunseri, C., E. Okunseri, Q. Xiang, J.M. Thorpe, and A. Szabo. 2014. Prescription of opioid and nonopioid analgesics for dental care in emergency departments: Findings from the National Hospital Ambulatory Medical Care Survey. *Journal of Public Health Dentistry* 74(4):283-292.

O'Neil, M., and K.L. Hannah. 2010. Understanding the cultures of prescription drug abuse, misuse, addiction, and diversion. *The West Virginia Medical Journal* 106(4 Spec. No.): 64-70.

Ossipov, M.H., Y. Lopez, D. Bian, M.L. Nichols, and F. Porreca. 1997. Synergistic antinociceptive interactions of morphine and clonidine in rats with nerve-ligation injury. *Anesthesiology* 86(1):196-204.

Osterberg, L., and T. Blaschke. 2005. Adherence to medication. *New England Journal of Medicine* 353(5):487-497.

Paice, J.A., C. Lacchetti, T. Campbell, A. Cheville, M. Citron, L.S. Constine, A. Cooper, P. Glare, F. Keefe, L. Koyyalagunta, M. Levy, C. Miaskowski, S. Otis-Green, P. Sloan, and E. Bruera. 2016. Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *Journal of Clinical Oncology* 34(27):3325-3345.

Paley, C.A., M.I. Johnson, O.A. Tashani, and A.M. Bagnall. 2015. Acupuncture for cancer pain in adults. *Cochrane Database of Systematic Reviews* 10:CD007753.

Palmer, R.E., D.S. Carrell, D. Cronkite, K. Saunders, D.E. Gross, E. Masters, S. Donevan, T.R. Hylan, and M. VonKroff. 2015. The prevalence of problem opioid use in patients receiving chronic opioid therapy: Computer-assisted review of electronic health record clinical notes. *Pain* 156(7):1208-1214.

Pan, G. 2016. *Challenges in assessing real world use and abuse of pain medicines*. PowerPoint presentation, FDA Science Board meeting, March. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM489209.pdf (accessed April 17, 2017).

Patetsos, E., and E. Horjales-Araujo. 2016. Treating chronic pain with SSRIs: What do we know? *Pain Research and Management* 2016:2020915.

Payne, R., E. Anderson, R. Arnold, L. Duensing, A. Gilson, C. Green, C. Haywood, S. Passik, B. Rich, L. Robin, N. Shuler, and M. Christopher. 2010. A rose by any other name: Pain contracts/agreements. *The American Journal of Bioethics* 10(11):5-12.

Pedersen, L., P.C. Borchgrevink, I.I. Riphagen, and O.M. Fredheim. 2014. Long- or short-acting opioids for chronic non-malignant pain? A qualitative systematic review. *Acta Anaesthesiologica Scandinavia* 58(4):390-401.

Peixoto, R.D., and P. Hawley. 2015. Intravenous lidocaine for cancer pain without electrocardiographic monitoring: A retrospective review. *Journal of Palliative Medicine* 18(4):373-377.

Penko, J., J. Mattson, C. Miaskowski, and M. Kushel. 2012. Do patients know they are on pain medication agreements? Results from a sample of high-risk patients on chronic opioid therapy. *Pain Medicine* 13(9):1174-1180.

Persaud, N., and G.R. Strichartz. 2002. Micromolar lidocaine selectively blocks propogating ectopic impulses at a distance from their site of origin. *Pain* 99(1-2):333-340.

Persaud, R., G. Garas, S. Silva, C. Stamatoglou, P. Chatrath, and K. Patel. 2013. An evidence-based review of botulinum toxin (Botox) applications in non-cosmetic head and neck conditions. *JRSM Short Reports* 4(2):10.

Pirbudak, L., A. Sevinc, G. Maralcan, and E. Kilic. 2014. Pain management with intrathecal clonidine in a colon cancer patient with opioid hyperalgesia: Case presentation. *Agri* 26(2):93-96.

Pollo, A., M. Amanzio, A. Arslanian, C. Casadio, G. Maggi, and F. Benedetti. 2001. Response expectancies in placebo analgesia and their clinical relevance. *Pain* 93(1):77-84.

Poree, L., E. Krames, J. Pope, T.R. Deer, R. Levy, and L. Schultz. 2013. Spinal cord stimulation as treatment for complex regional pain syndrome should be considered earlier than last resort therapy. *Neuromodulation* 16(2):125-141.

Portenoy, R.K., C. Ugarte, I. Fuller, and G. Haas. 2004. Population-based survey of pain in the United States: Differences among white, African American, and Hispanic subjects. *The Journal of Pain* 5(6):317-328.

Preskorn, S.H., B. Baker, S. Kolluri, F.S. Menniti, M. Krams, and J.W. Landen. 2008. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective *N*-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *Journal of Clinical Psychopharmacology* 28(6):631-637.

Price, D.D., D.G. Finniss, and F. Benedetti. 2008. A comprehensive review of the placebo effect: Recent advances and current thought. *Annual Review of Psychology* 59:565-590.

Quill, T.E. 1983. Partnerships in patient care: A contractual approach. *Annals of Internal Medicine* 98(2):228-234.

Rasubala, L., L. Pernapati, X. Velasquez, J. Burk, and Y.F. Ren. 2015. Impact of a mandatory prescription drug monitoring program on prescription of opioid analgesics by dentists. *PLoS One* 10(8):e0135957.

Rathmell, J.P., H.T. Benzon, P. Dreyfuss, M. Huntoon, M. Wallace, R. Baker, K.D. Riew, R.W. Rosenquist, C. Aprill, N.S. Rost, A. Buvanendran, D.S. Kreiner, N. Bogduk, D.R. Fourney, E. Fraifeld, S. Horn, J. Stone, K. Vorenkamp, G. Lawler, J. Summers, D. Kloth, D. O'Brien, and S. Tutton. 2015. Safeguards to prevent neurologic complications after epidural steroid injections: Consensus opinions from a multidisciplinary working group and national organizations. *Anesthesiology* 122(5):974-984.

Ren, Z.Y., J. Shi, D.H. Epstein, J. Wang, and L. Lu. 2009. Abnormal pain response in pain-sensitive opiate addicts after prolonged abstinence predicts increased drug craving. *Psychopharmacology (Berlin)* 204(3):423-429.

Rhodin, A., M. Stridsberg, and T. Gordh. 2010. Opioid endocrinopathy: A clinical problem in patients with chronic pain and long-term oral opioid treatment. *Clinical Journal of Pain* 26(5):374-380.

Richardson, J.D., S. Kilo, and K.M. Hargreaves. 1998. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain* 75(1):111-119.

Riley, J.L., 3rd, B.A. Hastie, T.L. Glover, R.B. Fillingim, R. Staud, and C.M. Campbell. 2010. Cognitive-affective and somatic side effects of morphine and pentazocine: Side-effect profiles in healthy adults. *Pain Medicine* 11(2):195-206.

Ringwalt, C., H. Gugelmann, M. Garrettson, N. Dasgupta, A.E. Chung, S.K. Proescholdbell, and A.C. Skinner. 2014. Differential prescribing of opioid analgesics according to physician specialty for Medicaid patients with chronic noncancer pain diagnoses. *Pain Research and Management* 19(4):179-185.

Ringwalt, C., H. Gugelmann, and A.C. Skinner. 2015. Racial disparities across provider specialties in opioid prescriptions dispensed to Medicaid beneficiaries with chronic noncancer pain. *Pain Medicine* 16(4):633-640.

Robbins, W.R., P.S. Staats, J. Levine, H.L. Fields, R.W. Allen, J.N. Campbell, and M. Pappagallo. 1998. Treatment of intractable pain with topical large-dose capsaicin: Preliminary report. *Anesthesia and Analgesia* 86(3):579-583.

Rubin, D.I. 2007. Epidemiology and risk factors for spine pain. *Neurology Clinics* 25(2):353-371.

Rubinstein, S.M., M. van Middelkoop, W.J. Assendelft, M.R. de Boer, and M.W. van Tulder. 2011. Spinal manipulative therapy for chronic low-back pain. *Cochrane Database of Systematic Reviews* (2):CD008112.

Sacerdote, P., A. Brini, P. Mantegazza, and A.E. Panerai. 1987. A role for serotonin and beta-endorphin in the analgesia induced by some tricyclic antidepressant drugs. *Pharmacology, Biochemistry, and Behavior* 26(1):153-158.

SAMHSA (Substance Abuse and Mental Health Services Administration). 2015. *Treatment Episode Data Set (TEDS) 2003–2013. National Admissions to Substance Abuse Treatment Services.* https://www.samhsa.gov/data/sites/default/files/2003_2013_TEDS_National/2003_2013_Treatment_Episode_Data_Set_National.pdf (accessed January 10, 2017).

Sanders, R.D., and M. Maze. 2007. Alpha2-adrenoceptor agonists. *Current Opinion in Investigational Drugs* 8(1):25-33.

Sardar, K., M.A. Rashid, M.R. Khandoker, and A.N.M.N. Khan. 2016. Anticonvulsants and antidepressants in chronic pain management. *Journal of Recent Advances in Pain* 2(3):90-93.

Scascighini, L., V. Toma, S. Dober-Spielmann, and H. Sprott. 2008. Multidisciplinary treatment for chronic pain: A systematic review of interventions and outcomes. *Rheumatology (Oxford)* 47(5):670-678.

Schiltenwolf, M., M. Akbar, A. Hug, U. Pfuller, S. Gantz, E. Neubauer, H. Flor, and H. Wang. 2014. Evidence of specific cognitive deficits in patients with chronic low back pain under long-term substitution treatment of opioids. *Pain Physician* 17(1):9-20.

Schmader, K.E. 2002. Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. *Clinical Journal of Pain* 18(6):350-354.

Schmidt-Hansen, M., M.I. Bennett, S. Arnold, N. Bromham, and J.S. Hilgart. 2015. Oxycodone for cancer-related pain. *Cochrane Database of Systematic Reviews* 2:CD003870.

Schofferman, J., and G. Kine. 2004. Effectiveness of repeated radiofrequency neurotomy for lumbar facet pain. *Spine (Philadelphia, PA 1976)* 29(21):2471-2473.

Schumacher, M.A. 2010. Transient receptor potential channels in pain and inflammation: Therapeutic opportunities. *Pain Practice* 10(3):185-200.

Sehgal N., J. Colson, and H.S. Smith. 2013. Chronic pain treatment with opioid analgesics: Benefits versus harms of long-term therapy. *Expert Review in Neurotherapeutics* 13(11):1201-1220.

Semple, D.M., A.M. McIntosh, and S.M. Lawrie. 2005. Cannabis as a risk factor for psychosis: Systematic review. *Journal of Psychopharmacology* 19(2):187-194.

Simone, D.A., M. Nolano, T. Johnson, G. Wendelschafer-Crabb, and W.R. Kennedy. 1998. Intradermal injection of capsaicin in humans produces degeneration and subsequent reinnervation of epidermal nerve fibers: Correlation with sensory function. *Journal of Neuroscience* 18(21):8947-8959.

Sinatra, R. 2010. Causes and consequences of inadequate management of acute pain. *Pain Medicine* 11(12):1859-1871.

Sindrup, S.H., and T.S. Jensen. 1999. Efficacy of pharmacological treatments of neuropathic pain: An update and effect related to mechanism of drug action. *Pain* 83(3):389-400.

Singer, J.B., S. Lewitzky, E. Leroy, F. Yang, X. Zhao, L. Klickstein, T.M. Wright, J. Meyer, and C.A. Paulding. 2010. A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury. *Nature Genetics* 42(8):711-714.

Slater, H., A.M. Briggs, S. Bunzli, S.J. Davies, A.J. Smith, and J.L. Quintner. 2012. Engaging consumers living in remote areas of Western Australia in the self-management of back pain: A prospective cohort study. *BMC Musculoskeletal Disorders* 13:69.

Smith, C.A., M. Armour, X. Zhu, X. Li, Z.Y. Lu, and J. Song. 2016a. Acupuncture for dysmenorrhoea. *Cochrane Database of Systematic Reviews* 4:CD007854.

Smith, S.R., B.R. Deshpande, J.E. Collins, J.N. Katz, and E. Losina. 2016b. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: Systematic analytic review. *Osteoarthritis and Cartilage* 24(6):962-972.

Souzdalnitski, D., G.R. Rech, A. Naydinskiy, D. Suzdalnitskaya, R.V. Isakov, and M. Guirguis. 2014. Ketamine in perioperative analgesia for knee surgeries: Review of evidence from randomized controlled trials. *Techniques in Regional Anesthesia and Pain Management* 18(4):130-136.

Stagg, N.J., H.P. Mata, M.M. Ibrahim, E.J. Henriksen, F. Porreca, T.W. Vanderah, and T. Philip Malan. 2011. Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: Role of endogenous opioids. *Anesthesiology* 114(4):940-948.

Stewart, M.J., C.G. Maher, K.M. Refshauge, R.D. Herbert, N. Bogduk, and M. Nicholas. 2007. Randomized controlled trial of exercise for chronic whiplash-associated disorders. *Pain* 128(1-2):59-68.

Stoicea, N., D. Russell, G. Weidner, M. Durda, N.C. Joseph, J. Yu, and S.D. Bergese. 2015. Opioid-induced hyperalgesia in chronic pain patients and the mitigating effects of gabapentin. *Frontiers in Pharmacology* 6:104.

Sun, E.C., B.D. Darnall, L.C. Baker, and S. Mackey. 2016. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. *JAMA Internal Medicine* 176(9):1286-1293.

Tan, M., L.S. Law, and T.J. Gan. 2015a. Optimizing pain management to facilitate enhanced recovery after surgery pathways. *Canadian Journal of Anaesthesia* 62(2):203-218.

Tan, P.D., J.S. Barclay, and L.J. Blackhall. 2015b. Do palliative care clinics screen for substance abuse and diversion? Results of a national survey. *Journal of Palliative Medicine* 18(9):752-757.

Tanabe, M., K. Takasu, Y. Takeuchi, and H. Ono. 2008. Pain relief by gabapentin and pregabalin via supraspinal mechanisms after peripheral nerve injury. *Journal of Neuroscience Research* 86(15):3258-3264.

Tang, Y.Y., B.K. Holzel, and M.I. Posner. 2015. The neuroscience of mindfulness meditation. *Nature Reviews Neuroscience* 16(4):213-225.

Todd, K.H., C. Deaton, A.P. D'Adamo, and L. Goe. 2000. Ethnicity and analgesic practice. *Annals of Emergency Medicine* 35(1):11-16.

Trang, T., R. Al-Hasani, D. Salvemini, M.W. Salter, H. Gutstein, and C.M. Cahill. 2015. Pain and poppies: The good, the bad, and the ugly of opioid analgesics. *Journal of Neuroscience* 35(41):13879-13888.

Tsang, A., M. Von Korff, S. Lee, J. Alonso, E. Karem, M.C. Angermeyer, G.L. Borges, E.J. Bromet, K. Demytteneare, G. de Girolamo, R. de Graaf, O. Gureje, J.P. Lepine, J.M. Haro, D. Levinson, M.A. Oakley Brown, J. Posada-Villa, S. Seedat, and M. Watanabe. 2008. Common chronic pain conditions in developed and developing countries: Gender and age differences and comorbidity with depression-anxiety disorders. *The Journal of Pain* 9(10):883-891.

Tsuda, M. 2016. Microglia in the spinal cord and neuropathic pain. *Journal of Diabetes Investigation* 7(1):17-26.

Turner, J.A., S.M. Shortreed, K.W. Saunders, L. LeResche, and M. Von Korff. 2016. Association of levels of opioid use with pain and activity interference among patients initiating chronic opioid therapy: A longitudinal study. *Pain* 157(4):849-857.

Ushikubi, F., E. Segi, Y. Sugimoto, T. Murata, T. Matsuoka, T. Kobayashi, H. Hizaki, K. Tuboi, M. Katsuyama, A. Ichikawa, T. Tanaka, N. Yoshida, and S. Narumiya. 1998. Impaired febrile response in mice lacking the prostaglandin E receptor subtype EP3. *Nature* 395(6699):281-284.

Vadalouca, A., E. Raptis, E. Moka, P. Zis, P. Sykioti, and I. Siafaka. 2012. Pharmacological treatment of neuropathic cancer pain: A comprehensive review of the literature. *Pain Practice* 12(3):219-251.

van Middelkoop, M., S.M. Rubinstein, A.P. Verhagen, R.W. Ostelo, B.W. Koes, and M.W. van Tulder. 2010. Exercise therapy for chronic nonspecific low-back pain. Best practice and research. *Clinical Rheumatology* 24(2):193-204.

van Ojik, A.L., P.A. Jansen, J.R. Brouwers, and E.N. van Roon. 2012. Treatment of chronic pain in older people: Evidence-based choice of strong-acting opioids. *Drugs & Aging* 29(8):615-625.

van Tulder, M.W., D.C. Cherkin, B. Berman, L. Lao, and B.W. Koes. 1999. The effectiveness of acupuncture in the management of acute and chronic low back pain. A systematic review within the framework of the Cochrane collaboration back review group. *Spine (Philadelphia, PA 1976)* 24(11):1113-1123.

Veliz, P., Q. Epstein-Ngo, E. Austic, C. Boyd, and S.E. McCabe. 2015. Opioid use among interscholastic sports participants: An exploratory study from a sample of college students. *Research Quarterly for Exercise and Sport* 86(2):205-211.

Vermaak, V., N.K. Briffa, B. Langlands, C. Inderjeeth, and J. McQuade. 2015. Evaluation of a disease specific rheumatoid arthritis self-management education program, a single group repeated measures study. *BMC Musculoskeletal Disorders* 16:214.

Vickers, A.J., A.M. Cronin, A.C. Maschino, G. Lewith, H. MacPherson, N.E. Foster, K.J. Sherman, C.M. Witt, and K. Linde. 2012. Acupuncture for chronic pain: Individual patient data meta-analysis. *Archives of Internal Medicine* 172(19):1444-1453.

Vijayaraghavan, M., J. Penko, D. Guzman, C. Miaskowski, and M.B. Kushel. 2011. Primary care providers' judgments of opioid analgesic misuse in a community-based cohort of HIV-infected indigent adults. *Journal of General Internal Medicine* 26(4):412-418.

Vijayaraghavan, M., J. Penko, D. Guzman, C. Miaskowski, and M.B. Kushel. 2012. Primary care providers' views on chronic pain management among high-risk patients in safety net settings. *Pain Medicine* 13(9):1141-1148.

Volkow, N., and A.T. McClellan. 2016. Opioid abuse in chronic pain: Misconceptions and mitigation strategies. *New England Journal of Medicine* 374:1253-1263.

VonKorff, M. 2013. Opioids for chronic musculoskeletal pain: Putting patient safety first. *Pain* 154(12):2583-2585.

Voon, P., K. Hayashi, M.J. Milloy, P. Nguyen, E. Wood, J. Montaner, and T. Kerr. 2015. Pain among high-risk patients on methadone maintenance treatment. *The Journal of Pain* 16(9):887-894.

Vowles, K.E., K. Witkiewitz, G. Sowden, and J. Ashworth. 2014. Acceptance and commitment therapy for chronic pain: Evidence of mediation and clinically significant change following an abbreviated interdisciplinary program of rehabilitation. *Journal of Pain* 15(1):101-113.

Vowles, K.E., M.L. McEntee, P.S. Julnes, T. Forhe, J.P. Ney, and D.N. van der Goes. 2015. Rates of opioids misuse, abuse and addiction in chronic pain: A systematic review and data synthesis. *Pain* 156(4):569-576.

Walker, B.F., S.D. French, W. Grant, and S. Green. 2011. A Cochrane review of combined chiropractic interventions for low-back pain. *Spine (Philadelphia, PA 1976)* 36(3):230-242.

Wang, Z.Y., S.Y. Shi, S.J. Li, F. Chen, H. Chen, H.Z. Lin, and J.M. Lin. 2015. Efficacy and safety of duloxetine on osteoarthritis knee pain: A meta-analysis of randomized controlled trials. *Pain Medicine* 16(7):1373-1385.

Waxman, S.G., T.R. Cummins, S. Dib-Hajj, J. Fiell, and J.A. Black. 1999. Sodium channels, excitability of primary sensory neurons, and the molecular basis of pain. *Muscle & Nerve* 22(9):1177-1187.

Webster, L.R., and R.M. Webster. 2005. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the Opioid Risk Tool. *Pain Medicine* 6(6):432-442.

Weiland, B.M., A.G. Wach, B.P. Kanar, M.T. Castele, M.F. Sosovicka, M.R. Cooke, and P.A. Moore. 2015. Use of opioid pain relievers following extraction of third molars. *Compendium of Continuing Education in Dentistry* 36(2):107-111.

Werner, M.U., F.M. Perkins, K. Holte, J.L. Pedersen, and H. Kehlet. 2001. Effects of gabapentin in acute inflammatory pain in humans. *Regional Anesthesia and Pain Medicine* 26(4):322-328.

Wetherell, J.L., N. Afari, T. Rutledge, J.T. Sorrell, J.A. Stoddard, A.J. Petkus, B.C. Solomon, D.H. Lehman, L. Liu, A.J. Lang, and J.H. Atkinson. 2011. A randomized, controlled trial of acceptance and commitment therapy and cognitive-behavioral therapy for chronic pain. *Pain* 152(9):2091-2107.

White, A., N.E. Foster, M. Cummings, and P. Barlas. 2007. Acupuncture treatment for chronic knee pain: A systematic review. *Rheumatology (Oxford)* 46(3):384-390.

Whiting, P.F., R.F. Wolff, S. Deshpande, M. Di Nisio, S. Duffy, A.V. Hernandez, J.C. Keurentjes, S. Lang, K. Misso, S. Ryder, S. Schmidlkofer, M. Westwood, and J. Kleijinen. 2015. Cannabinoids for medical use: A systematic review and meta-analysis. *Journal of the American Medical Association* 313(24):2456-2473.

WHO (World Health Organization). 1986. *Cancer pain relief*. Geneva, Switzerland: WHO.

Wiffen, P.J., B. Wee, and R.A. Moore. 2016. Oral morphine for cancer pain. *Cochrane Database of Systematic Reviews* 4:CD003868.

Wiffen, P.J., S. Derry, R.B. Bell, A.S. Rice, T.R. Tölle, T. Phillips, and R.A. Moore. 2017. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 6:CD007938.

Williams, A.C., C. Eccleston, and S. Morley. 2012. Psychological therapies for management of chronic pain (excluding headache) in adults. *Cochrane Database of Systematic Reviews* 11:CD007407.

Woolf, C.J., and R.J. Mannion. 1999. Neuropathic pain: Aetiology, symptoms, mechanisms, and management. *Lancet* 353(9168):1959-1964.

Yaksh, T.L., D.H. Farb, S.E. Leeman, and T.M. Jessell. 1979. Intrathecal capsaicin depletes substance P in the rat spinal cord and produces prolonged thermal analgesia. *Science* 206(4417):481-483.

Yaksh, T.L., X.Y. Hua, I. Kalcheva, N. Nozaki-Taguchi, and M. Marsala. 1999. The spinal biology in humans and animals of pain states generated by persistent small afferent input. *Proceedings of the National Academy of Sciences of the United States of America* 96(14):7680-7686.

Yi, P., and P. Pryzbylkowski. 2015. Opioid induced hyperalgesia. *Pain Medicine* 16(Suppl. 1):S32-S36.

Younger, J., N. Noor, R. McCue, and S. Mackey. 2013. Low-dose naltrexone for the treatment of fibromyalgia: Findings of a small, randomized, double blind, placebo controlled, counter balanced, crossover trial assessing daily pain levels. *Arthritis & Rheumatology* 65(2):529-538.

Younger, J., L. Parkitny, and D. McLain. 2014. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clinical Rheumatology* 33(4):451-459.

Yuan, Q.L., P. Wang, L. Liu, F. Sun, Y.S. Cai, W.T. Wu, M.L. Ye, J.T. Ma, B.B. Xu, and Y.G. Zhang. 2016. Acupuncture for musculoskeletal pain: A meta-analysis and meta-regression of sham-controlled randomized clinical trials. *Scientific Reports* 6:30675.

Zakine, J., D. Samarcq, E. Lorne, M. Moubarak, P. Montravers, S. Beloucif, and H. Dupont. 2008. Postoperative ketamine administration decreases morphine consumption in major abdominal surgery: A prospective, randomized, double-blind, controlled study. *Anesthesia and Analgesia* 106(6):1856-1861.

Zamora-Legoff, J.A., S.J. Achenbach, C.S. Crowson, M.L. Krause, J.M. Davis, and E.L. Matteson. 2016. Opioid use in patients with rheumatoid arthritis 2005-2014: A population-based comparative study. *Clinical Rheumatology* 35(5):1137-1144.

Zeidan, F., J.A. Grant, C.A. Brown, J.G. McHaffie, and R.C. Coghill. 2012. Mindfulness meditation-related pain relief: Evidence for unique brain mechanisms in the regulation of pain. *Neuroscience Letters* 520(2):165-173.

Zeidan, F., N.M. Emerson, S.R. Farris, J.N. Ray, Y. Jung, J.G. McHaffie, and R.C. Coghill. 2015. Mindfulness meditation-based pain relief employs different neural mechanisms than placebo and sham mindfulness meditation-induced analgesia. *The Journal of Neuroscience* 36(46):15307-15325.

Zeppetella, G., and A.N. Davies. 2013. Opioids for the management of breakthrough pain in cancer patients. *Cochrane Database of Systematic Reviews* 10:CD004311.

Zwisler, S.T., J. Hallas, M.S. Larsen, G. Handberg, S. Mikkelsen, and T.P. Enggaard. 2015. Opioid prescriptions before and after high-energy trauma. *Journal of Opioid Management* 11(4).

3

Progress and Future Directions in Research on Pain and Opioid Use Disorder

The past several years have seen a number of advances in research on pain and opioid use disorder (OUD). This chapter provides a brief overview of some of these key developments, with a focus on those that have taken place since the publication of the 2011 Institute of Medicine (IOM) report *Relieving Pain in America* (IOM, 2011). It also identifies areas for future research to inform efforts by the U.S. Food and Drug Administration (FDA) and other organizations to address the opioid epidemic. The chapter reviews developments and research needs in basic pain research; the neurobiology of the reward pathway and the intersection of pain and OUD; preclinical and translational research, including the development of new analgesics; clinical pain research, including optimizing opioid analgesia in the context of comprehensive pain management and opioid risks, the role of interventional pain therapies, and the potential of precision health care; and research at the intersection of pain and OUD. The chapter concludes with a summary that includes the committee's recommendation for this portion of its charge. The evidence presented in this chapter strongly argues for research to elucidate the biology of pain, to discover novel nonaddictive analgesics, and to refine substantially the ability to deliver analgesia at the level of the individual patient—that is, precision analgesia.

BASIC PAIN RESEARCH

Opioid Analgesics

The search for an effective means of relieving pain and suffering has been ongoing since the dawn of civilization. What overarching lessons have been learned and successes achieved that may help propel identification of the next generation of analgesic agents with reduced risk of addiction or organ toxicity? Clearly opioid analgesics, originally derived from the opium poppy and acting principally at the μ opioid receptors (MOPRs), represent one of the most effective analgesic classes to date. Much of modern synthetic opioid analgesic development revolves around the original action of morphine at the MOPRs. The success of exogenous opioids in treating painful conditions reflects the fact that MOPRs are expressed at multiple sites along the pain detecting and modulating pathway, which includes specialized peripheral sensory neurons, signaling through the dorsal horn of the spinal cord, and ultimately transmission to and from multiple centers of the brain. Therefore, MOPR activation functions in a highly coordinated manner to provide a reduction in pain perception.

Unfortunately, MOPR activation also is linked to a range of unwanted side effects, including its action on reward centers (dependence, addiction); reduced intestinal motility (constipation); and suppression of respiratory drive, which can result in overdose and death (Fields, 2007). Until recently, it had been fanciful to consider that the analgesic properties of MOPR agonists could be separated from these unwanted side effects. However, as a result of leveraging advances in MOPR signaling, it is now appreciated that Gi/o coupling drives predominantly analgesic responses, whereas MOPR coupling to β-arrestin may drive opioid reward and respiratory depression. The concept of identifying a G protein "biased" ligand that can preferentially activate the Gi/o analgesic linkage of MOPR signaling away from β-arrestin is being pursued through classical screening of compounds (Chen et al., 2013b; DeWire et al., 2013) and computational screening of MOPR-biased ligand candidates (Manglik et al., 2016). Although it remains to be seen whether these MOPR-biased candidates will translate into useful analgesics in humans, encouraging steps are being taken, including an active clinical trial of one of the candidate compounds (DeWire et al., 2013).

Inflammation

A tissue's response to injury, whether caused by infection, trauma, metabolic catastrophe, progression of disease/cancer, or ischemia, involves a complex cellular cascade of responses designed to alert and protect the organism and begin the process of healing. This response typically entails

inflammation of the affected tissue and pain and/or heightened pain sensitivity (hyperalgesia and allodynia, respectively) that when it persists can degrade a person's quality of life. Inflammation that continues well past the period of expected healing or despite appropriate treatment remains one of the great medical challenges. Regardless of its source, the management of inflammatory pain often is limited to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) for short periods because of the reduced risk of gastrointestinal bleeding, kidney injury, and adverse cardiovascular effects. Given the multiple overlapping pathways recruited during inflammation, effective analgesic management would appear to require action at multiple points of the inflammatory cascade, analogous to the sites of action of opioids throughout the pain pathway. What research advances in this area show promise for the development of novel analgesic strategies that would both spare protective and restorative pathways and act effectively against inflammatory pain?

Part of the answer may lie at the intersection between the primary afferent nociceptor (peripheral nervous system) and the innate immune system (Guan et al., 2016). Nociceptors are specialized C-type and thinly myelinated Aδ sensory neurons dedicated to the detection of painful stimuli, especially products of inflammation. Two important receptor channels, TRPV1 and TRPA1, expressed in nociceptors, have been identified and found to respond to multiple endogenous inflammatory products and noxious physical stimuli (Julius, 2013; Schumacher, 2010; Zygmunt and Högestätt, 2014). Importantly, because of the relatively high level of TRPV1/TRPA1 expression in nociceptors (rather than in sensory neurons responsible for simple touch or proprioception), the development of a high-affinity antagonist has been pursued in the hope of identifying compounds capable of blocking nociceptor activation (pain) despite the ongoing tissue production of inflammatory mediators. Considerable challenges have arisen in the clinical translation of TRPV1 antagonists with the concurrent development of hyperthermia (fever) due to core temperature dysregulation (Gavva et al., 2008). Research is ongoing to devise a TRPV1 antagonist that provides analgesia while maintaining the detection of acute pain and central homeostatic mechanisms (Gomtsyan and Szallasi, 2015). Investigation into the development of TRPA1 receptor antagonists for the treatment of pain also is ongoing (Schenkel et al., 2016).

While efforts to develop clinically useful TRP channel antagonists are under way, numerous complementary efforts are focused on identifying and blocking the action of inflammatory mediators at prostanoid and purinergic receptors. These receptor systems play multiple roles, including augmenting the responsiveness of TRPV1 under inflammatory conditions. In this regard, one of the principal proinflammatory products of arachidonic acid metabolism, the prostanoid PGE_2, is understood to drive inflammatory

hyperalgesia through various receptor subtypes (Chen et al., 2013a). For example, the inflammation and pain that arise from endometriosis have been linked to EP2 and EP4 receptor activation, and specific antagonists acting at these receptor sites show therapeutic promise in preclinical models (Arosh et al., 2015; Greaves et al., 2017). Moreover, the development of antagonists to certain purinergic (ATP [adenosine triphosphate]-gated channel) receptor subtypes (P2X3) and the metabotropic P2Y receptor show promise in the treatment of inflammatory pain (Burnstock, 2016; Park and Kim, 2017; Viatchenko-Karpinski et al., 2016).

Another perspective is the observation that pain-transducing components are upregulated under persistent tissue inflammation/injury. Therefore, the relative overexpression (or underexpression) of critical gene products within the pain pathway (peripheral and central) represents both a point of dysregulation and, in turn, an opportunity to better study what is driving changes in nociceptive gene expression, one type of plasticity change proposed to drive chronic pain. Research into whether there is a plausible way to reverse such pathophysiologic changes in a network of genes, perhaps through the control of nuclear transcription factors or micro–ribonucleic acids (RNAs), is emerging (Chu et al., 2011; Neumann et al., 2015; Zavala et al., 2014).

Pain Transmission

The ability of nociceptor activation to signal the central nervous system of real or impending tissue damage relies on the transmission of that signal by specialized voltage-gated sodium channels (VGSCs) that propagate depolarizing action potentials along axons. As presented in Chapter 2, the analgesic properties of local anesthetic action rely on the ability to block VGSCs expressed in nociceptors. Although the pharmacology of local anesthetics has been exploited for anesthesia and analgesia based on their discrete application adjacent to nerves and the spinal cord, their general properties to block all sodium channels, including those expressed in heart and motor neurons, have significantly limited their widespread application as analgesic agents. With advances in molecular pharmacology and genetics over the past decade, one subtype of VGSCs has risen to prominence as a plausible analgesic target. Nav1.7 is a VGSC that has been linked to human pain conditions, based on defects in its gene *SCN9A* leading to either loss-of-function (congenital insensitivity to pain) or gain-of-function mutations that drive a rare spontaneous pain syndrome (erythromelalgia), as well as other painful neuropathies. The development of Nav1.7-selective blocking agents has been highly challenging; however, several lead candidates have emerged and are under advanced preclinical testing or clinical trial (Cao et al., 2016; Shcherbatko et al., 2016). Research on selective antagonists

of other members of this family of VGSCs (Nav1.8, 1.9) is under way, but also faces tremendous challenges.

Beyond the proposed Nav1.7 selectivity of candidate blocking agents, properties that allow blockade of only activated (open) forms of the channel may provide an additional measure of clinical safety and reduction of potential offsite effects. Research in this area may also reveal the effectiveness of previously established pharmaceuticals for subsets of neuropathic pain conditions, such as carbamazepine, an agent typically reserved for the treatment of trigeminal neuralgia (Alexandrou et al., 2016; Geha et al., 2016). Whether this class of channel blockers will be applicable to a broad range of neuropathic pain conditions or only for rare conditions is unknown. Given the limited scope of existing disease-based preclinical models of neuropathic pain and the complexity of the human genetic and epigenetic factors that influence susceptibility, much more work is required to synthesize these concepts for broader therapeutic utility.

Despite their prominent role in the detection of noxious stimuli (pain transduction), primary afferent nociceptors do not necessarily encode the final perception of pain. Rather, perception of pain is the result of a complex set of neural, glial, and cellular connections with both ascending and descending modulatory components (for a review, see Peirs and Seal, 2016). The basic structure of this pain pathway begins with the majority of nociceptive input entering the central nervous system through the spinal dorsal horn, roughly dividing into the superficial layers of the dorsal spinal cord as well as input into deeper layers associated with non-nociceptive sensory input, such as simple touch. Whether at superficial or deeper spinal levels, nociceptive input is dynamically regulated by both local spinal circuits and synaptic connections with descending pathways onto the secondary-order dorsal horn neurons. Following crossover, nociceptive signaling is transmitted to higher centers via the spinothalamic tracts that split, divide, and project into and through multiple brain nuclei within the pons, midbrain, and thalamic regions. Although the somatosensory cortex is considered a potential resting place for the perception of pain, the experience of pain is inherently complex and dependent on multiple brain regions.

Building on advances in the peripheral nociceptors mentioned above, a better understanding of spinal neural circuits, especially those that modulate mechanical allodynia, could reveal modality-specific excitatory microcircuits and distinct pain pathway "gates" that could be modified to better treat inflammatory and neuropathic pain (Peirs and Seal, 2016). Although interventions capable of selectively influencing the perception of pain at higher brain centers remain elusive, advances in understanding of the cognitive processing of pain perception offer hope. Something as apparently simple as distraction that reduces pain illustrates that the perception of pain relies on cognitive processes and learning (Wiech, 2016). Therefore,

a detailed understanding of placebo analgesia and how individual expectations of an effective resolution of pain impact the success of any particular analgesic strategy is a critical area for further research (see the discussion of placebo analgesia in Chapter 2).

Innate Immunity

Intersecting with the transduction/transmission of nociceptive pain is activation of the innate immune system designed to initiate the acute inflammatory response to both infectious and sterile injury (Guan et al., 2016). In the case of bacterial infection, innate immune responses are triggered through pattern recognition receptors (PRRs) by components of microorganisms known as pathogen-associated molecular patterns (PAMPs) and/or by factors released by stressed or injured host cells that are collectively known as damage-associated molecular patterns (DAMPs) (Takeuchi and Akira, 2010). The binding of PAMPs or DAMPs to their cognate PRRs triggers a cascade that ultimately leads to the expression and/or activation of numerous inflammatory mediators including cytokines and chemokines with enhanced leukocyte trafficking and activation within tissues. PRRs are expressed not only in leukocytes but also in glial and neuronal cells and are postulated to contribute to neuropathic pain and other pain syndromes, such as sickle cell disease (Guan et al., 2016; Qi et al., 2011). DAMPs also can induce acute inflammation via PRRs and have been implicated in chronic neuropathic pain.

Although early leukocyte responses are designed to contain the extent of infection or injury, dysregulation of the inflammatory response with overexpression of proinflammatory mediators can be deleterious. In this regard, monocytes and macrophages are major contributors to later-phase inflammatory infiltrates and are well known to drive peripheral hyperalgesia (Ji et al., 2016). CCL2, a monocytic chemokine linked to neuropathic pain, also has been implicated in inflammatory pain, in part through its action on CCR2-expressing macrophages and the release of reactive oxygen species (ROS) (Hackel et al., 2013). With recent advances in understanding of the structure of CCR2 and its binding to antagonists (Zheng et al., 2016), it may be hoped that a new generation of CCR2 antagonists with properties to treat both inflammatory and neuropathic pain will emerge.

Members of the toll-like receptor (TLR) family and the receptor for advanced glycation end products (RAGE) are emerging as significant contributors to the pathogenesis of inflammation and pain (Brederson et al., 2016), as both are bound and activated by multiple endogenous agonists, including high-mobility group box 1 protein (HMGB1). TLRs also are expressed on monocytes and macrophages. Targeting cross-talk molecules such as HMGB1 and its receptors represents a novel direction in inflamma-

tion and chronic pain research. Since the immune system and nervous system are linked bidirectionally, there is evidence that activation of TLR- and RAGE-dependent pathways contributes to the development of chronic pain. Importantly, TLR agonists can directly activate nociceptors and increase levels of TRPV1 expression in dorsal root ganglion neurons (Wadachi and Hargreaves, 2006). Since the TLR4 and RAGE agonist HMGB1, a molecule previously associated with sepsis, has emerged as an important participant in neuroinflammatory pain states, strategies based on the blockade of HMGB1 and/or downregulation of the overexpression of TLR4 or RAGE also represent novel directions in inflammatory pain research.

Although this section has thus far focused on either blocking or downregulating proinflammatory receptors/factors, an alternative paradigm is the enhancement of molecules that combat excessive inflammation and pain. Within this category is another class of molecules with therapeutic potential in the treatment of inflammatory pain—resolvins—which not only regulate the resolution of acute inflammation but also can directly inhibit nociceptor activation (Park et al., 2011; Xu et al., 2013). However, evidence for their importance as an endogenous system regulating inflammation is lacking (Skarke et al., 2015).

Emerging from basic science on the metabolism of the insect juvenile hormone mimic R20458 (Gill et al., 1972, 1974), a new group of chemical mediators—the epoxy fatty acids (EpFAs)—has come to light and been found to play important roles in cellular signaling and pain (Zhang et al., 2014). Following purification of the enzyme (soluble epoxide hydrolase [sEH]) responsible for the degradation (hydrolysis) of this class of fatty acids, inhibitors of the sEH enzyme were developed. It was found that inhibition of sEH prevented experimental models of acute inflammation and concomitant pain behaviors (Schmelzer et al., 2005). Curiously, other models of pain not considered "inflammatory," such as mechanical nerve injury or diabetic neuropathy, also were prevented by sEH inhibition (Inceoglu et al., 2012). More recently, research has focused on the mechanism underlying the prevention of experimental neuropathic pain, with a focus on the prevention of subcellular organelle stress in the peripheral nervous system.

EpFA-mediated analgesia, if translated successfully to treat human pain, may represent a promising analgesic approach. EpFA is inactive in the absence of pain, is nonsedating, is active over a large range of pain models, synergizes with NSAIDs, and has no addictive properties in rodents. Its preclinical profile has been shown to be as good as or better than that of other medications currently used to treat neuropathic pain, and it may have other applications in the field of pain that have yet to be explored.

Neuropathic Pain

Following peripheral nerve injury, spinal cord microglia, the tissue-resident immune-like macrophages of the central nervous system, become activated, signaling the central nervous system in a pattern of neuroinflammation (Guan et al., 2016). The pain associated with partial nerve injury is of a type that appears to engender fundamentally different mechanisms driving the sensation of pain. This is exemplified not only by certain unique characteristics of the associated painful sensations but also by the relative resistance of this pain to analgesics typically effective in the treatment of inflammatory pain, such as NSAIDs. The pain is incited by a range of insults, from postherpetic neuralgia, to diabetic neuropathy, to traumatic disruption (surgical interventions), to chemotherapy. From the perspective of the nervous system, the chronic pain resulting from such injuries may represent the consequence of unexpected survival.

Despite the extensive use of anticonvulsants, tricyclic antidepressants, opioids, and topical preparations, the majority of patients suffering from chronic neuropathic pain obtain only partial relief in the face of significant medication side effects (see also Chapter 2). Efforts to develop new and more effective therapies rely on understanding of the underlying mechanism(s) of neuropathic pain, an area of ongoing research. Understanding how spinal microglia drive neuropathic pain may hold promise for the development of a new class of analgesic agents. Based on findings derived from experimental models of nerve injury, research continues to focus on the role of microglial activation in the development of chronic neuropathic pain and possible therapeutic targets (Ji et al., 2014). Importantly, the link between peripheral nerve injury and microglial activation has been poorly understood. A recent study identified colony-stimulating factor 1 (CSF1) as a critical signaling factor, upregulated in injured sensory neurons and transported to the spinal cord, where it targeted the microglial CSF1 receptor (CSF1R). Moreover, the downstream microglial membrane adaptor protein DAP12 was required for nerve injury upregulation of pain-related microglial genes and the ensuing experimental neuropathic pain behaviors. These findings suggest that both CSF1 and DAP12 are potential targets for further investigation and pharmacotherapy of neuropathic pain (Guan et al., 2016).

However, spinal microglial activation is not triggered solely by nerve injury, as there is evidence that certain peripheral inflammatory stimuli (e.g., formalin) can activate spinal microglia that can be reduced by the downregulation of microglial p38 (Tan et al., 2012). Surprisingly such formalin-induced spinal microglial activation cannot be blocked by local anesthetic treatment of the peripheral nerve, suggesting multiple routes of microglial activation. Under these inflammatory conditions, it has been proposed that caspase-6 (CASP6) is upregulated in the central terminals of

primary afferent neurons and is released in the spinal cord. The resultant cascade activates spinal cord microglia and stimulates microglial TNF (tumor necrosis factor)-α synthesis and release through p38 and extracellular signal-regulated kinase (ERK)-mediated pathways. The blockade of spinal CASP6 under painful pathophysiologic conditions such as bone cancer, sickle cell disease, and inflammatory bowel disease may represent an important research opportunity in analgesic development.

The Need for Improved Research Methods

If the perception of pain is not "caused" by a single factor, looking for a single, highly restricted receptor target may be an inherently limited approach from the outset. The notion of a "blockbuster" analgesic drug that can be utilized on a widespread population basis with little physician oversight, propelled forward by a simple pain model in genetically identical male rodents, is fraught with difficulties. Absent a change in approach, the current problem with the use of opioids in the treatment of severe chronic pain may be repeated. One size clearly does not fit or help all. Therefore, research aimed at determining the impact of genetics, sex, and other variables in experimental models of pain is essential. Another critical stumbling block is the inability to translate reliably what appeared to be extremely promising preclinical analgesic targets developed in rodents (mice or rats), but when tested in humans had little to no analgesic efficacy and/or were associated with intractable adverse effects/toxicity. As described elsewhere, the development of humanized preclinical models of pain (in vitro and in vivo) will be required to establish more reliably clinically relevant basic and translational pain science. Progress in this regard cannot come too soon, as investigators are experiencing increased pressure to demonstrate earlier and earlier proof of concept. Providing additional review and revision of current pain research methods and models may hold promise for a more successful translation of the basic science of pain.

The need for improved research methods is evidenced by the fact that, despite robust research in pain-related areas of neuroscience, inflammation, and other fields, few novel analgesics have been introduced in the past 20 years. New drugs have been designed primarily to interact with established targets such as opioid receptors, cyclooxygenase, neurotransmitter reuptake proteins, and previously targeted ion channel constituents. Thus, while drugs offering improved pharmacokinetics and side effect profiles are available, the efficacy of pharmacological tools has not improved appreciably. This failure is not due to a lack of targets identified using animal models. In fact, analgesic programs targeting NK1 receptors, NMDA (*N*-Methyl-D-aspartate) receptors, cytokine/chemokine signaling, and other targets strongly supported in animal studies have been successful in bringing mol-

ecules to advanced stages of human testing, only to have poor efficacy and side effects halt their development. The costs of these failures have been high. This failure of translation has been widely recognized, and many have commented on the challenges facing this type of research (Chaplan et al., 2010; Clark, 2016; Mao, 2012; Woolf, 2010).

One of the principal problems believed to limit analgesic development efforts relates to the pain models selected for laboratory use. Many investigators and pharmaceutical companies have used models bearing little similarity to the clinical syndromes they were intended to represent. For example, such irritants as carrageenan and formalin often are used to represent inflammatory pain such as that resulting from trauma-induced tissue injury or inflammatory arthritis even though there is little evidence for shared mechanisms. Another example is the common use of models of nerve injury, typically within days of the occurrence of injuries. The typical forms of clinical neuropathic pain, however, often do not entail discrete injury to isolated branches of peripheral nerves (e.g., diabetic neuropathy) and may entail symptoms present for years. Degenerative diseases of the joints and axial spine, as well as trauma, are among the most common etiologies for pain complaints bringing patients to pain clinics (Crombie et al., 1998), but animal models designed specifically to mimic these conditions are employed relatively infrequently in pain research. For many types of pain, there are models possessing higher face validity, and they might be used preferentially. It is also possible, although more expensive and perhaps less convenient, to use large-animal models for some types of pain studies, such as large-breed dogs for studies of osteoarthritis, which may occur naturally or after surgically induced injuries (Brimmo et al., 2016; Harman et al., 2016; Knazovicky et al., 2016). Likewise, analgesic research in dogs and other species that develop cancers has been employed successfully (Brown et al., 2015).

Another approach to selection of a laboratory pain model is to choose one for which there is strong evidence of a mechanism present in the test animal that likely exists in the human pain patient as well (Woolf, 2010). Such a model would in theory provide a system in which observations might be most relevant to improving analgesia in clinical populations. Yet while laboratories are starting to adopt this approach, understanding of the mechanisms supporting pain conditions, including back pain, fibromyalgia, and others, is relatively limited, which in turn limits the confidence one can have in the selection of laboratory models.

A set of factors closely related to pain models themselves comprises factors known to affect the prevalence of painful diseases, pain intensity, rates of response to treatments, and side effects of medications. Many such factors have been identified, including sex, weight, age, nutritional status, genetic background, depression, and anxiety (see also the discussion of

differences in pain experiences and treatment effectiveness among subpopulations in Chapter 2). Clearly, some of these factors are more easily represented in laboratory research than others. Relevant laboratory observations demonstrating the importance of some of these factors are the mouse strain dependence in displaying nociceptive sensitization after nerve injury (Mogil et al., 1999), the strain dependence of responsiveness to analgesics such as opioids (Liang et al., 2006), and the sex dependence of analgesic responses to modulators of glial activity (Brings and Zylka, 2015). Likewise, genetic differences have a strong impact on the degrees of tolerance (Liang et al., 2006), physical dependence (Liang et al., 2006), and use of reinforcement behaviors (Berrettini et al., 1994) displayed by laboratory animals, suggesting that care is necessary in selecting a particular strain or breed of animal for pain and analgesic research.

A second major area of concern surrounding the use of animals in preclinical pain research involves the types of measures used in assessing pain-like responses. Because pain is defined as a sensory and emotional experience, one cannot directly infer that pain in animals is identical to that experienced by humans. Researchers therefore tend to rely on behavioral responses. Some of the more popular methods for assessing "pain" in animals actually assess withdrawal behaviors in response to noxious stimuli, such as heat and mechanical pressure applied to an animal's hind paw. These evoked responses are rapidly available, readily quantifiable, and easy for laboratory staff to employ, but they do not well represent major drivers of clinical pain complaints, which are more likely to involve spontaneous pain (Maier et al., 2010). In some types of pain syndromes, allodynia can be reduced by the use of medication; however, the resulting differences in spontaneous or overall pain are small (Rauck et al., 2015). To address this problem, laboratories have recently turned to more sophisticated methods of testing involving operant pain models or models in which place preference is used to detect an ongoing aversive pain state (King et al., 2009b). Quantifying flinching, guarding, vocalization and other nonevoked pain measures may also provide means of assessing spontaneous aspects of pain. Another approach to assessment of the effects of a candidate analgesic molecule on model animals involves quantifying an activity or function, such as running on an exercise wheel or the normalization of abnormal gait (Amagai et al., 2013; Cobos et al., 2012; Ishikawa et al., 2015). Conducting such measurements in the preclinical setting is consistent with the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines for analgesic research, which emphasize incorporating measures of function into clinical studies (Turk et al., 2003).

Beyond the models and measures used for preclinical research, however, is the issue of improving the transparency of reporting and reproducibility of the research. Problems related to faulty study design, inappropriate data

processing, and other procedural issues are believed to contribute to the poor reproducibility of laboratory results, an issue that results in approximately $28 billion in wasted research and development efforts each year in the United States (Freedman et al., 2015). To address these problems two sets of guidelines have been developed. First is the Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines (Drummond et al., 2010), aimed at enhancing the transparency of laboratory research by requiring the reporting of details of the experimental design, animal care, disposition of animal subjects, blinding of investigators, and other factors potentially affecting the experimental results. A second, related effort is the construction and dissemination of the guidelines of the Preclinical Pain Research Consortium for Investigating Safety and Efficacy (PPRECISE) Working Group (Andrews et al., 2016), which stress the identification of a primary hypothesis and outcome measure, as well as the use of power calculations to justify cohort sizes.

Summary

Basic pain research is progressing across multiple interconnected fronts. These include mechanisms related to MOPR-biased analgesia, inflammation, pain transmission, innate immunity, and treatment of neuropathic pain. MOPR-biased analgesia may one day allow the separation of opioid-induced analgesia from opioid-induced respiratory depression or addiction by uncoupling MOPRs from the β-arrestin pathway. The diverse approaches discussed in this section demonstrate that one-size-fits-all pain management is neither achievable nor preferable, however, and that difficulties in translating discoveries into clinical pain medicine persist. Further studies to determine the impact of clinical characteristics (e.g., genetics and sex) are necessary to improve experimental models of pain.

The translation of the basic science of pain into effective therapies is limited by the failure of preclinical models to reflect the human condition and the inability to target pain networks. The development of humanized preclinical models of pain (in vitro and in vivo) could be instrumental to more reliably establishing clinically relevant basic and translational pain science. Such models could incorporate the functional as well as the organic response to pain, and assess pain's affective and cognitive components. Such research would benefit from quantitative biomarkers of pain and its relief that translate from model systems to humans, as well as studies of the impact of sex and aging on pain. These efforts, in turn, would require precise molecular phenotyping of both animal models of pain and patients to identify those models with the highest predictive validity for specific human pain phenotypes. The reproducibility of basic pain research and its

subsequent impact on clinical pain medicine could be improved through more rigorous reporting guidelines and greater transparency.

THE NEUROBIOLOGY OF THE REWARD PATHWAY AND THE INTERSECTION OF PAIN AND OPIOID USE DISORDER

Neurobiology of the Reward Pathway

Although multiple brain regions constitute a reward network, the mesolimbic system is a key network node that regulates reward. Dopamine (DA) transmission in the mesolimbic system via the ventral tegmental area (VTA) to the nucleus accumbens (NAc) has long been recognized for its role in motivation (Wise et al., 1995). Natural rewards, as well as rewarding drugs (such as opioids), activate mesolimbic neurons to elicit DA release in the NAc (Devine et al., 1993; Giuliano et al., 2013; Le et al., 2009; Xiao and Ye, 2008). DA neurons in the VTA respond by burst firing following salient stimuli, and phasic bursting of DA neurons is sufficient to produce reward-seeking behavior (Kim et al., 2013; Tsai et al., 2009). The GABAergic input onto DA neurons includes the NAc, the ventral pallidum, the rostromedial tegmental nucleus (RMTg), and the bed nucleus of stria terminalis, among others, and has been estimated to make up at least 70 percent of synaptic input onto DA neurons (Matsui et al., 2014; Omelchenko and Sesack, 2005; Tepper and Lee, 2007; Watabe-Uchida et al., 2012).

The opioid system is involved in modulating pain and reward. Opioid receptors are a group of G protein-coupled receptors divided into three families: the MOPRs, the delta opioid receptors (DOPRs), and the kappa opioid receptors (KOPRs). These receptors are activated by three classes of endogenous opioid peptides—beta-endorphin, dynorphin, and enkephalin—that are derived from three precursor peptides. The selectivity and distribution of the opioid peptide and receptor systems suggest that encephalin and beta-endorphin act through the MOPRs and DOPRs, and dynorphin through the KOPRs. The opioid receptors and their peptides are distributed throughout the central and peripheral nervous system in a distinct but overlapping manner (Mansour et al., 1988). The MOPRs are widely distributed throughout the brainstem, midbrain, and forebrain structures, and mediate most of the analgesia and reinforcing effects of opioid agonists such as morphine (Kieffer and Gavériaux-Ruff, 2002). DOPRs, on the other hand, are highly expressed in forebrain regions (Mansour et al., 1988). Activation of DOPRs produces minimal analgesia in acute pain models but develops an analgesic effect in rodent models of chronic pain (Cahill et al., 2007; Pradhan et al., 2011). KOPR and MOPR expression overlaps throughout the brain. MOPRs located in the mesolimbic pathway are thought to mediate the reinforcing properties of opioids and natural

reinforcers via regulation of extracellular DA within the NAc (Devine et al., 1993; Giuliano et al., 2013; Le et al., 2009; Xiao and Ye, 2008). This effect is mediated by inhibition of GABA release in the VTA through activation of local presynaptic MOPRs on GABA interneurons or on GABA projections from the RMTg (Matsui et al., 2014; Siuda et al., 2015). MOPR activation on these GABA neurons then leads to an increase in DA release in the NAc through a disinhibition mechanism (Johnson and North, 1992) and/or through local activation of MOPRs in the NAc core and shell (Hipólito et al., 2008).

In contrast to MOPRs, KOPR agonists block the rewarding effects of MOPR agonists by acting to decrease DA release in the NAc (Niikura et al., 2010). As mentioned above, KOPR and MOPR expression overlaps widely throughout the brain, and in these regions the two have a "push-and-pull" relationship. Expression of KOPRs has been detected in the VTA, NAc, prefrontal cortex, amygdala, and other areas implicated in the modulation of reward (Peckys and Landwehrmeyer, 1999; Shippenberg, 2009). KOPR activation in the NAc leads to dysphoria and other aversive effects (Land et al., 2008; Shirayama et al., 2004; Van't Veer and Carlezon, 2013). Expression and release of dynorphin, the endogenous KOPR agonist, is dynamically regulated by reward, stress, and the opioid or other drug taken (Carlezon et al., 1998; Land et al., 2008). Thus, these dynorphin/KOPR-mediated alterations in reward states are likely to be directly linked with changes in DA transmission.

Neurobiology of the Pain Processing Pathway

As described by Garland and colleagues (2013), the brain actively regulates nociception via interactions between descending pain modulatory system (Heinricher et al., 2009; Reynolds, 1969) and corticocortical networks (Rainville, 2002) rather than passively receiving nociceptive information from the body. The descending pain modulatory system influences nociceptive input from the spinal cord through a network of cortical, subcortical, and brainstem structures (including the prefrontal cortex, anterior cingulate cortex, insula, amygdala, hypothalamus, periaqueductal grey region, rostral ventromedial medulla, and dorso-lateral pons) (Tracey and Mantyh, 2007). This system is believed to be the means by which the central nervous system inhibits nociceptive signals at the spinal outputs (Heinricher et al., 2009). Endogenous and exogenous opioids have been found to relieve pain by targeting the descending pain modulatory system, particularly in the periaqueductal grey region of the brain, which is involved in processing the placebo analgesia (Besson, 1999; Tracey, 2010). In addition, acute single-dose administration of opioids has been found to lead to analgesia in healthy individuals by reducing sensory evaluation processes, as is demonstrated by

reductions in activation of brain regions that correspond with lower-level afferent processes (Wagner et al., 2007; Wise et al., 2002) and by modulation of neurotransmission in the substantia gelatinosa of the dorsal horn of the spine (Le Bars et al., 1980; Yaksh, 1987).

In addition, a recent review alluded to earlier highlights the influence of cognitive processes on pain perception (Wiech, 2016). It is thought that pain perception is determined by expectations and their modification through learning. The powerful influence of cognitive processes and learning mechanisms on the way pain is perceived is highlighted by placebo analgesia and pain relief through distraction (see also Chapter 2).

Opioid analgesia operates through both neuropharmacologic and psychological mechanisms. In addition to lessening the sensory aspects of pain, opioids may alleviate the affective dimensions of pain (e.g., suffering) (Garland et al., 2013). Analgesia induced through acute opioid administration in healthy individuals has been found to operate in part through the modulation of neural circuits that play a role in the regulation of attention, emotion, and neurovisceral integration (Becerra et al., 2006; Oertel et al., 2007; Thayer and Lane, 2009; Wagner et al., 2007). As with other drugs that are misused, opioids also stimulate mesolimbic DA reward systems (Johnson and North, 1992), and opioid-induced DA release in the NAc associated with positive mood and reward may promote pain management. While most of the available evidence regarding the psychobiological mechanisms of opioid-induced analgesia comes from research involving healthy individuals exposed to pain induction in the laboratory setting, the development of co-occurring chronic pain and OUD over time may modify the neurobiological response to opioids in ways that are of clinical importance (Garland et al., 2013), as discussed in the next section.

Neurobiology of the Intersection Between Pain and Opioid Use Disorder

It is well documented that positive reinforcement is decreased in the presence of chronic pain (Cahill et al., 2013; Hipólito et al., 2015; Leitl et al., 2014a,b; Martin et al., 2004; Shippenberg et al., 1988). This chronic pain-induced alteration has been linked to a decrease in reinforcer-induced dopaminergic transmission (Hipólito et al., 2015; Loggia et al., 2014; Niikura et al., 2010). Despite this evidence, only a few preclinical studies have assessed the impact of pain on opioid intake. Most studies have used a conditioned place paradigm to test the reinforcing properties of opioids in rodents undergoing neuropathic or chronic pain (Cahill et al., 2013; Narita et al., 2005; Ozaki et al., 2002; Taylor et al., 2015). Of interest, Wu and colleagues (2014) revealed that the known reinforcing doses of morphine were unable to induce a place preference under painful conditions. However, animals exposed to chronic pain developed a clear preference for the

morphine-paired side when the dose of morphine was increased (Wu et al., 2014). In line with these findings, rodents self-administering opioids while experiencing pain showed a decrease in their consumption of low drug doses compared with controls (Hipólito et al., 2015; Lyness et al., 1989; Martin and Ewan, 2008; Taylor et al., 2015; Wade et al., 2013), but this opioid consumption increased when high doses were accessible (Hipólito et al., 2015). Together these important results suggest a rightward shift in the dose response for opioid consumption in conditions of chronic pain that correlates with modifications in dopaminergic transmission from the VTA to the NAc (Hipólito et al., 2015). The dopaminergic release in the NAc is highly controlled by the opioid system, and Hipolito and colleagues (2015) demonstrated that inflammatory pain induces a desensitization of MOPRs in the VTA. These changes in opioid receptor function lead to decreased heroin- and DAMGO ([D-Ala^2, *N*-MePhe^4, Gly-ol]-enkephalin)-induced DA release in the NAc. As mentioned above, the KOPR system may also be involved in these changes in DA release. Evidence points to a role for the KOPR system in many of the changes induced by chronic pain (Cahill et al., 2014).

In conjunction with the data showing that inflammatory pain decreases morphine- and heroin-induced NAc DA release and impairs the rewarding effects of morphine (Hipólito et al., 2015; Narita et al., 2005), Narita and colleagues (2005) showed that pain-induced attenuation in place preference can be reversed by systemic or local NAc blockade of KOPRs using norbinaltorphimine (NorBNI), a highly selective antagonist for KOPRs. The aversive component of exogenous KOPR stimulation, measured by place preference conditioning, also is suppressed when animals are experiencing inflammatory pain conditions (Shippenberg et al., 1988), suggesting the presence of a kappa opioid tone during painful conditions that induces a sustained dysphoric state.

There is, however, some controversy regarding the role of the dynorphin/kappa opioid system in the regulation of reinforcing properties of reward during pain. Some studies showed that KOPR antagonism did not reverse the pain-induced decrease in intracranial self-stimulation of the mesolimbic pathway in rats (Leitl et al., 2014a,b). These discrepancies could be explained by the presence of hot and cold spots (areas that appear particularly attuned to either accentuate or suppress reward response), two distinct areas in the NAc shell in which activation of KOPRs can drive either aversive or reinforcing behaviors (Al-Hasani et al., 2015; Castro and Berridge, 2014). Systemic application of KOPR antagonists likely targets both of these discrete areas, while microinjections of KOPR agonists/antagonists to specifically target these discrete areas in the NAc could yield opposing behaviors and interpretations.

Finally, it is important to acknowledge the role of other brain regions (besides the VTA and the NAc) critical in the regulation of pain, stress, and

reward responses. The amygdala is very much involved in the processing of both positive and negative valence (see the review by Janak and Tye, 2015). Specifically, the basolateral amygdala (BLA) and the central nucleus of the amygdala play important roles in affective pain, in addition to better-studied roles in the processing of mood and fear disorders, as well as reinforcement (Pare and Duvarci, 2012; Veinante et al., 2013). More recently, it has been shown that the habenula and NAc dopaminergic neurons drive inhibitory antireward tone during stress and pain conditions (Lee and Goto, 2011). The lateral hypothalamus, a region critical to positive reinforcement, also plays a role in the pain response through sensory mechanisms (Ezzatpanah et al., 2015). These structures contribute as well to increases in norepinephrine, corticotropin-releasing hormone (CRH), vasopressin, hypocretin, and substance P, driving a stress-like emotional state.

Summary

Pain and reward are processed by overlapping brain structures. This finding is supported by clinical and preclinical evidence showing that positive or negative reinforcement (i.e., rewarding properties of opioids or the rewarding effect of pain relief, respectively) is decreased by the presence of pain. In this regard, preclinical studies have shown that pain promotes opioid dose escalation in animals with a prior history of opioid intake. However, additional studies are needed at both the preclinical and clinical levels. Much of the available evidence regarding the mechanisms underlying opioid analgesia and reward comes from studies of healthy individuals, and such studies would benefit from including individuals with chronic pain.

PRECLINICAL AND TRANSLATIONAL RESEARCH

Development of New Analgesics

Despite the complexity entailed in researching pain described thus far, modern approaches examining pain at the genetic and mechanistic levels are relatively recent. Much more remains to be discovered by researchers seeking to translate their findings into clinical applications. This section describes some of these opportunities toward the development of nonaddictive alternatives to the opioid analgesics currently on the market.

Biased Opioid Receptor Ligands

The concept of ligands interacting with receptors differentially to modulate their interaction with downstream signaling pathways and effector systems has been extant for decades but has gained considerable traction in

the past 5 years (Kenakin, 2015; Reiter et al., 2012). The recognition that receptor conformation may be dynamically and variably altered by interaction with distinct ligands has coincided with the emergence of diverse tools relevant to dissection of spatiotemporal patterns of opioid receptor (OR) signaling, consequences of downstream pathway activation, and the in vivo consequences of such biased approaches. Developments of direct relevance to the opioid field include structural elucidation of μ, κ, and δ ORs in the basal and bound state; intracellular OR domains complexed with the rat rhodopsin receptor (optogenetic activation); and tissue-specific deletions of ORs and their endogenous ligands in mice (Bruchas and Roth, 2016). Although the clinical importance of these discoveries remains to be established, several examples illustrate the speed at which this field is evolving.

Engagement of MOPRs by a ligand such as morphine recruits both inhibitory guanosine-5'-triphosophate (GTP) binding proteins such as Gi/o and β-arrestin, which serves ultimately to terminate G protein-dependent signaling. The βγ subunit of the G protein dissociates, permitting the α subunit to inhibit adenylate cyclase and indirectly activate kinases such as JNK (c-Jun N-terminal kinases) and ERK. In the meantime, the βγ subunit activates inwardly rectifying potassium channels to increase membrane hyperpolarization and inhibit voltage-gated calcium ion channels and hence neuronal hyperpolarization. These actions combine to explain the analgesia consequent to MOPR activation (Dogra and Yadav, 2015). However, ligand engagement also activates G protein receptor kinases that phosphorylate the intracellular tails of ORs, attracting β-arrestins that result directly and indirectly in activation of the ERK and p38 signaling pathways. Experiments in β-arrestin-depleted mice revealed this to be the pathway that may drive such effects as tolerance, respiratory depression, and constipation with certain opioids, such as morphine (Raehal and Bohn, 2014). Yet while the ability to segregate analgesic efficacy from a range of troubling adverse effects has clear translational implications, screening for such biased ligands is complicated by contextual influences that complicate translation of ligand bias from in vitro systems to rodent systems, let alone to humans (Kenakin, 2015). Nonetheless, several promising examples have emerged (Gupta et al., 2016; White et al., 2014), and one compound already has advanced from encouraging results of conserved analgesia with reduced respiratory and gastrointestinal adverse effects in 200 abdominoplasty patients in phase II to a larger randomized trial (Kingwell, 2015).

An exciting element of this work is the increasing recognition of OR heterodimerization as an in vivo phenomenon and the possibility that what are regarded as specific OR ligands may also engage, perhaps preferentially, heterodimers, perhaps to augment their analgesic efficacy. Screening approaches have yielded bivalent ligands, antibodies, and membrane permeable peptides that target heterodimers, for example, of the MOPRs/

DOPRs. These approaches, combined with approaches mentioned above, should clarify the underlying biology and the promise of such heterodimers as drug targets (Fujita et al., 2015). Heterodimerization may extend beyond the OR family; for example, heterodimerization of the KOPRs with the neurotensin receptor induces a switch of the former from G protein activation to β-arrestin-based signaling (Liu et al., 2016).

Abuse-Deterrent Formulations of Opioids

Although not representing an innovation in changing the intrinsic activity of opioid action, abuse-deterrent formulations (ADFs) are opioid medications that have been reformulated to reduce the likelihood that the medication will be "abused." For example, some opioids have been reformulated to discourage manipulation by either making the pill difficult to manipulate or rendering it ineffective or unpleasant once manipulated. In addition to ADFs currently on the market, such as agonist/antagonist combinations (e.g., oxycodone plus naloxone) and crush-resistant extended-release (ER) formulations (e.g., oxymorphone), a number of new technologies are in development. These include formulations designed to limit the rate or extent of release of opioids when multiple pills are ingested; cause the pill to turn to gel if dissolved; irritate the nasal passages if snorted; and slow the release of the drug into the brain, thereby reducing euphoria (Bulloch, 2015). Many opioid analgesics, such as morphine, activate primarily the MOPRs, which relieves pain but is also associated with such side effects as respiratory depression. KOPR agonists currently in development are intended instead to activate the KOPRs, potentially providing pain relief without the MOPR-associated side effects (Beck et al., 2016).

Eicosanoids, Cannabinoids, and Transient Receptor Potential Channels

As mentioned in Chapter 2, prostaglandins E_2 and I_2, particularly but not exclusively formed by cyclooxygenase (COX)-2, mediate pain and inflammation; suppression of their formation accounts for the analgesic and anti-inflammatory actions of NSAIDs. Unfortunately, COX-2-dependent formation of these same eicosanoids serves a protective function in the cardiovascular system, where their suppression has resulted in myocardial infarction and stroke; hypertension and heart failure; and in mice, evidence of accelerated atherogenesis (Grosser et al., 2010). For these reasons, attention has focused on the microsomal prostaglandin E (PGE) synthase (S)-1, the enzyme downstream of COX that largely accounts for PGE_2 formation (Chandrasekhar et al., 2016). When this enzyme is blocked or deleted, its prostaglandin H2 (PGH2) substrate, formed by COX, is available for rediversion to other PG synthases. Global deletion of microsomal

prostaglandin E synthase (MPGES)-1 in mice largely retains the analgesic efficacy of NSAIDs as assessed in mice, but augments rather than depresses prostacycline (PCI2). This coincides with attenuation or abrogation of the enhanced thrombogesis, hypertension, and atherogenesis seen in COX-2 knockout mice (Yang and Chen, 2016). Indeed, deletion of MPGES-1 in myeloid cells conserves this profile (Chen et al., 2014), and the impact of targeting macrophage MPGES-1 is under investigation. A phase II study of an MPGES-1 inhibitor found rediversion to augment PGI2 formation in volunteers (Jin et al., 2016). An open question is how faithfully MPGES-1 inhibitors will conserve the analgesic efficacy of NSAIDs in human pain syndromes, given that in some settings in rodent models, PGI2 has been shown to mediate pain and inflammation (Sugita et al., 2016). PGE2 activates 4 E prostanoid (P) receptors. As mentioned previously, EP3 mediates the hyperthermic effects of PGE2 and the EP1 (Johansson et al., 2011), EP2 (Ganesh, 2014), and EP4 (St-Jacques and Ma, 2014) receptors, just as the I prostanoid receptor (Honda et al., 2006) may mediate pain. While antagonists for all four of these receptors have been developed, it is unclear how safely such drugs could be used as analgesics given the importance of these PGs in cardioprotection.

These PGs mediate pain, at least in part, by sensitizing transient receptor potential (TRP) channels in nociceptors to activation by thermal, mechanical, or chemical stimuli. TRPs have particular relevance to the neuropathic pain that complicates diabetes, traumatic nerve injury, and chemotherapeutic drug administration. Besides PGs, other inflammatory mediators, such as bradykinin, nitric oxide (NO), and nerve growth factor (NGF), can subserve a similar function (Basso and Altier, 2017). Aside from the PG metabolites of arachidonic acid, p450 catalyzed metabolites (epoxyeicosatrienoic acids [EETs]) can sensitize nociceptors, especially TRPA1 and TRPV4, and deletion and inhibition of the soluble epoxide hydrolase that catalyzes their formation has shown promise in preclinical models (Wagner et al., 2016). Yet while TRPs themselves (TRPV1/A1, TRPV4/M8) have emerged as diverse and attractive targets for analgesic drug development given their role in inflammatory and neuropathic pain, concurrent impairment of their endogenous signaling functions (e.g., thermal regulation for TRPV1) may limit their clinical application (Dai, 2016; Mickle et al., 2016). Indeed, the fact that TRPs sustain some physiological functions, such as thermoregulation and hyperthermia, has complicated the early human pharmacology of TRPV1 antagonists. Also in model systems, their role may be highly context dependent: they serve as protective cellular sensors of warning signals under physiological conditions, but may contribute to pain and inflammation under pathological conditions (Dai, 2016).

Cannabinoids are lipids closely related to the eicosanoid family. The principal endogenous cannabinoids, anandamide and 2-arachidonoylglyc-

erol (2-AG), are formed in postsynaptic neurons and act centrally on cannabinoid receptor type 1 (CB1) G protein-coupled receptors (GPRs) that are expressed on presynaptic neurons, thereby regulating neurotransmitter release. Although there is some evidence that they are also expressed centrally, CB2 receptors generally are expressed peripherally on both neurons and immune cells. The principal psychoactive constituent of cannabis, Δ9-tetrahydro cannabinol (THC) is active on both CB1 and CB2 receptors. Anandamide levels are regulated by its breakdown through the action of fatty acid amide hydrolase (FAAH), while 2-AG levels are regulated by monoacylglycerol lipase (MAGL), which accounts for ~85 percent of the hydrolysis, and by α/β hydrolase domain-containing 6 (ABHD6) and ABHD12, which also hydrolyze 2-AG to arachidonic acid and glycerol. Cannabinoids act as well on other receptors, such as GPR18 and GPR55, and may act in concert with TRP channels and MOPRs (Maguire and France, 2016) in a bidirectional manner (Zádor and Wollemann, 2015) to modulate the expression of pain.

Cannabinoid action in the amygdala is of particular interest given the coincidence of pain with depression and the modulating effects of cannabinoids on both the physical perception of and emotive response to pain (Huang et al., 2016). Cannabinoids have been shown to be effective in several settings as analgesics in humans, albeit limited by central side effects such as drowsiness. There is some evidence for sex-dependent differences in mice in the analgesic response to cannabinoids (Cooper and Haney, 2016). Legalization of cannabis use for cancer pain has been advancing at the state level. Beyond the development of biased agonist ligands for cannabinoid receptors as novel analgesics with an improved adverse effect profile (Diez-Alarcia et al., 2016; Mallipeddi et al., 2016), interest in enhancing the formation of anadamide by inhibition of FAAH (Guindon, 2017; Pawsey et al., 2016) has been tempered by a severe reaction (a cerebellar syndrome including generalized ataxia, dysarthria, and nystagmus) to at least one such compound in healthy volunteers (Kerbrat et al., 2016).

Sodium Channel Blockade

VGSCs are crucial to the transmission of electrical signals in sensory neurons, and specific patterns of sodium current activity, such as persistent and resurgent currents, also are likely to be relevant to nociception (Barbosa and Cummins, 2016). The importance of sodium channels in pain is illustrated nicely by human genetics; gain-of-function mutations of Nav1.7, Nav1.8, and Nav1.9, which are expressed preferentially in peripheral neurons, cause pain in such syndromes as erythromelalgia (Brown, 2016; Rolyan et al., 2016), while loss-of-function mutations of Nav1.7 result in loss of pain in otherwise healthy people (Emery et al., 2016). A

painful neuropathy caused by the chemotherapeutic oxaliplatin has been linked to mutations in Nav1.6, a VGSC linked also to the conversion of acute to chronic pain (Barbosa and Cummins, 2016). Optogenetic silencing of Nav1.8 positive afferents alleviates inflammatory and neuropathic pain (Daou et al., 2016).

While mutational analysis has tied pain perception particularly to the α subunit of VGSCs, auxiliary subunits, such as β, and multiple auxiliary proteins, such as fibroblast growth factor homologous factors, may bind to and regulate α subunits and modulate aspects of nociception. Acid-sensing ion channels (ASICs) are activated with acidification of the synaptic cleft and exhibit specificity for sodium, although some also allow passage of calcium. Gene depletion in mice has implicated ASICs in mechanosensation, and several drugs targeting ASICs are in clinical trials (Boscardin et al., 2016).

VGSCs are complex drug targets given their multiple subunits, numerous configurations, and auxiliary binding proteins and the necessity of restricting targeting to the periphery. For example, to achieve selectivity with respect to tissue expression requires avoiding disruption of cardiac conductivity. Selectivity also may be enhanced by targeting microproteins to less conserved elements of VGSCs, such as voltage sensing, rather than pore residues (Barbosa and Cummins, 2016; Shcherbatko et al., 2016).

Nerve Growth Factor

NGF sensitizes and proliferates nociceptors augmenting the response to painful stimuli and has an established place in both neuropathic and inflammatory models of pain. Proliferation of nociceptor axons and terminals in target tissues is a particular feature of NGF action in cancer pain (Miyagi et al., 2016), driving a dramatic increase of small nerve fiber proliferation in bone (Kelleher et al., 2017). Perhaps unsurprisingly, NGF is believed to play an important role in the transition of acute to chronic pain. NGF (and its pro-NGF form) activates (1) a high-affinity tropomyosin receptor kinase (trk)A receptor, selectively expressed on peripheral terminals of Aδ and peptidergic unmyelinated C fibers, and (2) a lower-affinity, more ubiquitously expressed and promiscuous p75 neurotropin receptor, a member of the TNF receptor superfamily. While activation of the former promotes neuronal proliferation, activation of the latter promotes apoptosis. Despite these contrasting effects, the two receptors also can interact to modulate downstream effects, adding a layer of complexity that is incompletely understood. Although several anti-NGF monoclonal antibodies completed phase III trials and were effective analgesics, they also accelerated disease progression in patients with osteoarthritis and were put on clinical hold in 2010 by the FDA (Chang et al., 2016). This hold was released in March

2015, and translational and clinical trials (Miller et al., 2017) of diverse therapeutic modalities, including sequestration of free NGF, prevention of NGF binding, and inhibition of trk function, are being pursued (Chang et al., 2016).

Interleukin (IL)-6

This T cell-derived cytokine plays a central role in host defense against infection but also has been implicated in neuropathic pain. Unlike NGF, which is restricted to the periphery but transported retrogradely along axons complexed with its trkA receptor, IL-6 is upregulated in the central nervous system, where it promotes neuronal proliferation and restrains apoptosis. Both IL-6 and its soluble receptor can sensitize nocireceptors. This has prompted interest in the possibility that targeting the sIL-6R, leaving the canonical IL-6R untouched, might achieve analgesia while leaving the immunologic functions of the cytokine intact (Kelleher et al., 2017).

Emerging Drug Targets

Human genetic studies have revealed a relationship between variants in guanosine triphosphate (GTP) cyclohydrolase 1, which reduces tetrahydrobiopterin (BH4), and decreased pain. In mice, production of BH4 is increased by damaged nerves and attendant infiltrating macrophages, while reduction of BH4, by interfering with its degradation, reduces injury-induced hypersensitivity without interfering with the protective properties of nociception (Latremoliere et al., 2015). BH4 is an essential cofactor for enzymes relevant to generation of catecholamines, NO, and serotonin, all of which are mediators of hypersensitivity. For example, nitric oxide synthase (NOS)1 in neurons and NOS2 in macrophages have cumulative effects on NO generation and hypersensitivity (Choi et al., 2016; Kuboyama et al., 2011).

Purinoreceptors are activated by adenosine (P1) or adenosine triphosphate (ATP)/adenosine diphosphate (ADP) (P2; P2X ion channels and P2Y G protein-coupled receptors). Such nucleotides are released by most cells in response to mechanical stimulation and are rapidly inactivated by ecto-ADPases. P2Y-dependent ATP-induced hyperalgesia is transduced via TRPV1 channels. P2X7 receptors mediate pain caused by the chemotherapeutic oxaliplatin, while activation of glial P2Y12 receptors appears to be important in neuropathic pain. P2X3, P2X2/3, P2X4, P2X7, and P2Y12 have attracted attention as drug targets for both neuropathic and inflammatory pain (Burnstock, 2016; Matsumura et al., 2016; Teixeira et al., 2016).

Other areas of emerging interest include the potential of potassium channel openers as analgesics (Busserolles et al., 2016) and elucidation of

the role of store-operated calcium channels in the biology of nociception (Munoz and Hu, 2016).

Summary

A number of opportunities have emerged in recent years toward the development of nonaddictive alternatives to the opioids available on the market. Those of direct relevance to opioids include biased ligands directed at opioid receptors and continued development of new abuse-deterrent technologies. Other developments include inhibitors of the microsomal PGE synthase, drugs targeting VGSCs, anti-NGF biologics, transient receptor potential cation channel antagonists, cannabinoid receptor agonists, excitatory amino acid receptor blockers, anticytokine signaling drugs, neuromodulation, and agents directed at other targets. Specialized channels expressed in primary afferent nociceptors, such as TRP channels, serve as cellular sensors of actual or impending tissue injury and are targets for a new class of analgesic development. The selective blockade of pain transmission from the sensory terminals to the spinal cord may be possible through targeting of subtypes of VGSCs.

CLINICAL RESEARCH

Clinical pain research has continued since the IOM (2011) report *Relieving Pain in America* was issued. As discussed in Chapter 2 of the present report, opioids, while effective in the short and intermediate terms, lack data to support their chronic long-term use. Moreover, significant adverse effects are associated with chronic use of high-dose opioids (Chou et al., 2015). Research aimed at separating the beneficial pain-relieving effects of opioids from those that cause harm is under way (Manglik et al., 2016; Schneider et al., 2016). This section summarizes promising clinical research into the management of pain and opioid risk, including nonpharmacologic and interventional approaches, and the potential role of precision health care in improving clinical practice and health outcomes with respect to pain management.

Optimizing Opioid Analgesia in the Context of Comprehensive Pain Management and Opioid Risk

Opioid Prescribing for Chronic Pain

Many professional organizations have published standards of care for judicious prescribing of opioids for chronic pain (Dowell et al., 2016; Mai et al., 2015; Nuckols et al., 2014). Full disclosure of the risks versus benefits

of initiating opioid therapy is encouraged, along with individual assessment of the risk of opioid misuse. Several instruments have been developed to assess this risk based on patient self-report, including the Screener and Opioid Assessment for Patients in Pain, Revised (SOAPP-R) (Butler et al., 2009), the Opioid Risk Tool (ORT) (Webster and Webster, 2005), and the Current Opioid Misuse Measure (COMM) (Butler et al., 2010), among others. Such instruments can be used along with other information to guide decision making regarding an appropriate pain management plan. A review that involved an analysis of studies on the accuracy of the SOAPP-R, the ORT, and other instruments for predicting opioid misuse showed mixed results, with several studies having methodological shortcomings (Chou et al., 2015). Another review of studies on instruments (including the COMM and other self-report measures) used to assess the safety, efficacy, or misuse of current opioid therapy found that most studies demonstrated statistical significance, but had bias and generalizability limitations. Data on feasibility of use in clinical settings were limited by a lack of testing in those settings (Becker et al., 2013). Additional research could examine the accuracy of opioid risk assessment tools across multiple populations, including their role in improving outcomes related to misuse, overdose, and OUD, and test their use in clinical practice (Becker et al., 2013; Chou et al., 2015).

Given the potential to reduce dose-dependent risks, opioid dose reduction in the context of long-term opioid therapy is an area of ongoing research. Von Korff and colleagues (2016) report results from an interrupted time series analysis in Washington State examining changes between 2006 and 2014 in percentages of (1) patients being prescribed opioid therapy in doses exceeding 120 morphine-equivalent dose (MED)/day, and (2) patients receiving excess opioid days supplied. After release of a state-level chronic pain management guideline, as well as a health plan's initiative to reduce high-dose opioid prescribing, the authors found that while prescribers exposed to the state guideline alone decreased high-dose prescribing (from 20.6 percent to 13.6 percent) and excess opioid days supplied (from 20.1 percent to 14.7 percent), those prescribers additionally receiving guidance from the health plan initiative displayed significantly higher decreases on the same metrics (from 16.8 percent to 6.3 percent and 24 percent to 10 percent, respectively) (Von Korff et al., 2016). Similarly, research on an opioid dose reduction program in a U.S. Department of Veterans Affairs (VA) health care system found dramatic relative changes in prescribing of a variety of opioid medications before and after program implementation (notably, with a parallel increase in prescription of oxycodone immediate-release [IR]) (Westanmo et al., 2015). Importantly, the authors report that patient complaints were lower than they had anticipated, but stress that prescribers, despite believing that patient safety had improved, continued to express a need for more comprehensive pain management services. Becker

and colleagues (2017) report similar success at an Opioid Reassessment Clinic to which high-complexity patients with pain (e.g., with co-occurring OUD) could be referred by primary care physicians.

Stepped Care

Stepped care is a patient-centered, multimodal approach to pain management that emphasizes treatment goals and a stepwise modification plan should goals fail to be reached or other complications arise (Cleeland et al., 2003). Research demonstrates improved outcomes for patients with chronic pain compared with usual care, including reduced pain-related disability, pain interference, and pain severity (Bair et al., 2015), and the approach also is associated with improved quality of life and cost savings (Hill et al., 2011). The Stepped Care to Optimize Pain Care Effectiveness (SCOPE) study showed success at integrating stepped care models into the primary care setting through the use of telehealth mechanisms (e.g., automated symptom monitoring via phone or Internet, with related optimization of analgesic management) (Kroenke et al., 2014).

Nonpharmacologic Pain Therapies

As discussed in Chapter 2, nonpharmacologic therapies are a promising option for various types of pain, and research has begun to formally establish associations with improved outcomes. For example, multiple studies have demonstrated the effectiveness of various nonpharmacologic therapies in chronic low back pain. Massage has been found to be superior for improving function and decreasing pain compared with usual care, with benefit extending many weeks after treatment (Cherkin et al., 2011). Similarly, Lamb and colleagues (2012) report durable improvement in pain and disability outcomes 1 year after group cognitive-behavioral therapy for low back pain; their long-term data indicate an average duration of effect of 34 months. Randomized trials studying other treatment modalities, such as tai chi, yoga, stretching classes, spinal manipulation, and physical therapy, also have demonstrated effectiveness for such conditions as low back pain, subacute neck pain, and osteoarthritis (Bronfort et al., 2012; Sherman et al., 2011; Wang et al., 2016).

Interventional Pain Therapies

Research in the area of interventional pain therapies, traditionally comprising small case series, observational studies, nonrandomized trials, and trials without controls, is slowly improving in quality. (See Chapter 2 for further discussion of these therapies.) Low back and neck pain account

for the majority of medical visits for pain and the majority of disability in industrialized nations. Epidural steroid injections, most often administered for painful radiculopathy, are the most frequently performed of all pain procedures (Bicket et al., 2015), and epidural injections for chronic radicular pain have increased dramatically over the past 10 years (Manchikanti et al., 2013). The mechanism of pain relief from the injections remains unclear. Unlike NSAIDs, which are cyclooxygenase inhibitors resulting in prostaglandin reduction, steroids act via the lipoxygenase pathway, reducing leukotriene formation. Steroids also inhibit phospholipase A2, the enzyme responsible for arachidonic acid production (Baqai and Bal, 2009).

The data on efficacy for epidural steroid injections are varied despite more than 45 randomized controlled trials (RCTs) and many reviews. Review articles by interventional physicians tend to find more positive results relative to reviews by noninterventional physicians, and patient selection is important in the variability of the results (Cohen et al., 2013). A review of articles published from 1953 to 2013 found that there was evidence of a positive result lasting less than 3 months from epidural steroid injections in more than half of the controlled studies in selected individuals, and the incidence of serious complications was rare if the injections were administered with proper precautions. More positive results were seen with use of transforaminal versus interlaminar or caudal techniques, and in radicular pain from lumbar herniated disc compared with spinal stenosis or axial pain (Cohen et al., 2013).

A systematic review of 3,641 patients in 43 studies evaluating control injections found that what is injected in the epidural space is not as important as previously thought, and injection of steroid may not be essential for pain relief. Epidural injection of local anesthetic only or even saline may provide similar results, a finding that may have relevance in diabetic patients with radicular pain (Bicket et al., 2013). Spine surgery rates also have increased significantly over the past 10 years, as has disability from spinal pain. A 2015 systematic review and meta-analysis of 26 studies, 22 of which were RCTs, provided unconvincing results regarding the surgery-sparing effect of epidural steroids. There was moderate evidence, falling short of statistical significance, that epidural steroid injections had a small effect on preventing surgery in the short term, and there was no effect on the need for surgery in the long term (Bicket et al., 2015).

An area in which research activity has recently increased is the field of neuromodulation for the treatment of pain. Spinal cord stimulation (SCS) has been used to treat neuropathic pain of the extremities for many years (Deer et al., 2014). A 2005 RCT found that SCS provided superior analgesia and was more cost-effective relative to repeat surgery for failed back surgery patients with persistent lumbar radicular pain who were candidates for surgery (North et al., 2005).

A Cochrane review found that SCS provided better pain relief and analgesic sparing with decreased amputations compared with standard conservative treatment for nonreconstructable chronic critical leg ischemia (Ubbink and Vermeulen, 2013). Although lumbar radicular pain frequently is treated successfully with SCS, low back pain often is more challenging. Traditional SCS is at 40–60 Hz. High-frequency (10 kHz) SCS recently emerged as another form of SCS, and evidence for the claim of superior relief of low back and leg pain is discussed below.

With the emergence of new paresthesia-free SCS it is now possible to conduct placebo-controlled trials. In an RCT of 198 patients with chronic back and leg pain, 84.5 percent of participants who received the 10 kHz SCS experienced 50 percent relief of their back pain and 83 percent relief of their leg pain at 3 months. By contrast, participants who received traditional SCS experienced 43.8 percent and 55.5 percent reductions in their back and leg pain, respectively (Kapural et al., 2015). Likewise, a multicenter RCT showed that high-frequency stimulation provided at least 50 percent relief of low back and leg pain and was superior to traditional low-frequency SCS for 2 years (Kapural et al., 2016).

The new burst SCS, like high-frequency stimulation, is paresthesia-free. Burst stimulation (40 Hz burst with five spikes at 500 Hz/burst) is described as using both spinal and supraspinal analgesic mechanisms in relieving pain and suffering. Electroencephalogram (EEG) activity and current density were measured in the anterior cingulate and prefrontal cortex of patients with SCS with traditional tonic (40 Hz), burst, and placebo stimulation. Pain was reduced with tonic stimulation, then further reduced with burst stimulation, with EEG activity suggesting a supraspinal effect. Prior functional magnetic resonance imaging studies had demonstrated that tonic stimulation modulates the lateral pain pathways, whereas burst stimulation activates both the medial affective and lateral pain pathways (DeRidder et al., 2010). A small randomized, placebo-controlled trial comparing tonic, burst, and placebo stimulation found that all types of SCS provided better analgesia relative to placebo. Burst stimulation improved back, limb, and general pain by more than 50 percent, versus 30–52 percent relief with tonic stimulation (DeRidder et al., 2013). More recently, spinal stimulation has been compared with a more selective targeting of the dorsal root ganglion (DRG) for the treatment of complex regional pain syndromes, with promising outcomes (Deer et al., 2017).

It is important to note that clinical research on interventional pain therapies often is observational and involves low numbers of patients. Nonetheless, some organizations are attempting to extract quality data from these studies that practitioners can apply to their practice. The Spine Intervention Society (SIS) has published guidelines on intervention for spine

pain (SIS, 2014), and a few reviews suggest that adherence to these guidelines may improve outcomes.

Clinical interventions for the treatment of chronic headache also have been investigated. For example, cervical medial branch injections can be administered to provide analgesia for cervicogenic headache and neck pain. A 2016 systematic review of eight publications on radiofrequency denervation found that if performed as described by SIS guidelines, cervical radiofrequency neurotomy is effective, with minor risks. (One of the authors served in the standards division of SIS.) The majority of patients were pain-free at 6 months, and more than one-third were pain-free at 1 year. The number of sessions needed to provide complete pain relief was two, and side effects were minor and temporary (Engel et al., 2016).

When peripheral nerve blocks are performed for headaches, they are most often occipital, particularly for posterior headaches. A review of five RCTs of greater occipital nerve blocks, four of which were double-blinded, found that all were small studies with 4- to 8-week follow-up that showed partial or complete relief of headache. The addition of a steroid to local anesthetic was not found to offer additional benefit (Ambrosini and Schoenen, 2016).

Botulinum toxin was FDA approved in 2010 for chronic migraine in patients who experienced at least 15 headaches per month for 3 or more months and whose headaches had migraine features for at least 8 of those days (Khalil et al., 2014). The largest double-blind, placebo-controlled trials were all industry sponsored (Aurora et al., 2011).

Precision Health Care and Pain Management

Precision health care is focused on defining a true disease state/condition using pathophysiological mechanisms, congruent with the concept of clinical validity. In contrast, personalized health care applies to optimization of a therapeutic approach specific to an individual versus a population. This section highlights the differences in these concepts as applied to the state of the science on opioid prescribing for chronic pain management.

Diagnosis of Chronic Pain

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). In many instances, pain has no identifiable cause (i.e., is idiopathic), a feature that largely encompasses many of the pain syndromes diagnosed today, such as complex regional pain syndrome, fibromyalgia, and chronic pelvic pain. Even for the most common chronic musculoskeletal pain condition, chronic low back pain, many cases have no identifiable etiology (Giesecke et al., 2004).

Studies suggest that genetics contribute substantially to the risk of developing chronic pain (Hocking et al., 2012; Nielsen et al., 2012). In an analysis of data from a Scottish cohort study (n = 7,644 people in 2,195 extended families), for example, the heritability of any chronic pain and severe chronic pain was found to be 16 percent and 30 percent, respectively, after adjusting for shared household effects, age, body mass index, occupation, and physical activity, among other factors (Hocking et al., 2012). A systematic review of more than 50 twin studies of pain showed heritability of 50 percent for migraine, tension-type headache, and chronic widespread pain; 35 percent for back and neck pain; and 25 percent for irritable bowel syndrome (Nielsen et al., 2012). Other than rare monogenetic familial pain conditions (e.g., familial migraine with aura or erythromelalgia), however, chronic pain does not follow the Mendelian transmission model but encompasses aggregates of endophenotypes, each of which may be governed by Mendelian law (Zorina-Lichtenwalter et al., 2016). Criteria for the endophenotype construct state that the endophenotypes must (1) be associated with the disease of interest, (2) be heritable, (3) be manifest in subjects independently of active pathology, and (4) cosegregate with disease in pedigree studies (Gottesman and Gould, 2003). Endophenotypes of chronic pain include the pain phenotype (location, severity, frequency, duration, presence of peripheral and central sensitization such as hyperalgesia and allodynia) and associated symptoms, including anxiety, depression, and sleep disturbance (Zorina-Lichtenwalter et al., 2016).

Precision health care could improve diagnosis of pain by using omic approaches (genomics, metabolomics) to understand the pathophysiology of specific pain conditions and symptom phenotypes, along with advanced imaging techniques to detect functional changes in pain processing. There is significant interest in this area with respect to the potential for improving the prediction and diagnosis of pain, as well as advancing preventive strategies. At present, however, studies using candidate gene approaches have largely failed in reproducibility.

In summarizing the literature on analysis of single nucleotide polymorphisms (SNPs) associated with chronic pain, more than 200 of which are known to exist, Crow and colleagues (2013) note that three (*GCH1*, which

encodes GTP cyclohydrolase; *COMT*, an enzyme that eliminates catecholamines; and *OPRM1*, the MOPR gene) are particularly noteworthy for demonstrating the often contradictory findings in the field.

Studies of healthy volunteers and patients reporting persistent leg pain have shown associations between lower pain ratings and a *GCH1* haplotype (Campbell et al., 2009; Tegeder et al., 2006). In a larger cohort, however, neither the same association nor even the same haplotype was identified (Kim and Dionne, 2007), and similarly negative results were found in patients from a different ethnic population with HIV-associated neuropathy (Wadley et al., 2012). Likewise, research into the association between pain and *COMT* has thus far produced inconclusive and contradictory evidence. The first *COMT* SNP associated with pain was reported in 2003 (Zubieta et al., 2003) and has been confirmed in multiple patient and healthy volunteer groups (Diatchenko et al., 2005, 2006; Mukherjee et al., 2010), as well as animal models (Segall et al., 2010). Nevertheless, controversy exists over the importance of the original SNP (Val158Met) (Kim et al., 2006), and the association between increased pain and other *COMT* variants does not replicate across populations. For example, no association was found between chronic pain and *COMT* SNPs in a large study of more than 7,000 people (Hocking et al., 2010). Rather, the authors found an entirely different haplotype within the *ADRB2* gene (responsible for encoding the beta-2 adrenergic receptor) that predicted both pain severity and duration, even after controlling for gender, social class, body mass index, and other confounding factors (Hocking et al., 2010). Finally, while relationships between pain and SNPs in *OPRM1* have been reported for more than a decade (Bond et al., 1988; Wendel and Hoehe, 1998), a larger meta-analysis was unable to confirm these findings (Walter and Lotsch, 2009).

Heterogeneity in chronic pain may explain this lack of consensus, as inter- and intracohort variability could confound results (Crow et al., 2013). Thus, moving toward a more mechanism-based pain syndrome classification, aided by rigorous phenotyping, is a promising next step (Maier et al., 2010). Another issue, common in genetic association studies, is the exceedingly population-specific nature of findings, resulting in varying results across different ethnic cohorts.

Moreover, genome-wide association studies often capture gene variants that are more common (e.g., with a minor allelic frequency of ≥5 percent). Discouragingly small effect sizes frequently are identified for most variants, which explain only a fraction of the genetic contribution to a particular condition (Hardy and Singleton, 2009). More successful approaches could include examining structural variation, such as copy number variation (WTCC, 2010), or even highly penetrant rare variants (e.g., those with a minor allelic frequency of less than 1 percent) (Gibson, 2011). Recent studies examining variants in European, South Asian, and African popula-

tions used exon sequencing across large cohorts and found the vast majority of variants (about 90 percent) to be rare (Nelson et al., 2012; Tennessen et al., 2012). In a healthy twin cohort study, an attempt to demonstrate an association between pain sensitivity and rare variants was inconclusive, but the authors (Williams et al., 2012) did identify a cluster of 30 genes within the angiotensin II pathway that segregated with thermal pain perception.

Better methods for precisely identifying the mechanisms underlying an individual patient's pain could improve pain management. If clinical research is focused on advancing the methods of pain phenotyping and classification of pain endophenotypes, therapeutics can be targeted to the individual's physiology. Such potential avenues being explored in patients with chronic pain include quantitative sensory phenotyping, imaging of peripheral nociceptors, study of pain mediators in bodily fluids (i.e., "inflammatory soup"), and the genetic and epigenetic approaches outlined above (Sommer, 2016).

Among patients with chronic pain, however, variability in the etiologies and types of pain and the high frequency of mental health comorbidities in this population (Campbell et al., 2015) make it difficult to determine whether long-term opioid analgesics are effective for improving pain severity, function, and quality of life (Chou et al., 2015; Knaggs, 2015; Robinson et al., 2015; Sehgal et al., 2013). Until researchers and clinicians have a better understanding of the mechanisms underlying chronic pain and improved diagnostic accuracy for chronic pain conditions is achieved, the treatment of chronic pain will continue to be driven by a hypothesis about the source of pain and traditional trial and error.

Pain Modulation Profile

Painful conditions can undergo modulation, either suppression or augmentation at the central nervous system. The inhibitory modulation system is known to be activated by painful stimuli, exercise, and muscle contraction (Nir and Yarnitsky, 2015). The exact mechanisms of pain modulation are not fully understood; however, it is widely believed that activation of the endogenous opioid system and release of peripheral and central beta-endorphins (Bement and Sluka, 2005; Stagg et al., 2011) play a major role in this phenomenon. Other suggested mechanisms include activation of neurotransmitters such as serotonin and norepinephrine (Dietrich and McDaniel, 2004) and involvement of the adenosinergic (Martins et al., 2013) and endocannabinoid systems.

A faulty pain modulation system has been shown to be associated with such chronic pain conditions as fibromyalgia (Graven-Nielsen et al., 2000; Price et al., 2002; Staud et al., 2003), tension-type headache, musculoskeletal pain (Ashina et al., 2006; Pielsticker et al., 2005), trigeminal

neuropathies (Nasrin-Heir et al., 2015), migraine (Weissman-Fogel et al., 2003), chronic low back pain (Kleinbohl et al., 2006), irritable bowel syndrome (King et al., 2009a), and temporomandibular disorders (Maixner et al., 1998; Raphael et al., 2009; Sarlani and Greenspan, 2005; Sarlani et al., 2004). Among healthy subjects, pain modulation competence is reduced with age (Edwards et al., 2003), which may explain the increase in chronic pain among older adults.

Recent studies have shown that patients with less efficient pain modulation suffer more from chronic postsurgical pain (Yarnitsky et al., 2008) and experience greater therapeutic efficacy from certain medications, such as duloxetine, relative to patients with a normal pain modulation system (Yarnitsky et al., 2012). This finding may suggest that a pain modulation profile can be used as a tool for predicting the development of chronic pain and individualized pain management outcomes (Yarnitsky, 2015). Further research could examine the association among pain modulation profile, pain intensity, and treatment outcome in various chronic pain conditions and in response to various treatment options.

Relevance to Opioid Prescribing for Chronic Pain

Studies estimate that approximately 50 percent of the likelihood an individual will suffer from addiction has a genetic basis (Meshkin et al., 2015). The exposure to opioid medications in the health care setting could be a triggering event for some people (as noted in Chapter 2). In addition, individual differences in drug metabolism affect opioid efficacy. For instance, some opioids, such as hydrocodone and codeine, are known to be pro-drugs, and require metabolic conversion to an active metabolite (e.g., hydromorphone and morphine, respectively) for pharmacodynamic benefit. Genetic polymorphism of the enzyme CYP2D6 has been reported to lead to variable hydrocodone and codeine metabolism (Monte et al., 2014). Patients with deficient CYP2D6 activity produce very low concentrations of active drug, leading to suboptimal pain relief. In contrast, patients with duplication of active CYP2D6 genes are ultra-rapid metabolizers and produce relatively high concentrations of active drug, which can lead to toxicity. Therefore, testing the metabolic profile of the patient ahead of prescribing could assist with the selection of an opioid medication.

Genetic screening tests have been developed based on identified genes involved in opioid response, opioid metabolism, and addiction risk (Arthur, 2013; Deer et al., 2013). Further research could determine whether these tools can guide pain management practice by providing prescribers with important information regarding patients' risk for opioid tolerance and OUD.

Summary

The movement toward pragmatic, practice-based trials is an important current trend in pain research. Many such trials are still under way, but they represent a critical step forward in clinical pain research. The ideal balance of opioid reduction in the context of more comprehensive pain management (e.g., stepped care models) continues to be investigated. Nonpharmacologic therapies can be effective, particularly for lower back pain, and can have long-lasting effects on such outcomes as pain intensity and disability. Interventional techniques to relieve pain hold promise, but research on these techniques is still developing. Precision health care (broadly defined) has the potential to improve clinical pain research and management. However, further research could better characterize the association among pain modulation profiles, pain intensity, and treatment outcomes in various pain conditions and in response to various treatment options.

INTERSECTION OF PAIN AND OPIOID USE DISORDER

As discussed briefly at the end of Chapter 2, pain and reward are processed within overlapping brain structures. Before this report turns in earnest from pain management and relevant research to addressing the opioid epidemic, this section addresses several key issues related to the critical intersection of the two. In keeping with the focus of this chapter, research gaps are identified that if filled could prove crucial to helping to resolve the current crisis.

Motivations for Initiating Misuse of Prescription Opioids

As indicated in the discussion of terminology in Box 1-2 in Chapter 1, this report uses the term "misuse" to refer to any use of prescription opioids outside the specifications of a prescription, whether by patients for whom the drugs have been prescribed or by other persons. This definition encompasses a heterogeneous cluster of situations, such as using medications without a prescription, using more medication than prescribed, combining prescribed drugs with other drugs or alcohol, and engaging in activities not recommended while taking the medication. A number of studies have found that misuse of prescription opioid medications is common (SAMHSA, 2013), although how common is difficult to determine in light of the wide range of motivations and behaviors encompassed by the term and the varied circumstances under which patients for whom opioids were lawfully prescribed initiate misuse. The purpose of this section is to anchor the dry term "misuse" in the diverse desires and frailties of humankind and the vicissitudes of social life, and to call attention to the need to operationalize

various motivations and behaviors bearing on the transition from initiation of use of prescription opioids to misuse and subsequent problems.

Pervasiveness of Misuse

Any prescription medication that produces pleasurable effects or potential functional benefits poses an inherent risk of misuse. For instance, using leftover antibiotics to treat a self-diagnosed sinus infection or using nonprescribed Adderall (indicated for the treatment of attention deficit hyperactivity disorder and narcolepsy) to facilitate studying for a school test constitutes prescription drug misuse. In addition to alleviating pain, opioid medications can produce feelings of pleasure, relaxation, and contentment (NIDA, 2017), and because of their broad effects, it can be challenging to determine specifically why people initiate misuse. As a consequence, some motives for misuse (e.g., the undertreatment of pain) may be difficult to recognize. How opioid medications are prescribed can further complicate the task of classifying misuse. Under the directive of a health professional to "take when necessary to control pain," patients have flexibility in determining how often they use a dose of a prescription opioid they have been prescribed. If patients are using opioid medications in a way they believe is necessary to control their pain, the concept of misuse may not apply or be impossible to distinguish from prescribed use. This can generally pose a challenge to prescribers because opioids can produce tolerance, meaning that with use over time, they become less effective. In an effort to control pain, a logical clinical outcome might be to increase the medication dose, something the patient may desire. It is therefore unsurprising that a number of studies have found that the most common type of opioid medication misuse involves users self-escalating the prescribed dose. Among an 85-patient sample being discharged from the emergency department, for example, Beaudoin and colleagues (2014) discovered that 42 percent self-reported misusing their opioid medications. Of those misusers, 92 percent reported escalating their dose without a health care provider's direction, while 36 percent reported using the drug for a reason other than pain.

Equally important, opportunities for misuse of opioid medications may arise as a benign consequence of a patient (or a patient's parent or guardian) not knowing the proper way to take or store the medication or dispose of medication that is unused. In a large study (n = 501) of 8th and 9th graders, for example, Ross-Durow and colleagues (2013) found that 46 percent of the adolescents had been prescribed controlled medications, including pain medications, in the past 6 months, and the majority had unsupervised access to these drugs. Patients may even share their opioid medications in an honest effort to help others, such as family members, who are in pain (Kennedy-Hendricks et al., 2016).

Pain

The complexity of the relationship between pain and addiction is highlighted by the multiple trajectories of opioid misuse. Consider, for example, an all-too-common trajectory reported in open-ended/qualitative interviewing: a person is prescribed opioids for a legitimate pain condition and then starts using more than was prescribed after becoming tolerant to the drug's effects. Increases in level of use can also produce neurobiologic effects that, in turn, can create a new motive for increased use. Because patients are now taking higher doses, or after exhausting their supply have begun to experience symptoms of opioid withdrawal, a more potent form and/or route of administration (e.g., injecting) may become appealing, or heroin may become an alternative because it costs less and involves fewer barriers to use relative to opioid medications (Mars et al., 2014). The motive for misuse of opioid medication thus transitions from initial prescribed use to control pain, to misuse to manage pain, to nonmedical use, and then finally to heroin use. If a person is in acute pain from an injury, it is commonly believed that opioids will act to help relieve the suffering that follows, regardless of its duration and whether the source is prescribed or nonmedical. As this example illustrates, however, as use of opioids continues from days to weeks to months, the motivation to continue using them may become more complex, going well beyond the drugs' original purpose or capability, and being in pain and not having legitimate (i.e., prescribed) or consistent access to opioids may motivate some people to seek and misuse these drugs.

Another common scenario is described by Rigg and Monnat (2015), who found that in rural areas of the country with large populations of laborers who worked in mining and other intensely physical industries, levels of untreated or undertreated chronic pain were high. Because of the limited numbers of health care facilities in these often-remote areas, prescribing large volumes of pain medicines was a common and efficient practice. It should also be noted that early in the opioid epidemic, these communities did not have local heroin markets to compete with pain medications, which allowed the demand for those medications to grow unabated and saturate the community.

Such scenarios may be attributable to a host of factors, such as difficulties in diagnosing and measuring pain, variations in prescribers' training and practices, and the maldistribution of health care facilities and health care providers. These localized factors may, in turn, be a product of much larger shortcomings of the health care system that have unintended consequences. Some studies have shown that people of color are less likely than whites to be prescribed opioids (Pletcher et al., 2008; Singhal et al., 2016), while others have shown that providers may have different expectations

regarding the risk of opioid misuse based on a patient's race (Becker et al., 2011; Vijayaraghavan et al., 2011). Although on balance this observation may be equivocal with regard to the current opioid crisis, such structural barriers demonstrate why misuse may occur more frequently among certain groups than others.

Emotional Distress

The pain-relieving and other effects of opioids (e.g., the feelings of pleasure, relaxation, and contentment that opioids can induce) (NIDA, 2017) may give rise to use of these drugs to manage stress, depression, anxiety, or other acute psychological states or chronic mental health disorders (DiJulio et al., 2016; Feingold et al., 2017; Vorspan et al., 2015), which may be caused or worsened by social conditions (such as poverty, unemployment, lack of opportunity, and hopelessness). In these instances of misuse, the intended medical indications of opioids to alleviate physical pain may be coopted by treatment of these mental or social conditions. In the absence of a diagnosed medical condition verifying physical pain, this sort of misuse often is viewed as unacceptable. Nevertheless, people do use opioid medications to self-medicate. Even if this type of use is characterized as nonmedical use, users may perceive specific benefits in relieving some health-related conditions. Complicating this situation is the co-occurrence of mental health challenges and other chronic conditions, especially functionally debilitating pain. The inability to work, walk, or engage in enjoyable activities can greatly impact even the most resilient of patients with extensive coping skills and supports, leading to depression, anxiety, and potentially initiation or reinitiation of substance misuse. Data support the correlation between depression (Turner and Liang, 2015) and diagnosis of substance use disorder (SUD) (Zedler et al., 2014) among people prescribed opioids as a risk factor for overdose. Moreover, medications used to treat anxiety and depression (e.g., benzodiazepines) may be coprescribed with an opioid, contributing to an increased risk of overdose (Park et al., 2015; Sun et al., 2017). The ways in which the dynamics of hopelessness, lack of opportunity, poverty, undertreated pain (both physical and emotional), and reduced access to medical care have collided with nonmedical use of opioids are perhaps most obvious in the rural communities devastated by the opioid epidemic discussed above. It should be noted, moreover, that during the time in which these communities were being inundated with these medications from pill mills and other legal and illegal suppliers, they were also suffering from the effects of an economic recession.

Nonmedical Use

As motives for the initiation of misuse of opioid medications become increasingly removed from or unrelated to the drugs' original or intended medical purpose, one could argue that the term "misuse" no longer applies. The final, and perhaps most important, group to consider here are the many people who misuse prescription opioids with no pretense, thought, or concern regarding their medical uses. Here the ability of these drugs to alter consciousness in a pleasurable way motivates use, and such misuse is simply another form of illegal recreational drug use. There is no intended medical purpose for the use, and the user is only seeking the euphoric condition these drugs produce. A major challenge for understanding the problems and consequences associated with the initiation of opioid misuse is identifying the different ways people might misuse these drugs while understanding that misusers may have multiple motives for their use and that their motives may change or adapt over time. Distinguishing empirically between motivations related to alleviation of pain or distress and reward seeking is a challenging but important task at both the neural and experiential levels.

Considerations for Research on Pain and Opioid Use Disorder

Much attention in the literature has been paid to pain as a potential precondition in some opioid misuse and addiction (Fishbain et al., 2008, Martell et al., 2007; Wasan et al., 2009). Pain is a trigger for self-medication, and is without question a significant risk factor for opioid misuse (Amari et al., 2011). However, one of the challenges hindering understanding of opioid risks in pain patients is the lack of consensus on the definition of terms such as "misuse," "problematic use," and "aberrant use" (as reflected in the COMM questionnaire; the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition [DSM-IV]; Portenoy's Prescription Drug Use Questionnaire [PDUQ]; the Brief Risk Interview; ORT; the Aberrant Drug Behavior Index; and the Prescription Opioid Therapy Questionnaire). Even if these assessments are used accurately, clinicians often are unable to predict misuse and addiction liability. For instance, chronic pain patients may develop tolerance and physical dependence, often in the absence of an OUD diagnosis, yet still resort to such aberrant behaviors as dose escalation to control poorly alleviated pain (Back et al., 2009). Even if there were universal agreement on the definition of misuse, efforts to use self-report assessments to identify pain patients who may be at risk for opioid misuse have been largely ineffective (Chou et al., 2014). An important first step in adequately identifying opioid risk is characterization of the neurobiological interaction between chronic pain and opioid use. Given the role of the brain's reward circuitry in opioid addiction (Martin-Soelch et al., 2001;

Ross and Peselow, 2009), discussed earlier, this circuit is an ideal target for study of pain-induced vulnerability to opioid risk.

Treating chronic pain while avoiding misuse is particularly difficult in patients with a history of SUD. This is not an inconsiderable problem given that an estimated 5–17 percent of the U.S. population has a diagnosed SUD (Prater et al., 2002; SAMHSA, 2014; Warner et al., 1995). Unfortunately, nearly half of chronic pain patients with SUD diagnoses have reported that opioids prescribed to relieve their pain were the root cause of their disorder (Jamison et al., 2000). It is well established that prior substance use (including use of nicotine and alcohol) is a strong predictor of opioid misuse (Novy et al., 2012; Turk et al., 2008). At the same time, however, there is a significant risk of undertreating people with serious pain, particularly if the SUD diagnosis involves opioids. In fact, 80 percent of methadone maintenance patients in one study reported recent pain, and 37 percent reported chronic pain (Rosenblum et al., 2003). It is this population in particular that is at greatest risk; the presence of pain creates a vicious downward spiral (described by Garland et al., 2013) whereby pain may trigger hypervigilance and catastrophizing and lead to self-medication. The relative low cost and abundance of heroin (compared with prescription opioid analgesics) is an important motivating factor when patients transition from prescription opioids to illicit drugs (Cicero et al., 2015). This cascade of events substantially increases the risk for misuse and overdose, given the unpredictable purity of illicit fentanyl and heroin (DEA, 2015; Mars et al., 2015). On the other hand, a recent meta-analysis (Dennis et al., 2015) suggests that pain may actually be a protective factor in the consumption of illicit opioids. These discrepancies in the literature further highlight the importance of mechanistic investigations into the neurobiology of opioid-treated pain in populations with prior opioid exposure.

Considerations Relating to Developmental Neuroscience and Adolescence

Exposure to opioids at a vulnerable point in time increases the potential for SUD, and younger age is a known vulnerability (85 percent of SUDs are manifested by age 35 [Trigeiro et al., 2016]). Nonmedical use of opioids in adolescence has been classified into subtypes, including reward seeking (or sensation seeking) and self-treatment for various sources of pain. In the latter group, prescription opioids are thought to be used to self-treat physical pain and psychological symptoms following traumatic or stressful events (Young et al., 2012). In one survey of 7th to 12th graders, for example, the most common reason for nonmedical use was "to relieve pain" (n = 91, 62.8 percent), followed by "to get high" (n = 23, 15.9 percent) and "to experiment" (n = 16, 11.0 percent). Of this sample, 12.3 percent (n = 323) were identified as medical users, 2.7 percent (n = 70) as nonmedical self-

treaters, and 2.5 percent (n = 66) as nonmedical sensation seekers. Thus, pain provides a pathway to adolescent misuse of opioids, which began to rise in the 1990s in concert with the development of stronger medications and more aggressive pain treatment (although rates for 12th graders are down significantly from a peak of 9.5 percent in 2004 [Johnston et al., 2017]). And high school seniors who misuse prescription pain medications are more likely to misuse other controlled substances as young adults (McCabe et al., 2013).

More generally, as noted earlier in this report, nonmedical use of opioids is most prevalent among young adults aged 18–25, and exposure to opioids represents a major risk for OUD. Risk taking, including experimentation with illicit drugs and alcohol, peaks in adolescence and young adulthood (IOM and NRC, 2011, 2015), laying the groundwork for substance misuse. During this developmental period, social, cognitive, and biological factors combine to create inordinate vulnerabilities to substance misuse and, ultimately, SUD (Casey et al., 2011; Reyna and Farley, 2006; Rudolph et al., 2017). Although many of these outcomes play out over a lifetime, increases in overdose deaths caused by heroin and synthetic opioids can be detected beginning at age 15 (Rudd et al., 2016a,b). Understanding these developmental factors is an essential part of designing effective risk communications, public health programs, and policies to combat nonmedical use of opioids. Moreover, prevention and intervention at this stage of life has tremendous potential for improving lifelong educational, economic, and health outcomes.

Specifically, behavioral and brain research indicates that adolescents are more responsive to rewards (e.g., food, money, and drugs) than are children or adults, and this is related to their risk taking (Bjork and Pardini, 2015; Galvan et al., 2007; Reyna et al., 2011; Romer and Hennessy, 2007). Neurodevelopmental theories of risk taking build on this finding and point to the earlier maturation of subcortical reward and emotional circuitry, especially in the amygdala and striatum, compared with emotional regulation and cognitive control areas of the brain (e.g., prefrontal cortex [Casey et al., 2015]). In addition, connectivity between these regions develops. For example, resting-state connectivity analyses have shown greater connectivity between the amygdala (an emotion area used as a seed region) and the prefrontal and parietal cortices (e.g., the right middle frontal gyrus, left cingulate gyrus, left precuneus, and right inferior parietal lobule) in risk-taking compared with non-risk-taking adolescents (Dewitt et al., 2014). (Note that greater rather than lesser connectivity between emotional and cognitive systems, as postulated in neural imbalance models, is associated with risk taking, a contradiction that could be resolved by further research.) Nevertheless, research supports the conclusion that the risk of SUD is present for young people without psychological disease because these drugs

hijack the normal reward system, which is already primed and is less likely to be inhibited by cognitive control systems.

Neural imbalance between reward responsiveness and cognitive control appears to be an inevitable product of brain maturation. Although brain development is known to be shaped by experience, however, not enough is known about how experience (and what specific features of experience) sculpts the brain. For example, research could examine what kinds of experience lead to what kinds of brain growth, pruning, and neural connectivity and the functional implications of these developments for human behavior. Indeed, Feldstein Ewing and colleagues (2017) have shown that response to treatment for SUD in adolescents is associated with changing connectivity to the orbitofrontal part of the brain. Thus, considering research on risk taking as a whole, it is likely that adolescent brain development can be modified by specific experiences that reduce vulnerabilities to SUD.

In addition, effects of cognitive representation (i.e., how people "frame" or interpret the gist of their options) on risk taking have been established, and initial research has demonstrated that these mental representations can be modified and that doing so can reduce self-reported risk taking in adolescents (e.g., Fischhoff, 2008; Reyna and Mills, 2014). These effects illustrate the fact that pain, SUD, and other psychological phenomena are a function of subjective constructions rather than purely objective reality. Cognitive representations influence risk perceptions, risk preferences, and emotional responses, which in turn determine decisions to misuse substances. These decisions also occur in a social context that determines behavior, but is rarely understood beyond noting superficial differences in demographics or countries. Social norms are just one example of a highly relevant social factor. Social norms interact with developmental and individual differences in risk taking, changing the frequencies and kinds of risk taking manifested in adolescence (Mills et al., 2008; Rudolph et al., 2017; Steinberg et al., 2017). Therefore, cognitive representation, reward responsiveness, and cognitive control are likely modifiable—providing inroads for prevention and treatment—and their effects on vulnerability to SUD require a deeper mechanistic understanding of the interplay among social, cognitive, emotional, and neurobiological factors.

Basic Research on the Intersection Between Pain and Opioid Use Disorder

As discussed earlier, opioids, like other drugs that are misused, activate the structures within the mesolimbic reward pathway via MOPRs, DOPRs, and KOPRs. Binding of opioid agonists within this circuitry elicits the release of the neurotransmitter dopamine, which is critically involved in encoding reward and reinforcement. It is worth noting that pain relief

itself is rewarding, a phenomenon that is attributed to the activation of this system (Becker et al., 2012). Data from both human and animal studies indicate that chronic pain induces dramatic changes in the functionality of the reward system, both directly through diminished dopamine neurotransmission and indirectly through dysregulation of the opioid receptor systems (Hipólito et al., 2015; Martikainen et al., 2015; Narita et al., 2004; Taylor et al., 2015). During inflammatory pain, MOPRs in this circuitry are desensitized, which may be due to a pain-induced increase in the release of endogenous opioid peptides (Schrepf et al., 2016). There is also top-down management of these processes by the hippocampus, given the role this structure plays in the reinstatement of drug-seeking behavior (Portugal et al., 2014). Pain-induced alterations in the reward pathway, including the altered value of reward and opioids (Loggia et al., 2014), could play a vital role in the vulnerability of patients to opioid misuse. Despite recent efforts to characterize pain-induced sensitivity to opioids, many unanswered questions remain. Although heroin use has recently been linked to several genetic polymorphisms (Hancock, 2015; Nelson et al., 2016), these have not been studied specifically in pain patients. The identification of "abuse-vulnerable" genetic markers or implementation of other biological screening tools would be of great utility, given the relative inadequacy of self-report and provider assessments of "abuse liability" (Chou et al., 2014).

The alterations in the dopaminergic system induced by either pain or stress can generate long-term modifications in the reinforcing values of opioids and thus lead to misuse. Therefore, it is important to elucidate how these modifications manifest at the cellular level in the mesolimbic pathway. To date, few studies have assessed the impact of pain and stress together on opioid intake in rodent models. One critical factor that is particularly pertinent when studying chronic pain–induced disorders is experimental/sampling time. Many preclinical models used previously were deemed failures (Yalcin and Barrot, 2014), but this may simply have been due to timing. Many of the same studies carried out during the first 3 weeks of pain induction versus after the first 3 weeks have shown strikingly opposite results (see the review by Yalcin and Barrot, 2014).

In addition to the importance of improving models of chronic pain and stress to assess their involvement in misuse liability, a deeper understanding of the intricate details of neuromodulation and signaling within key brain structures is critical. Recently, two studies revealed that KOPR activation in discrete regions of the NAc not only is anhedonic and aversive but also can be reinforcing (Al-Hasani et al., 2015; Castro and Berridge, 2014). Remarkably, these studies revealed the presence of both hedonic and anhedonic KOPR areas in the NAc in both mice and rats (Al-Hasani et al., 2015; Castro and Berridge, 2014). These findings enhance understanding of the

complexity of the KOPR system in regulating the rewarding and aversive components of external stimuli and demand further study of how these newly identified systems modulate the pain experience.

There is clear comorbidity between chronic pain and stress-induced pathologies. Concomitant dysregulation of mesolimbic dopaminergic transmission is thought to increase vulnerability to opioid misuse. To reduce the misuse potential of opioid analgesics, a better understanding of the interactions between pain and stress systems is required. Stress-related systems, such as the kappa opioid system, have been identified as key to the regulation of dopamine release during pain and stress. This system may be crucially involved in driving the pathological changes that result in misuse and potential fatalities.

Summary

A major challenge for understanding the problems and consequences associated with the initiation of opioid misuse is identifying the different ways in which people may misuse these drugs while understanding that misusers may have multiple motives that may evolve over time (e.g., pain relief; management of stress, depression, or anxiety). These complexities need to be borne in mind as this report reviews the scientific literature bearing on the use and misuse of prescription opioids and strategies for ensuring the public's health.

An important first step in identifying opioid risk is characterization of the neurobiological interaction between chronic pain and opioid use. Pain is a trigger for self-medication and a significant risk factor for opioid misuse. Treating chronic pain while avoiding misuse is particularly problematic for patients with a prior history of SUD, and more evidence could help determine the degree of risk for OUD when people with serious pain are undertreated.

During adolescence and young adulthood, social, cognitive, and biological factors combine to create inordinate vulnerabilities to substance misuse and, ultimately, SUD. Effective prevention and treatment of OUD requires a deeper mechanistic understanding of how cognitive representation, reward responsiveness, and cognitive control interact in the developing brain; their interplay with pain; how these factors are shaped by the social context of risk taking in youth; and how these factors can be modified to reduce unhealthy risk taking.

A better understanding of the interactions among pain, reward, and stress systems, including pain-induced alterations in the reward pathway, will help inform and reduce the misuse potential of opioids.

SUPPORT FOR RESEARCH

In the absence of an institute dedicated to pain medicine, it appears that the National Institute on Drug Abuse (NIDA) has been the partner most willing to venture beyond its initial mandate in support of education and research for state-of-the-art pain management and prevention. This initiative has taken the form of various workshops, editorials, and position papers (Reuben et al., 2015; Volkow et al., 2016), but these have been mainly supportive efforts, valuable insofar as they help chart a course forward but unable to meet the need for a sustained research program. Moving forward, it will take a unified mandate across all National Institutes of Health (NIH) institutes to muster the resources needed to adequately address the area of pain medicine and, in turn, the opioid crisis. A recent commitment by NIDA and NIH to invest in overdose-reversal interventions, treatments for OUD, and nonaddictive treatments for chronic pain holds great promise (Volkow and Collins, 2017).

SUMMARY AND RECOMMENDATION

Chronic pain and OUD represent complex human conditions affecting millions of Americans and causing untold disability and loss of function. Helping individuals experiencing chronic pain regain meaningful function will require the development of therapies beyond new medications alone. Little is known about why individuals who use prescribed opioids to alleviate pain develop OUD, yet this outcome has become a driving force in the opioid epidemic. Research aimed at improving understanding of OUD and the relationships among pain, opioids, and the brain reward pathways is an essential prerequisite for developing successful treatments. Research is needed to improve understanding of the neurobiology of pain and support the discovery of innovative treatments, including nonaddictive analgesics and nonpharmacologic approaches at the level of the individual patient.

Recommendation 3-1. Invest in research to better understand pain and opioid use disorder. Given the significant public health burden of pain and opioid use disorder (OUD) in the United States, the National Institutes of Health, the Substance Abuse and Mental Health Services Administration, the U.S. Department of Veterans Affairs, industry, and other relevant research sponsors should consider greater investment in research on pain and OUD, including but not limited to research aimed at

- improving understanding of the neurobiology of pain;
- developing the evidence on promising pain treatment modalities and supporting the discovery of innovative treatments, including

nonaddictive analgesics and nonpharmacologic approaches at the level of the individual patient; and

- improving understanding of the intersection between pain and OUD, including the relationships among use and misuse of opioids, pain, emotional distress, and the brain reward pathway; vulnerability to and assessment of risk for OUD; and how to properly manage pain in individuals with and at risk for OUD.

REFERENCES

Alexandrou, A.J., A.R. Brown, M.L. Chapman, M. Estacion, J. Turner, M.A. Mis, A. Wilbrey, E.C. Payne, A. Gutteridge, P.J. Cox, R. Doyle, D. Printzenhoff, Z. Lin, B.E. Marron, C. West, N.A. Swain, R.I. Storer, P.A. Stupple, N.A. Castle, J.A. Hounshell, M. Rivara, A. Randall, S.D. Dib-Hajj, D. Krafte, S.G. Waxman, M.K. Patel, R.P. Butt, and E.B. Stevens. 2016. Subtype-selective small molecule inhibitors reveal a fundamental role for nav1.7 in nociceptor electrogenesis, axonal conduction and presynaptic release. *PLoS One* 11(4):e0152405.

Al-Hasani, R., J.G. McCall., G. Shin, A.M. Gomez, G.P. Schmitz, J.M. Bernardi, C.O. Pyo, S.I. Park, C.M. Marcinkiewcz, N.A. Crowley, M.J. Krashes, B.B. Lowell, T.L. Kash, J.A. Rogers, and M.R. Bruchas. 2015. Distinct subpopulations of nucleus accumbens dynorphin neurons drive aversion and reward. *Neuron* 87(5):1063-1077.

Amagai, Y., A. Tanaka, A. Matsuda, K. Oida, K. Jung, S. Nishikawa, H. Jang, S. Ishizaka, and H. Matsuda. 2013. Topical application of ketoprofen improves gait disturbance in rat models of acute inflammation. *Biomedical Research International* 2013:540231.

Amari, E., J. Rehm, E. Goldner, and B. Fischer. 2011. Nonmedical prescription opioid use and mental health and pain comorbidities: A narrative review. *Canadian Journal of Psychiatry* 56(8):495-502.

Ambrosini, A., and J. Schoenen. 2016. Invasive pericranial nerve interventions. *Cephalgia* 36(12):1156-1169.

Andrews, N.A., A.I. Basbaum, J.S. Mogil, F. Porreca, A.S. Rice, C.J. Woolf, G.L. Currie, R.H. Dworkin, J.C. Eisenach, S. Evans, J.S. Gewandter, T.D. Gover, H. Handwerker, W. Huang, S. Iyengar, M.P. Jensen, J.D. Kennedy, N. Lee, J. Levine, K. Lidster, I. Machin, M.P. McDermott, S.B. McMahon, T.J. Price, S.E. Ross, G. Scherrer, R.P. Seal, E.S. Sena, E. Silva, L. Stone, C.I. Svensson, D.C. Turk, and G. Whiteside. 2016. Ensuring transparency and minimization of methodologic bias in preclinical pain research: PPRECISE considerations. *Pain* 157(4):901-909.

Arosh, J.A., J. Lee, D. Balasubbramanian, J.A. Stanley, C.R. Long, M.W. Meagher, K.G. Osteen, K.L. Bruner-Tran, R.C. Burghardt, A. Starzinski-Powitz, and S.K. Banu. 2015. Molecular and preclinical basis to inhibit PGE2 receptors EP2 and EP4 as a novel nonsteroidal therapy for endometriosis. *Proceedings of the National Academy of Sciences of the United States of America* 112(31):9716-9721.

Arthur, B. 2013. Retrospective analysis of clinical and economic results of genotyping at-risk patients to guide narcotic detoxification. *The Journal of Pain* 14(4):S38.

Ashina, S., L. Bendtsen, M. Ashina, W. Magerl, and R. Jensen. 2006. Generalized hyperalgesia in patients with chronic tension-type headache. *Cephalalgia* 26(8):940-948.

Aurora, S., P. Winner, M.C. Freeman, E.L. Spierings, J.O. Heiring, R.E. DeGryse, A.M. VanDenburgh, M.E. Nolan, and C.C. Turkel. 2011. OnabotulinumtoxinA for treatment of chronic migraine: Pooled analysis of the 56-week PREEMPT Clinical Program. *Headache* 51(9):1358-1373.

Back, S.E., R.A. Payne, A.E. Waldrop, A. Smith, S. Reeves, and K.T. Brady. 2009. Prescription opioid aberrant behaviors: A pilot study of sex differences. *Clinical Journal of Pain* 25(6):477-484.

Bair, M.J., D. Ang, J. Wu, S.D. Outcalt, C. Sargent, C. Kempf, A. Froman, A.A. Schmid, T.M. Damush, Z. Yu, L.W. Davis, and K. Kroenke. 2015. Evaluation of stepped care for chronic pain (ESCAPE) in veterans of the Iraq and Afghanistan conflicts: A randomized clinical trial. *JAMA Internal Medicine* 175(5):682-689.

Baqai, A., and R. Bal. 2009. The mechanism of action and side effects of epidural steroids. *Techniques in Regional Anesthesia and Pain Management* 13(4):205-211.

Barbosa, C., and T. Cummins. 2016. Unusual voltage-gated sodium currents as targets for pain. *Current Topics in Membranes* 78:599-638.

Basso, L., and C. Altier. 2017. Transient receptor potential channels in neuropathic pain. *Current Opinion in Pharmacology* 32:9-15.

Beaudoin, F.L., S. Straube, J. Lopez, M.J. Mello, and J. Baird. 2014. Prescription opioid misuse among ED patients discharged with opioids. *The American Journal of Emergency Medicine* 32(6):580-585.

Becerra, L., K. Harter, R.G. Gonzalez, and D. Borsook. 2006. Functional magnetic resonance imaging measures of the effects of morphine on central nervous system circuitry in opioid-naive healthy volunteers. *Anesthesia and Analgesia* 103(1):208-216.

Beck, T.C., C.M. Reichel, S.M. Ghee, S.S. Bhadsavle, M.L. Kopfman, P.M. Woster, I.R. Kumarsinghe, and T.A. Dix. 2016. *Peptide-derived orally active kappa-opioid receptor agonists for peripheral pain in rats*. Poster presentation at American Academy of Pain Medicine. 2016 Annual Meeting. http://www.painmed.org/2016posters/poster100.pdf (accessed June 2, 2017).

Becker, S., W. Gandhi, and P. Schweinhardt. 2012. Cerebral interactions of pain and reward and their relevance for chronic pain. *Neuroscience Letters* 520(2):182-187.

Becker, W.C., J.L. Starrels, M. Heo, X. Li, M.G. Weiner, and B.J. Turner. 2011. Racial differences in primary care opioid risk reduction strategies. *Annals of Family Medicine* 9(3):219-225.

Becker, W.C., L. Fraenkel, E.J. Edelman, S.R. Holt, J. Glover, R.D. Kerns, and D.A. Fiellin. 2013. Instruments to assess patient-reported safety, efficacy or misuse of current opioid therapy for chronic pain: A systematic review. *Pain* 154(6):905-916.

Becker, W.C., S.N. Edmond, D.J. Cervone, A. Manhapra, J.J. Sellinger, B.A. Moore, and E.L. Edens. 2017. Evaluation of an integrated, multidisciplinary program to address unsafe use of opioids prescribed for pain. *Pain Medicine* [Epub ahead of print].

Bement, M.K., and K.A. Sluka. 2005. Low-intensity exercise reverses chronic muscle pain in the rat in a naloxone-dependent manner. *Archives of Physical Medicine and Rehabilitation* 86(9):1736-1740.

Berrettini, W.H., T.N. Ferraro, R.C. Alexander, A.M. Buchberg, and W.H. Vogel. 1994. Quantitative trait loci mapping of three loci controlling morphine preference using inbred mouse strains. *Nature Genetics* 7(1):54-58.

Besson, J.M. 1999. The neurobiology of pain. *Lancet* 353(9164):1610-1615.

Bicket, M.C., A. Gupta, C.H. Brown, and S.P. Cohen. 2013. Epidural injections for spinal pain. A systematic review and meta-analysis evaluating the "control" injections in randomized controlled trials. *Anesthesia* 119(4):907-931.

Bicket, M.C., J.M. Horowitz, H.T. Benzon, and S.P. Cohen. 2015. Epidural injections in prevention of surgery for spinal pain: Systematic review and meta-analysis of randomized controlled trials. *Spine Journal* 15(2):348-362.

Bjork, J.M., and D.A. Pardini. 2015. Who are those "risk-taking adolescents"? Individual differences in developmental neuroimaging research. *Developmental Cognitive Neuroscience* 11:56-64.

Bond, C., K.S. LaForge, M. Tian, D. Melia, S. Zhang, L. Borg, J. Gong, J. Schluger, J.A. Strong, S.M. Leal, J.A. Tischfield, M.J. Kreek, and L. Yu. 1998. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: Possible implications for opiate addiction. *Proceedings of the National Academy of Sciences of the United States of America* 95(16):9608-9613.

Boscardin, E., O. Alijevic, E. Hummler, S. Frateschi, and S. Kellenberger. 2016. The function and regulation of acid-sensing ion channels (ASICS) and the epithelial Na+ channel (ENaC): IUPHAR review 19. *British Journal of Pharmacology* 173(18):2671-2701.

Brederson, J.D., M. Strakhova, C. Mills, E. Barlow, A. Meyer, V. Nimmrich, M. Leddy, G. Simler, M. Schmidt, M. Jarvis, and S. Lacy. 2016. A monoclonal antibody against the receptor for advanced glycation end products attenuates inflammatory and neuropathic pain in the mouse. *European Journal of Pain* 20(4):607-614.

Brimmo, O.A., F. Pfeiffer, C.C. Bozynski, K. Kuroki, C. Cook, A. Stoker, S.L. Sherman, F. Monibi, and J.L. Cook. 2016. Development of a novel canine model for posttraumatic osteoarthritis of the knee. *Journal of Knee Surgery* 29(3):235-241.

Brings, V.E., and M.J. Zylka. 2015. Sex, drugs and pain control. *Nature Neuroscience* 18(8):1059-1060.

Bronfort, G., R. Evans, A.V. Anderson, K.H. Svendsen, Y. Bracha, and R.H. Grimm. 2012. Spinal manipulation, medication, or home exercise with advice for acute and subacute neck pain: A randomized trial. *Annals of Internal Medicine* 156(1 Part 1):1-10.

Brown, D.C., K. Agnello, and M.J. Iadarola. 2015. Intrathecal resiniferatoxin in a dog model: Efficacy in bone cancer pain. *Pain* 156(6):1018-1024.

Brown, E. 2016. Genetics: An incomplete mosaic. *Nature* 535(7611):S12-S13.

Bruchas, M.R., and B.L. Roth. 2016. New technologies for elucidating opioid receptor function. *Trends in Pharmacological Sciences* 37(4):279-289.

Bulloch, M. 2015. Abuse-deterrent opioids: A primer for pharmacists. *Pharmacy Times*, October 19. http://www.pharmacytimes.com/contributor/marilyn-bulloch-pharmd-bcps/2015/10/abuse-deterrent-opioids-a-primer-for-pharmacists (accessed June 2, 2017).

Burnstock, G. 2016. Purinergic mechanisms and pain. *Advances in Pharmacology* 75:91-137.

Busserolles, J., C. Tsantoulas, A. Eschalier, and J.A.L. García. 2016. Potassium channels in neuropathic pain: Advances, challenges, and emerging ideas. *Pain* 157:S7-S14.

Butler, S.F., S.H. Budman, K.C. Fernandez, G.J. Fanciullo, and R.N. Jamison. 2009. Cross-validation of a Screener to Predict Opioid Misuse in Chronic Pain Patients (SOAPP-R). *Journal of Addiction Medicine* 3(2):66-73.

Butler, S.F., S.H. Budman, G.J. Fanciullo, and R.N. Jamison. 2010. Cross validation of the current opioid misuse measure to monitor chronic pain patients on opioid therapy. *Clinical Journal of Pain* 26(9):770-776.

Cahill, C. M., S. V. Holdridge, and A. Morinville. 2007. Trafficking of delta-opioid receptors and other G-protein-coupled receptors: Implications for pain and analgesia. *Trends in Pharmacological Sciences* 28(1):23-31.

Cahill, C.M., L. Xue, P. Grenier, C. Magnussen, S. Lecour, and M.C. Olmstead. 2013. Changes in morphine reward in a model of neuropathic pain. *Behavioural Pharmacology* 24(3):207-213.

Cahill, C.M., A.M.W. Taylor, C. Cook, E. Ong, J.A. Morón, and C.J. Evans. 2014. Does the kappa opioid receptor system contribute to pain aversion? *Frontiers in Pharmacology* 5:253.

Campbell, C.M., R.R. Edwards, C. Carmona, M. Uhart, G. Wand, A. Carteret, Y. K. Kim, J. Frost, and J.N. Campbell. 2009. Polymorphisms in the GTP cyclohydrolase gene (GCH1) are associated with ratings of capsaicin pain. *Pain* 141(1-2):114-118.

Campbell, G., S. Nielsen, B. Larance, R. Bruno, R. Mattlick, W. Hall, N. Lintzeris, M. Cohen, K. Smith, and L. Degenhardt. 2015. Pharmaceutical opioid use and dependence among people living with chronic pain: Associations observed within the Pain and Opioids in Treatment (POINT) cohort. *Pain Medicine* 16(9):1745-1758.

Cao, L., A. McDonnell, A. Nitzsche, A. Alexandrou, P.P. Saintot, A.J.C. Loucif, A.R. Brown, G. Young, M. Mis, A. Randall, S. G. Waxman, P. Stanley, S. Kirby, S. Tarabar, A. Gutteridge, R. Butt, R.M. McKernan, P. Whiting, Z. Ali, J. Bilsland, and E.B. Stevens. 2016. Pharmacological reversal of a pain phenotype in iPSC-derived sensory neurons and patients with inherited erythromelalgia. *Science Translational Medicine* 8(335):335-356.

Carlezon, W.A., J. Thome, V.G. Olson, S.B. Lane-Ladd, E.S. Brodkin, N. Hiroi, R.S. Duman, R.L. Neve, and E.J. Nestler. 1998. Regulation of cocaine reward by CREB. *Science* 282(5397):2272-2275.

Casey, B.J., L.H. Somerville, I.H. Gotlib, O. Ayduk, N.T. Franklin, M.K. Askren, and Y. Shoda. 2011. Behavioral and neural correlates of delay of gratification 40 years later. *Proceedings of the National Academy of Sciences of the United States of America* 108(36):14998-15003.

Casey, B.J., A. Galván, and L. Somerville. 2015. Beyond simple models of adolescence to an integrated circuit-based account: A commentary. *Developmental Cognitive Neuroscience* 17:129-130.

Castro, D.C., and K.C. Berridge. 2014. Opioid hedonic hotspot in nucleus accumbens shell: Mu, delta, and kappa maps for enhancements of sweetness "liking" and "wanting." *Journal of Neuroscience* 34(12):4239-4250.

Chandrasekhar, S., A.K. Harvey, X.P. Yu, M.G. Chambers, J.L. Oskins, C. Lin, T.W. Seng, S.J. Thibodeaux, B.H. Norman, N.E. Hughes, M.A. Schiffler, and M.J. Fisher. 2016. Identification and characterization of novel microsomal prostaglandin e synthase-1 inhibitors for analgesia. *Journal of Pharmacology and Experimental Therapeutics* 356(3):635-644.

Chang, D.S., E. Hsu, D.G. Hottinger, and S.P. Cohen. 2016. Anti-nerve growth factor in pain management: Current evidence. *Journal of Pain Research* 9:373-383.

Chaplan, S.R., I.W. Eckert, and N.I. Carruthers. 2010. Drug discovery and development for pain. In *Translational pain research: From mouse to man*, edited by L. Kruger and A.R. Light. Boca Raton, FL: CRC Press. Pp. 391-404.

Chen, L., G. Yang, and T. Grosser. 2013a. Prostanoids and inflammatory pain. *Prostaglandins & Other Lipid Mediators* 104-105:58-66.

Chen, X.T., P. Pitis, G. Liu, C. Yuan, D. Gotchev, C.L. Cowan, D.H. Rominger, M. Koblish, S.M. DeWire, A.L. Crombie, J.D. Violin, and D.S. Yamashita. 2013b. Structure-activity relationships and discovery of a G protein biased μ opioid receptor ligand, [(3-methoxythiophen-2-yl)methyl]({2-[(9R)-9-(pyridin-2-yl)-6-oxaspiro-[4.5]decan-9-yl] ethyl})amine (TRV130), for the treatment of acute severe pain. *Journal of Medicinal Chemistry* 56(20):8019-8031.

Chen, L., G. Yang, J. Monslow, L. Todd, D.P. Cormode, J. Tang, G.R. Grant, J.H. DeLong, S.Y. Tang, J.A. Lawson, E. Pure, and G.A. FitzGerald. 2014. Myeloid cell microsomal prostaglandin E synthase-1 fosters atherogenesis in mice. *Proceedings of the National Academy of Sciences of the United States of America* 111(18):6828-6833.

Cherkin, D.C., K.J. Sherman, J. Kahn, R. Wellman, A.J. Cook, E. Johnson, J. Erro, K. Delaney, and R.A. Deyo. 2011. A comparison of the effects of 2 types of massage and usual care on chronic low back pain: A randomized, controlled trial. *Annals of Internal Medicine* 155(1):1-9.

Choi, E.Y., S.S. Lee, J.Y. Hyeon, S.H. Choe, B.R. Keum, J.M. Lim, D.C. Park, I.S. Choi, and K.K. Cho. 2016. Effects of β-Glucan on the release of nitric oxide by macrophages stimulated with lipopolysaccharide. *Asian-Australasia Journal of Animal Sciences* 29(11):1664-1674.

Chou, R., R. Deyo, B. Devine, R. Hansen, S. Sullivan, and J. Jarvik. 2014. *The effectiveness and risks of long-term opioid treatment of chronic pain: Evidence Report/Technology Assessment.* AHRQ publication 14-E005-EF. Rockville, MD: Agency for Healthcare Research and Quality.

Chou, R., J.A. Turner, E.B. Devine, R.N. Hansen, S.D. Sullivan, I. Blazina, T. Dana, C. Bougatsos, and R.A. Deyo. 2015. The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a National Institutes of Health Pathways to Prevention workshop. *Annals of Internal Medicine* 162(4):276-286.

Chu, K.L., P. Chandran, S.K. Joshi, M.F. Jarvis, P.R. Kym, and S. McGaraughty. 2011. TRPV1-related modulation of spinal neuronal activity and behavior in a rat model of osteoarthritic pain. *Brain Research* 1369:158-166.

Cicero, T., M.S. Ellis, and J. Harney. 2015. Shifting patterns of prescription opioid and heroin abuse in the United States. *New England Journal of Medicine* 373(18):1789-1790.

Clark, J.D. 2016. Preclinical pain research: Can we do better? *Anesthesiology* 125(5):846-849.

Cleeland, C.S., C.C. Reyes-Gibby, M. Schall, K. Nolan, J. Paice, J.M. Rosenberg, J.H. Tollett, and R.D. Kerns. 2003. Rapid improvement in pain management: The Veterans Health Administration and the Institute for Healthcare Improvement Collaborative. *Clinical Journal of Pain* 19(5):298-305.

Cobos, E.J., N. Ghasemlou, D. Araldi, D. Segal, K. Duong, and C.J. Woolf. 2012. Inflammation-induced decrease in voluntary wheel running in mice: A nonreflexive test for evaluating inflammatory pain and analgesia. *Pain* 153(4):876-884.

Cohen, S.P., M.C. Bicket, D. Jamison, I. Wilkinson, and J.P. Rathmell. 2013. Epidural steroids. A comprehensive evidence-based review. *Regional Anesthesia and Pain Medicine* 38(3):175-200.

Cooper, Z.D., and M. Haney. 2016. Sex-dependent effects of cannabis-induced analgesia. *Drug and Alcohol Dependence* 167:112-120.

Crombie, I.K., H.T. Davies, and W.A. Macrae. 1998. Cut and thrust: Antecedent surgery and trauma among patients attending a chronic pain clinic. *Pain* 76(1-2):167-171.

Crow, M., F. Denk, and S.B. McMahon. 2013. Genes and epigenetic processes as prospective pain targets. *Genome Medicine* 5(2):12.

Dai, Y. 2016. TRPs and pain. *Seminars in Immunopathology* 38(3):277-291.

Daou, I., H. Beaudry, A.R. Ase, J.S. Wieskopf, A. Ribeiro-da-Silva, J.S. Mogil, and P. Séguéla. 2016. Optogenetic silencing of Na_v1. 8-positive afferents alleviates inflammatory and neuropathic pain. *eNeuro* 3(1).

DEA (U.S. Drug Enforcement Administration). 2015. *National heroin threat assessment summary.* https://www.dea.gov/divisions/hq/2015/hq052215_National_Heroin_Threat_Assessment_Summary.pdf (accessed March 9, 2017).

Deer, T., G.A. Smith, B.J. Meshkin, J. Hubbard, M.S. Sinel, and B. Arthur. 2013. Pilot Investigate of the Likely Linkage (P.I.L.L.) between genetic variations in the mesolimbic dopamine system and elevated risk of opioid abuse in choice pain patients. *Journal of Addiction Medicine* 7(4):E1-E11.

Deer, T., N. Mekhail, D. Provenzano, J. Pope, E. Krames, M. Leong, R.M. Levy, D. Abejon, E. Buchser, A. Burton, A. Buvanendran, K. Dandido, D. Caraway, M. Cousins, M. DeJongste, S. Diwan, S. Eldabe, K. Gatzinsky, R.D. Foreman, S. Hayek, P. Kim, T. Kinfe, D. Kloth, K. Kumar, S. Rizvi, S.P. Lad, L. Liem, B. Linderoth, S. Makey, G. McDowell, P. McRoberts, L. Poree, J. Prager, L. Raso, R. Rauck, M. Russo, B. Simpson, B. Simpson, K. Slavin, P. Staats, M. Stanton-Hicks, P. Verrills, J. Wellington, K. Williams, and R. North. 2014. The appropriate use of neurostimulation of the spinal cord and peripheral nervous system for the treatment of chronic pain and ischemic diseases: The Neuromodulation Appropriateness Consensus Committee. *Neuromodulation* 17(6):515-550.

Deer, T.R., R.M. Levy, J. Kramer, L. Poree, K. Amirdelfan, E. Grigsby, P. Staats, A.W. Burton, A.H. Burgher, J. Obray, J. Scowcroft, S. Golovac, L. Kapural, R. Paicius, C. Kim, J. Pope, T. Yearwood, S. Samuel, W.P. McRoberts, H. Cassim, M. Netherton, N. Miller, M. Schaufele, E. Tavel, T. Davis, K. Davis, L. Johnson, and N. Mekhail. 2017. Dorsal root ganglion stimulation yielded higher treatment success rate for complex regional pain syndrome and causalgia at 3 and 12 months: A randomized comparative trial. *Pain* 158(4):669-681.

Dennis, B.B., M. Bawor, L. Naji, C.K. Chan, J. Varenbut, J. Paul, M. Varenbut, J. Daiter, C. Plater, G. Pare, D.C. Marsh, A. Worster, D. Desai, L. Thabane, and Z. Samman. 2015. Impact of chronic pain on treatment prognosis for patients with opioid use disorder: A systematic review and meta-analysis. *Substance Abuse* 9:59-80.

DeRidder, D., S. Vanneste, M. Plazier, E. van der Loo, and T. Menovsky. 2010. Burst spinal cord stimulation: Toward paresthesia-free pain suppression. *Neurosurgery* 66(5):986-990.

DeRidder, D., M. Plazier, N. Kamerling, T. Menovksy, and S. Vanneste. 2013. Burst spinal cord stimulation for limb and back pain. *World Neurosurgery* 80(5):642-649.

Devine, D.P., P. Leone, D. Pocock, and R.A. Wise. 1993. Differential involvement of ventral tegmental mu, delta and kappa opioid receptors in modulation of basal mesolimbic dopamine release: In vivo microdialysis studies. *Journal of Pharmacology and Experimental Therapeutics* 266(3):1236-1246.

DeWire, S.M., D.S. Yamashita, D.H. Rominger, G. Liu, C.L. Cowan, T.M. Graczyk, X.T. Chen, P.M. Pitis, D. Gotchev, C. Yuan, M. Koblish, M.W. Lark, and J.D. Violin. 2013. A g protein-biased ligand at the μ-opioid receptor is potently analgesic with reduced gastrointestinal and respiratory dysfunction compared with morphine. *Journal of Pharmacology and Experimental Therapeutics* 344(3):708-717.

DeWitt, S.J., S. Aslan, and F.M. Filbey. 2014. Adolescent risk-taking and resting state functional connectivity. *Psychiatry Research* 222(3):157-164.

Diatchenko, L., G.D. Slade, A.G. Nackley, K. Bhalange, A. Sigurdsson, I. Belfer, D. Goldman, K. Xu, S.A. Shabalina, D. Shagin, M.B. Max, S.S. Makarov, and W. Maixner. 2005. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Human Molecular Genetics* 14(1):135-143.

Diatchenko, L., A.G. Nackley, G.D. Slade, K. Bhalang, I. Belfer, M.B. Max, D. Goldman, and W. Maixner. 2006. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. *Pain* 125(3):216-224.

Dietrich, A., and W.F. McDaniel. 2004. Endocannabinoids and exercise. *British Journal of Sports Medicine* 38(5):536-541.

Diez-Alarcia, R., I. Ibarra-Lecue, Á.P. Lopez-Cardona, J. Meana, A. Gutierrez-Adán, L.F. Callado, E. Agirregoitia, and L. Urigüen. 2016. Biased agonism of three different cannabinoid receptor agonists in mouse brain cortex. *Frontiers in Pharmacology* 7:415.

DiJulio, B., B. Wu, and M. Brodie. 2016. *The Washington Post/Kaiser Family Foundation survey of long-term prescription painkiller users and their household members*. Publication 8942. Menlo Park, CA: Kaiser Family Foundation.

Dogra, S., and P.N. Yadav. 2015. Biased agonism at kappa opioid receptors: Implication in pain and mood disorders. *European Journal of Pharmacology* 763(Part B):184-190.

Dowell, D., T.M. Haegerich, and R. Chou. 2016. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *Morbidity and Mortality Weekly Report: Recommendations and Reports* 65(No. RR-1):1-49.

Drummond, G.B., D.J. Paterson, and J.C. McGrath. 2010. ARRIVE: New guidelines for reporting animal research. *Experimental Physiology* 95(8):841.

Edwards, R.R., R.B. Fillingim, and T.J. Ness. 2003. Age-related differences in endogenous pain modulation: A comparison of diffuse noxious inhibitory controls in healthy older and younger adults. *Pain* 101(1-2):155-165.

Emery, E.C., A.P. Luiz, and J.N. Wood. 2016. $Na_v1.7$ and other voltage-gated sodium channels as drug targets for pain relief. *Expert Opinion on Therapeutic Targets* 20(8):975-983.

Engel, A., G. Rappard, W. King, and D.J. Kennedy. 2016. The effectiveness and risks of fluoroscopically-guided cervical medial branch thermal radiofrequency neurotomy: A systematic review with comprehensive analysis of the published data. *Pain Medicine* 17(4):658-669.

Ezzatpanah, S., V. Babapour, B. Sadeghi, and A. Haghparast. 2015. Chemical stimulation of the lateral hypothalamus by carbachol attenuated the formalin-induced pain behaviors in rats. *Pharmacology, Biochemistry, and Behavior* 129:105-110.

Feingold, D., S. Brill, I. Goor-Aryeh, Y. Delayahu, and S. Lev-Ran. 2017. Misuse of prescription opioids among chronic pain patients suffering from anxiety: A cross-sectional analysis. *General Hospital Psychiatry* 47(July-August):36-42.

Feldstein Ewing, S.W., T. Chung, J.D. Caouette, A. Ketcherside, K.A. Hudson, and F.M. Filbey. 2017. Orbitofrontal cortex connectivity as a mechanism of adolescent behavior change. *Neuroimage* 151:14-23.

Fields, H.L. 2007. Should we be reluctant to prescribe opioids for chronic non-malignant pain? *Pain* 129(3):233-234.

Fischhoff, B. 2008. Assessing adolescent decision-making competence. *Developmental Review* 28(1):12-28.

Fishbain, D.A., B. Cole, J. Lewis, H.L. Rosomoff, and R.S. Rosomoff. 2008. What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review. *Pain Medicine* 9(4):444-459.

Freedman, L.P., I.M. Cockburn, and T.S. Simcoe. 2015. The economics of reproducibility in preclinical research. *PLoS Biology* 13(6):e1002165.

Fujita, W., I. Gomes, and L.A. Devi. 2015. Heteromers of μ-δ opioid receptors: New pharmacology and novel therapeutic possibilities. *British Journal of Pharmacology* 172(2):375-387.

Galvan, A., T.A. Hare, H. Voss, G. Glover, and B.J. Casey. 2007. Risk taking and the adolescent brain: Who is at risk? *Developmental Science* 10(2):F8-F14.

Ganesh, T. 2014. Prostanoid receptor EP2 as a therapeutic target. *Journal of Medicinal Chemistry* 57(11):4454-4465.

Garland, E.L., B. Froeliger, F. Zeidan, K. Partin, and M.O. Howard. 2013. The downward spiral of chronic pain, prescription opioid misuse, and addiction: Cognitive, affective, and neuropsychopharmacologic pathways. *Neuroscience & Biobehavioral Reviews* 37(10, Part 2):2597-2607.

Gavva, N.R., J.J. Treanor, A. Garami, L. Fang, S. Surapaneni, A. Akrami, F. Alvarez, A. Bak, M. Darling, and A. Gore. 2008. Pharmacological blockade of the vanilloid receptor TRPV1 elicits marked hyperthermia in humans. *Pain* 136(1):202-210.

Geha, P., Y. Yang, M. Estacion, B.R. Shulman, H. Tokuno, A.V. Apkarian, S.D. Dib-Hajj, and S.G. Waxman. 2016. Pharmacotherapy for pain in a family with inherited erythromelalgia guided by genomic analysis and functional profiling. *JAMA Neurology* 73(6):659-667.

Gibson, G. 2011. Rare and common variants: Twenty arguments. *Nature Reviews. Genetics* 13(2):135-145.

Giesecke, T., R.H. Gracely, M.A. Grant, A. Nachemson, F. Petzke, D.A. Williams, and D.J. Clauw. Evidence of augmented central pain processing in idiopathic chronic low back pain. *Arthritis and Rheumatism* 50(2):613-623.

Gill, S.S., B.D. Hammock, I. Yamamoto, and J.E. Casida. 1972. Preliminary chromatographic studies on the metabolites and photodecomposition products of the juvenoid 1-(4'-ethylphenoxy)-6,7-epoxy-3,7-dimethyl-2-octene. In *Insect juvenile hormones: Chemistry and action*, edited by J.J. Menn and M. Beroza. New York: Academic Press, Pp. 177-189.

Gill, S.S., B.D. Hammock, and J.E. Casida. 1974. Mammalian metabolism and environmental degradation of the juvenoid 1-(4'-ethylphenoxy)-3,7-dimethyl-6,7-epoxy-trans-2-octene and related compounds. *Journal of Agricultural and Food Chemistry* 22(3):386-395.

Giuliano, C., T.W. Robbins, D.R. Wille, E.T. Bullmore, and B.J. Everitt. 2013. Attenuation of cocaine and heroin seeking by mu-opioid receptor antagonism. *Psychopharmacology (Berlin)* 227(1):137-147.

Gomtsyan, A., and A. Szallasi. 2015. Targeting TRP channels: Beyond TRPV1. *Naunyn-Schmiedeberg's Archives of Pharmacology* 388(4):387.

Gottesman, I.I., and T.D. Gould. 2003. The endophenotype concept in psychiatry: Etymology and strategic intentions. *American Journal of Psychiatry* 160(4):636-645.

Graven-Nielsen, T., K.S. Aspegren, K.G. Henriksson, M. Bengtsson, J. Sorensen, A. Johnson, B. Gerdle, and L. Arendt-Nielsen. 2000. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. *Pain* 85(3):483-491.

Greaves, E., A.W. Horne, H. Jerina, M. Mikolajczak, L. Hilferty, R. Mitchell, S.M. Fleetwood-Walker, and P.T. Saunders. 2017. EP(2) receptor antagonism reduces peripheral and central hyperalgesia in a preclinical mouse model of endometriosis. *Scientific Reports* 7:44169.

Grosser, T., Y. Yu, and G.A. Fitzgerald. 2010. Emotion recollected in tranquility: Lessons learned from the COX-2 saga. *Annual Review of Medicine* 61:17-33.

Guan, Z., J. Hellman, and M. Schumacher. 2016. Contemporary views on inflammatory pain mechanisms: TRPing over innate and microglial pathways. *F1000Research* 5:F1000 Faculty Rev-2425.

Guindon, J. 2017. A novel inhibitor of endocannabinoid catabolic enzymes sheds light on behind the scene interplay between chronic pain, analgesic tolerance, and heroin dependence. *Neuropharmacology* 114:168-171.

Gupta, A., I. Gomes, E.N. Bobeck, A.K. Fakira, N.P. Massaro, I. Sharma, E. Cave, H.E. Hamm, J. Parello, and L.A. Devi. 2016. Collybolide is a novel biased agonist of κ-opioid receptors with potent antipruritic activity. *Proceedings of the National Academy of Sciences of the United States of America* 113(21):6041-6046.

Hackel, D., D. Pflücke, A. Neumann, J. Viebahn, S. Mousa, E. Wischmeyer, N. Roewer, A. Brack, and H.L. Rittner. 2013. The connection of monocytes and reactive oxygen species in pain. *PLoS One* 8(5):e63564.

Hancock, D.B., J.L. Levy, N.C. Gaddis, C. Glasheen, N.L. Saccone, G.P. Page, G.K. Hulse, D. Wildenauer, E.A. Kelty, S.G. Schwab, L. Degenhardt, N.G. Martin, G.W. Montgomery, J. Attia, E.G. Holliday, M. McEvoy, R.J. Scott, L.J. Bierut, E.C. Nelson, A.H. Kral, and E.O. Johnson. 2015. Cis-expression quantitative trait loci mapping reveals replicable associations with heroin addiction in OPRM1. *Biological Psychiatry* 78(7):474-484.

Hardy, J., and A. Singleton. 2009. Genomewide association studies and human disease. *New England Journal of Medicine* 360:1759-1768.

Harman, R., K. Carlson, J. Gaynor, S. Gustafson, S. Dhupa, K. Clement, M. Hoelzler, T. McCarthy, P. Schwartz, and C. Adams. 2016. A prospective, randomized, masked, and placebo-controlled efficacy study of intraarticular allogeneic adipose stem cells for the treatment of osteoarthritis in dogs. *Frontiers in Veterinary Science* 3:81.

Heinricher, M.M., I. Tavares, J.L. Leith, and B.M. Lumb. 2009. Descending control of nociception: Specificity, recruitment and plasticity. *Brain Research Reviews* 60(1):214-225.

Hill, J.C., D.G.T. Whitehurst, M. Lewis, S. Bryan, K.M. Dunn, N.E. Foster, K. Konstantinou, C.J. Main, E. Mason, S. Somerville, G. Sowden, K. Vohora, and E.M. Hay. 2011. Comparison of stratified primary care management for low back pain with current best practice (STarT back): A randomised controlled trial. *Lancet* 378(9802):1560-1571.

Hipólito, L., M.J. Sanchez-Catalan, I. Zanolini, A. Polache, and L. Granero. 2008. Shell/core differences in mu- and delta-opioid receptor modulation of dopamine efflux in nucleus accumbens. *Neuropharmacology* 55(2):183-189.

Hipólito, L., A. Wilson-Poe, Y. Campos-Jurado, J. Gonzalez-Romero, L. Virag, R. Whittington, S.D. Comer, S.M. Carlton, B.M. Walker, M.R. Bruchas, and J.A. Morón. 2015. Inflammatory pain promotes increased opioid self-administration: Role of dysregulated ventral tegmental area μ opioid receptors. *Journal of Neuroscience* 35(35):12217-12231.

Hocking, L.J., B.H. Smith, G.T. Jones, D.M. Reid, D.P. Strachan, and G.J. Macfarlane. 2010. Genetic variation in the beta2-adrenergic receptor but not catecholamine-O-methyltransferase predisposes to chronic pain: Results from the 1958 British Birth Cohort Study. *Pain* 149(1):143-151.

Hocking, L., A. Morris, A. Dominiczak, D. Porteous, and B. Smith. 2012. Heritability of chronic pain in 2195 extended families. *European Journal of Pain* 16(7):1053-1063.

Honda, T., E. Segi-Nishida, Y. Miyachi, and S. Narumiya. 2006. Prostacyclin-IP signaling and prostaglandin E2-EP2/EP4 signaling both mediate joint inflammation in mouse collagen-induced arthritis. *Journal of Experimental Medicine* 203(2):325-335.

Huang, W.J., W.W. Chen, and X. Zhang. 2016. Endocannabinoid system: Role in depression, reward and pain control (review). *Molecular Medicine Reports* 14(4):2899-2903.

Inceoglu, B., K.M. Wagner, J. Yang, A. Bettaieb, N.H. Schebb, S.H. Hwang, C. Morisseau, F.G. Haj, and B.D. Hammock. 2012. Acute augmentation of epoxygenated fatty acid levels rapidly reduces pain-related behavior in a rat model of type 1 diabetes. *Proceedings of the National Academy of Sciences of the United States of America* 109(28):11390-11395.

IOM (Institute of Medicine). 2011. *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington, DC: The National Academies Press.

IOM and NRC (National Research Council). 2011. *The science of adolescent risk-taking: Workshop report*. Washington, DC: The National Academies Press.

IOM and NRC. 2015. *Investing in the health and well-being of young adults*. Washington, DC: The National Academies Press.

Ishikawa, G., Y. Koya, H. Tanaka, and Y. Nagakura. 2015. Long-term analgesic effect of a single dose of anti-NGF antibody on pain during motion without notable suppression of joint edema and lesion in a rat model of osteoarthritis. *Osteoarthritis Cartilage* 23(6):925-932.

Jamison, R.N., J. Kauffman, and N.P. Katz. 2000. Characteristics of methadone maintenance patients with chronic pain. *Journal of Pain Symptom Management* 19(1):53-62.

Janak, P.H., and K.M. Tye. 2015. From circuits to behaviour in the amygdala. *Nature* 517(7534):284-292.

Ji, R.R., Z.Z. Xu, and Y.J. Gao. 2014. Emerging targets in neuroinflammation-driven chronic pain. *Nature Reviews Drug Discovery* 13(7):533-548.

Ji, R.R., A. Chamessian, and Y.Q. Zhang. 2016. Pain regulation by non-neuronal cells and inflammation. *Science* 354(6312):572-577.

Jin, Y., C.L. Smith, L. Hu, K.M. Campanalle, R. Stoltz, L.G. Huffman, T.A. McNearney, X.Y. Yang, B.L. Ackermann, R. Dean, A. Regev, and W. Landschulz. 2016. Pharmacodynamic comparison of LY3023703, a novel microsomal prostaglandin e synthase 1 inhibitor, with celecoxib. *Clinical Pharmacology and Therapeutics* 99(3):274-284.

Johansson, T., S. Narumiya, and H.U. Zeilhofer. 2011. Contribution of peripheral versus central EP1 prostaglandin receptors to inflammatory pain. *Neuroscience Letters* 495(2):98-101.

Johnson, S.W., and R.A. North. 1992. Opioids excite dopamine neurons by hyperpolarization of local interneurons. *Journal of Neuroscience* 12(2):483-488.

Johnston, L.D., O'Malley, P.M., Miech, R.A., Bachman, J.G., and J.E. Schulenberg. 2017. *Monitoring the Future national survey results on drug use, 1975-2016: Overview, key findings on adolescent drug use*. Ann Arbor: Institute for Social Research, The University of Michigan.

Julius, D. 2013. TRP channels and pain. *Annual Review of Cell and Developmental Biology* 29:355-384.

Kapural, L., C. Yu, M.W. Doust, B.E. Gliner, R. Vallejo, B.T. Sitzman, K. Amirdelfan, D.M. Morgan, L.L. Brown, T.L. Yearwood, R. Bundschu, A.W. Burton, T. Yang, R. Benyamin, and A.H. Burgher. 2015. Novel 10-kHz high frequency therapy (HF10 therapy) is superior to traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain. *Anesthesiology* 123(4):1-10.

Kapural, L., C. Yu, M.W. Doust, B.E. Gliner, R. Vallejo, B.T. Sitzman, K. Amirdelfan, D.M. Morgan, T.L. Yearwood, R. Bundschu, T. Yang, R. Benyamin, and A.H. Burgher. 2016. Comparison of 10kHz high-frequency and traditional low-frequency spinal cord stimulation for the treatment of chronic back and leg pain: 24-month results from a multicenter, randomized, controlled pivotal trial. *Neurosurgery* 79(5):667-677.

Kelleher, J.H., D. Tewari, and S.B. McMahon. 2017. Neurotrophic factors and their inhibitors in chronic pain treatment. *Neurobiology of Disease* 97(Part B):127-138.

Kenakin, T. 2015. The effective application of biased signaling to new drug discovery. *Molecular Pharmacology* 88(6):1055-1061.

Kennedy-Hendricks, A., A. Gielen, E. McDonald, E.E. McGinty, W. Shields, and C.L. Barry. 2016. Medication sharing, storage, and disposal practices for opioid medications among U.S. adults. *JAMA Internal Medicine* 176(7):1027-1029.

Kerbrat, A., J.C. Ferré, P. Fillatre, T. Ronzière, S. Vannier, B. Carsin-Nicol, S. Lavoué, M. Vérin, J.Y. Gauvrit, and Y. Le Tulzo. 2016. Acute neurologic disorder from an inhibitor of fatty acid amide hydrolase. *New England Journal of Medicine* 375(18):1717-1725.

Khalil, M., H.W. Zafar, V. Quarshie, and F. Ahmed. 2014. Prospective analysis of the use of onabotulinumtoxin A (BOTOX) in the treatment of chronic migraine; real-life data in 254 patients from Hull, U.K. *The Journal of Headache and Pain* 15:54.

Kieffer, B.L., and C. Gavériaux-Ruff. 2002. Exploring the opioid system by gene knockout. *Progress in Neurobiology* 66(5):285-306.

Kim, H., and R.A. Dionne. 2007. Lack of influence of GTP cyclohydrolase gene (GCH1) variations on pain sensitivity in humans. *Molecular Pain* 3:6.

Kim, H., D.P. Mittal, M.J. Iadarola, and R.A. Dionne. 2006. Genetic predictors for acute experimental cold and heat pain sensitivity in humans. *Journal of Medical Genetics* 43:e40.

Kim, T.I., J.G. McCall, Y.H. Jung, X. Huang, E.R. Suida, Y. Li, J. Song, Y.M. Song, H.A. Pao, R.H. Kim, C. Lu, S.D. Lee, I.S. Song, G. Shin, R. Al-Hasani, S. Kim, M.P. Tan, Y. Huang, F.G. Omenetto, J.A. Rogers, and M.R. Bruchas. 2013. Injectable, cellular-scale optoelectronics with applications for wireless optogenetics. *Science* 340(6129):211-216.

King, C.D., F. Wong, T. Currie, A.P. Mauderli, R.B. Fillingim, and J.L. Riley. 2009a. Deficiency in endogenous modulation of prolonged heat pain in patients with irritable bowel syndrome and temporomandibular disorder. *Pain* 143(3):172-178.

King, T., L. Vera-Portocarrero, T. Gutierrez, T.W. Vanderah, G. Dussor, J. Lai, H.L. Fields, and F. Porreca. 2009b. Unmasking the tonic-aversive state in neuropathic pain. *Nature Neuroscience* 12(11):1364-1366.

Kingwell, K. 2015. Pioneering biased ligand offers efficacy with reduced on-target toxicity. *Nature Reviews Drug Discovery* 14(12):809-810.

Kleinbohl, D., R. Gortelmeyer, H.J. Bender, and R. Holzl. 2006. Amantadine sulfate reduces experimental sensitization and pain in chronic back pain patients. *Anesthesia and Analgesia* 102(3):840-847.

Knaggs, R.D. 2015. SP0074 The global burden of use and abuse of opioids in non-malignant pain. *Annals of the Rheumatic Diseases* 74(Suppl. 2):20.

Knazovicky, D., E.S. Helgeson, B. Case, M.E. Gruen, W. Maixner, and B.D. Lascelles. 2016. Widespread somatosensory sensitivity in naturally occurring canine model of osteoarthritis. *Pain* 157(6):1325-1332.

Kroenke, K., E.E. Krebs, J. Wu, Z. Yu, N.R. Chumbler, and M.J. Bair. 2014. Telecare collaborative management of chronic pain in primary care: A randomized clinical trial. *Journal of the American Medical Association* 312(3):240-248.

Kuboyama, K., M. Tsuda, M. Tsutsui, Y. Toyohara, H. Tozaki-Saitoh, H. Shimokawa, N. Yanagihara, and K. Inoue. 2011. Reduced spinal microglial activation and neuropathic pain after nerve injury in mice lacking all three nitric oxide synthases. *Molecular Pain* 7(1):50.

Lamb, S.E., D. Mistry, R. Lall, Z. Hansen, D. Evans, E.J. Withers, and M.R. Underwood. 2012. Group cognitive behavioural interventions for low back pain in primary care: Extended follow-up of the back skills training trial (ISRCTN54717854). *Pain* 153(2):494-501.

Land, B.B., M.R. Bruchas, J.C. Lemos, M. Xu, E.J. Melief, and C. Chavkin. 2008. The dysphoric component of stress is encoded by activation of the dynorphin kappa-opioid system. *Journal of Neuroscience* 28(2):407-414.

Latremoliere, A., A. Latini, N. Andrews, S.J. Cronin, M. Fujita, K. Gorska, R. Hovius, C. Romero, S. Chuaiphichai, and M. Painter. 2015. Reduction of neuropathic and inflammatory pain through inhibition of the tetrahydrobiopterin pathway. *Neuron* 86(6): 1393-1406.

Le, M.J., J.A. Becker, K. Befort, and B.L. Kieffer. 2009. Reward processing by the opioid system in the brain. *Physiological Reviews* 89(4):1379-1412.

Le Bars, D., G. Guilbaud, D. Chitour, and J.M. Besson. 1980. Does systemic morphine increase descending inhibitory controls of dorsal horn neurones involved in nociception? *Brain Research* 202(1):223-228.

Lee, Y.A., and Y. Goto, Y. 2011. Neurodevelopmental disruption of cortico-striatal function caused by degeneration of habenula neurons. *PloS One* 6(4):e19450.

Leitl, M.D., S. Onvani, M.S. Bowers, K. Cheng, K.C. Rice, W.A. Carlezon, M.L. Banks, and S.S. Negus. 2014a. Pain-related depression of the mesolimbic dopamine system in rats: Expression, blockade by analgesics, and role of endogenous κ-opioids. *Neuropsychopharmacology* 39(3):614-624.

Leitl, M.D., D.N. Potter, K. Cheng, K.C. Rice, W.A. Carlezon, and S.S. Negus. 2014b. Sustained pain-related depression of behavior: Effects of intraplantar formalin and complete freund's adjuvant on intracranial self-stimulation (ICSS) and endogenous kappa opioid biomarkers in rats. *Molecular Pain* 10:62.

Liang, D.Y., T. Guo, G. Liao, W.S. Kingery, G. Peltz, and J.D. Clark. 2006. Chronic pain and genetic background interact and influence opioid analgesia, tolerance, and physical dependence. *Pain* 121(3):232-240.

Liu, H., T. Yanjun, J. Bingyuan, H. Lu, Q. Xin, Y. Jiang, L. Ding, J. Zhang, J. Chen, and B. Bai. 2016. Heterodimerization of the kappa opioid receptor and neurotensin receptor 1 contributes to a novel β-arrestin-2–biased pathway. *Biochimica et Biophysica Acta (BBA)—Molecular Cell Research* 1863(11):2719-2738.

Loggia, M.L., C. Berna, J. Kim, C.M. Cahalan, R.L. Gollub, A.D. Wasan, R.E. Harris, R.R. Edwards, and V. Napadow. 2014. Disrupted brain circuitry for pain-related reward/punishment in fibromyalgia. *Arthritis & Rheumatology* 66(1):203-212.

Lyness, W. H., F.L. Smith, J.E. Heavner, C.U. Iacono, and R.D. Garvin. 1989. Morphine self-administration in the rat during adjuvant-induced arthritis. *Life Sciences* 45(23): 2217-2224.

Maguire, D.R., and C.P. France. 2016. Interactions between cannabinoid receptor agonists and mu opioid receptor agonists in rhesus monkeys discriminating fentanyl. *European Journal of Pharmacology* 784:199-206.

Mai, J., G. Franklin, and D. Tauben. 2015. Guideline for prescribing opioids to treat pain in injured workers. *Physical Medicine & Rehabilitation Clinics of North America* 26(3): 453-465.

Maier, C., R. Baron, T.R. Tolle, A. Binder, N. Birbaumer, F. Birklein, J. Gierthmuhlen, H. Flor, C. Geber, V. Huge, E.K. Krumova, G.B. Landwehrmeyer, W. Magerl, C. Maihofner, H. Richter, R. Rolke, A. Scherens, A. Schwarz, C. Sommer, V. Tronnier, N. Uceyler, M. Valet, G. Wasner, and R.D. Treede. 2010. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Somatosensory abnormalities in 1,236 patients with different neuropathic pain syndromes. *Pain* 150(3):439-450.

Maixner, W., R. Fillingim, A. Sigurdsson, S. Kincaid, and S. Silva. 1998. Sensitivity of patients with painful temporomandibular disorders to experimentally evoked pain: Evidence for altered temporal summation of pain. *Pain* 76(1-2):71-81.

Mallipeddi, S., D.R. Janero, N. Zvonok, and A. Makriyannis. 2016. Functional selectivity at g-protein coupled receptors: Advancing cannabinoid receptors as drug targets. *Biochemical Pharmacology* 128:1-11.

Manchikanti, L., V. Pampati, F.J.E. Falco, and J.A. Hirsch. 2013. Assessment of the growth of epidural injections in the Medicare population from 2000 to 2011. *Pain Physician* 16(4):E349-E364.

Manglik, A., H. Lin, D.K. Aryal, J.D. McCorvy, D. Dengler, G. Corder, A. Levit, R.C. Kling, V. Bernat, and H. Hübner. 2016. Structure-based discovery of opioid analgesics with reduced side effects. *Nature* 537(7619):185-190.

Mansour, A., H. Khachaturian, M.E. Lewis, H. Akil, and S.J. Watson. 1988. Anatomy of CNS opioid receptors. *Trends in Neurosciences* 11(7):308-314.

Mao, J. 2012. Current challenges in translational pain research. *Trends in Pharmacological Sciences* 33(11):568-573.

Mars, S.G., P. Bourgois, G. Karandinos, F. Montero, and D. Ciccarone. 2014. "Every 'never' I ever said came true": Transitions from opioid pills to heroin injecting. *International Journal of Drug Policy* 25(2):257-266.

Mars, S.G., J.N. Fessel, P. Bourgois, F. Montero, G. Karandinos, and D. Ciccarone. 2015. Heroin-related overdose: The unexplored influences of markets, marketing and source-types in the United States. *Social Science & Medicine* 140:44-53.

Martell, B.A., P.G. O'Connor, R.D. Kerns, W.C. Becker, K.H. Morales, T.R. Kosten, and D.A. Fiellin. 2007. Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. *Annals of Internal Medicine* 146(2):116-127.

Martikainen, I.K., E.B. Nuechterlein, M. Peciña, T.M. Love, C.M. Cummiford, C.R. Green, C.S. Stohler, and J.K. Zubieta. 2015. Chronic back pain is associated with alterations in dopamine neurotransmission in the ventral striatum. *Journal of Neuroscience* 35(27):9957-9965.

Martin, T.J., and E. Ewan. 2008. Chronic pain alters drug self-administration: Implications for addiction and pain mechanisms. *Experimental and Clinical Psychopharmacology* 16(5):357-366.

Martin, T.J., N.L. Buechler, W. Kahn, J.C. Crews, and J.C. Eisenach. 2004. Effects of laparotomy on spontaneous exploratory activity and conditioned operant responding in the rat: A model for postoperative pain. *Anesthesiology* 101(1):191-203.

Martin-Soelch, C., A.F. Chevalley, G. Künig, J. Missimer, S. Magyar, A. Mino, W. Schultz, and K.L. Leenders. 2001. Changes in reward-induced brain activation in opiate addicts. *European Journal of Neuroscience* 14(8):1360-1368.

Martins, D.F., L. Mazzardo-Martins, F. Soldi, J. Stramosk, A.P. Piovezan, and A.R. Santos. 2013. High-intensity swimming exercise reduces neuropathic pain in an animal model of complex regional pain syndrome type I: Evidence for a role of the adenosinergic system. *Neuroscience* 234:69-76.

Matsui, A., B.C. Jarvie, B.G. Robinson, S.T. Hentges, and J.T. Williams. 2014. Separate GABA afferents to dopamine neurons mediate acute action of opioids, development of tolerance, and expression of withdrawal. *Neuron* 82(6):1346-1356.

Matsumura, Y., T. Yamashita, A. Sasaki, E. Nakata, K. Kohno, T. Masuda, H. Tozaki-Saitoh, T. Imai, Y. Kuraishi, and M. Tsuda. 2016. A novel P2X4 receptor-selective antagonist produces anti-allodynic effect in a mouse model of herpetic pain. *Scientific Reports* 6:32461.

McCabe, S.E., B.T. West, and C.J. Boyd. 2013. Leftover prescription opioids and nonmedical use among high school seniors: A multi-cohort national study. *Journal of Adolescent Health* 52(4):480-485.

Meshkin, B., K. Lewis, S. Kantorovich, N. Anand, and L. Davila. 2015. Adding genetic testing to evidence-based guidelines to determine the safest and most effective chronic pain treatment for injured workers. *International Journal of Biomedical Science* 11(4):157-165.

Mickle, A.D., A.J. Shepherd, and D.P. Mohapatra. 2016. Nociceptive TRP channels: Sensory detectors and transducers in multiple pain pathologies. *Pharmaceuticals* 9(4):72.

Miller, R.E., J.A. Block, and A.M. Malfait. 2017. Nerve growth factor blockade for the management of osteoarthritis pain: What can we learn from clinical trials and preclinical models? *Current Opinion in Rheumatology* 29(1):110-118.

Mills, B.A., V.F. Reyna, and S.M. Estrada. 2008. Explaining contradictory relations between risk perception and risk taking. *Psychological Science* 19(5):429-434.

Miyagi, M., T. Ishikawa, H. Kamoda, M. Suzuki, G. Inoue, Y. Sakuma, Y. Oikawa, K. Uchida, T. Suzuki, and K. Takahashi. 2016. The efficacy of nerve growth factor antibody in a mouse model of neuropathic cancer pain. *Experimental Animals* 65(4):337-343.

Mogil, J.S., S.G. Wilson, K. Bon, S.E. Lee, K. Chung, P. Raber, J.O. Pieper, H.S. Hain, J.K. Belknap, L. Hubert, G.I. Elmer, J.M. Chung, and M. Deyor. 1999. Heritability of nociception I: Responses of 11 inbred mouse strains on 12 measures of nociception. *Pain* 80(1-2):67-82.

Monte, A.A., K.J. Heard, J. Campbell, D. Hamamura, R.M. Weinshilboum, and V. Vasiliou. 2014. The effect of cyp2d6 drug-drug interactions on hydrocodone effectiveness. *Academic Emergency Medicine: Official Journal of the Society for Academic Emergency Medicine* 21(8):879-885.

Mukherjee, N., K.K. Kidd, A.J. Pakstis, W.C. Speed, H. Li, Z. Tarnok, C. Barta, S.L. Kajuna, and J.R. Kidd. 2010. The complex global pattern of genetic variation and linkage disequilibrium at catechol-O-methyltransferase. *Molecular Psychiatry* 15(2):216-225.

Munoz, F., and H. Hu. 2016. Chapter five—the role of store-operated calcium channels in pain. *Advances in Pharmacology* 75:139-151.

Narita, M., M. Suzuki, S. Imai, N. Narita, S. Ozaki, Y. Kishimoto, K. Oe, Y. Yajima, M. Yamazaki, and T. Suzuki. 2004. Molecular mechanism of changes in the morphine-induced pharmacological actions under chronic pain-like state: Suppression of dopaminergic transmission in the brain. *Life Sciences* 74(21):2655-2673.

Narita, M., Y. Kishimoto, Y. Ise, Y. Yajima, K. Misawa, and T. Suzuki. 2005. Direct evidence for the involvement of the mesolimbic kappa-opioid system in the morphine-induced rewarding effect under an inflammatory pain-like state. *Neuropsychopharmacology* 30(1):111-118.

Nasri-Heir, C., J. Khan, R. Benoliel, C. Feng, D. Yarnitsky, F. Kuo, C. Hirschberg, G. Hartwell, C.Y. Huang, G. Heir, O. Korczeniewska, S.R. Diehl, and E. Eliav. 2015. Altered pain modulation in patients with persistent postendodontic pain. *Pain* 156(10):2032-2041.

Nelson, M.R., D. Wegmann, M.G. Ehm, D. Kessner, P. St Jean, C. Verzilli, J. Shen, Z. Tang, S.A. Bacanu, D. Fraser, L. Warren, J. Aponte, M. Zawistowski, X. Liu, H. Zhang, Y. Zhang, J. Li, Y. Li, L. Li, P. Woollard, S. Topp, M.D. Hall, K. Nangle, J. Wang, G. Abecasis, L.R. Cardon, S. Zöllner, J.C. Whittaker, S.L. Chissoe, J. Novembre, and V. Mooser. 2012. An abundance of rare functional variants in 202 drug target genes sequenced in 14,002 people. *Science* 337(6090):100-104.

Neumann, E., H. Hermanns, F. Barthel, R. Werdehausen, and T. Brandenburge. 2015. Expression changes of microRNA-1 and its targets Connexin 43 and brain-derived neurotrophic factor in the peripheral nervous system of chronic neuropathic rats. *Molecular Pain* 11:39.

NIDA (National Institute on Drug Abuse). 2017. *How do opioids work?* https://teens.drugabuse.gov/teachers/mind-over-matter/opioids/how-do-opioids-work (accessed May 25, 2017).

Nielsen, C., G. Knudsen, and O.A. Steingrimsdottir. 2012. Twin studies of pain. *Clinical Genetics* 82(4):331-340.

Niikura, K., M. Narita, E.R. Butelman, M.J. Kreek, and T. Suzuki. 2010. Neuropathic and chronic pain stimuli downregulate central mu-opioid and dopaminergic transmission. *Trends in Pharmacological Sciences* 31(7):299-305.

Nir, R.R., and D. Yarnitsky. 2015. Conditioned pain modulation. *Current Opinion in Supportive and Palliative Care* 9(2):131-137.

North, R.B., D.H. Kidd, F. Farrokhi, and S.A. Piantadosi. 2005. Spinal cord stimulation versus repeated lumbosacral spine surgery for chronic pain: A randomized, controlled trial. *Neurosurgery* 56(1):98-106.

Novy, D.M., C. Lam, E.R. Gritz, M. Hernandez, L.C. Driver, and D. Koyyalagunta. 2012. Distinguishing features of cancer patients who smoke: Pain symptom burden, and risk for opioid misuse. *The Journal of Pain* 13(11):1058-1067.

Nuckols, T.K., L. Anderson, I. Popescu, A.L. Diamant, B. Doyle, P. DiCapua, and R. Chou. 2014. Opioid prescribing: A systematic review and critical appraisal of guidelines for chronic pain. *Annals of Internal Medicine* 160(1):38-47.

Oertel, B.G., C. Preibisch, T. Wallenhorst, T. Hummel, G. Geisslinger, H. Lanfermann, and J. L'otsch. 2007. Differential opioid action on sensory and affective cerebral pain processing. *Clinical Pharmacology and Therapeutics* 83(4):577-588.

Omelchenko, N., and S.R. Sesack. 2005. Laterodorsal tegmental projections to identified cell populations in the rat ventral tegmental area. *Journal of Comparative Neurology* 483(2):217-235.

Ozaki, S., M. Narita, M. Narita, M. Iino, J. Sugita, Y. Matsumura, and T. Suzuki. 2002. Suppression of the morphine-induced rewarding effect in the rat with neuropathic pain: Implication of the reduction in mu-opioid receptor functions in the ventral tegmental area. *Journal of Neurochemistry* 82(5):1192-1198.

Pare, D., and S. Duvarci. 2012. Amygdala microcircuits mediating fear expression and extinction. *Current Opinion in Neurobiology* 22(4):717-723.

Park, C.K., Z.Z. Xu, T. Liu, N. Lu, C.N. Serhan, and R.R. Ji. 2011. Resolvin D2 is a potent endogenous inhibitor for transient receptor potential subtype V1/A1, inflammatory pain, and spinal cord synaptic plasticity in mice: Distinct roles of resolvin D1, D2, and E1. *Journal of Neuroscience* 31(50):18433-18438.

Park, J.H., and Y.C. Kim. 2017. P2X7 receptor antagonists: A patent review (2010-2015). *Expert Opinion on Therapeutic Patents* 27(3):257-267.

Park, T.W., R. Saitz, D. Ganoczy, M.A. Illgen, and A.S. Bohnert. 2015. Benzodiazepine prescribing patterns and deaths from drug overdose among U.S. veterans receiving opioid analgesics: Case-cohort study. *British Medical Journal* 350:h2698.

Pawsey, S., M. Wood, H. Browne, K. Donaldson, M. Christie, and S. Warrington. 2016. Safety, tolerability and pharmacokinetics of FAAH inhibitor V158866: A double-blind, randomised, placebo-controlled phase I study in healthy volunteers. *Drugs in R&D* 16(2):181-191.

Peckys, D., and G.B. Landwehrmeyer. 1999. Expression of mu, kappa, and delta opioid receptor messenger RNA in the human CNS: A 33P in situ hybridization study. *Neuroscience* 88(4):1093-1135.

Peirs, C., and R.P. Seal. 2016. Neural circuits for pain: Recent advances and current views. *Science* 354(6312):578-584.

Pielsticker, A., G. Haag, M. Zaudig, and S. Lautenbacher. 2005. Impairment of pain inhibition in chronic tension-type headache. *Pain* 118(1-2):215-223.

Pletcher, M.J., S.G. Kertesz, M.A. Kohn, and R. Gonzales. 2008. Trends in opioid prescribing by race/ethnicity for patients seeking care in U.S. emergency departments. *Journal of the American Medical Association* 299(1):70-78.

Portugal, G.S., R. Al-Hasani, A.K. Fakira, J.L. Gonzalez-Romero, Z. Melyan, J.G. McCall, M.R. Bruchas, and J.A. Morón. 2014. Hippocampal long-term potentiation is disrupted during expression and extinction but is restored after reinstatement of morphine place preference. *Journal of Neuroscience* 34(2):527-538.

Pradhan, A.A., K. Befort, C. Nozaki, C. Gavériaux-Ruff, and B.L. Kieffer. 2011. The delta opioid receptor: An evolving target for the treatment of brain disorders. *Trends in Pharmacological Sciences* 32(10):581-590.

Prater, C.D., R.G. Zylstra, and K.E. Miller. 2002. Successful pain management for the recovering addicted patient. *Primary Care Companion to the Journal of Clinical Psychiatry* 4(4):125-131.

Price, D.D., R. Staud, M.E. Robinson, A.P. Mauderli, R. Cannon, and C.J. Vierck. 2002. Enhanced temporal summation of second pain and its central modulation in fibromyalgia patients. *Pain* 99(1-2):49-59.

Qi, J., K. Buzas, H. Fan, J.I. Cohen, K. Wang, E. Mont, D. Klinman, J.J. Oppenheim, and O.M.Z. Howard. 2011. Painful pathways induced by TLR stimulation of dorsal root ganglion neurons. *The Journal of Immunology* 186(11):6417-6426.

Raehal, K.M., and L.M. Bohn. 2014. β-arrestins: Regulatory role and therapeutic potential in opioid and cannabinoid receptor-mediated analgesia. *Handbook of Experimental Pharmacology* 219:427-443.

Rainville, P. 2002. Brain mechanisms of pain affect and pain modulation. *Current Opinion in Neurobiology* 12(2):195-204.

Raphael, K.G., M.N. Janal, S. Anathan, D.B. Cook, and R. Staud. 2009. Temporal summation of heat pain in temporomandibular disorder patients. *Journal of Orofacial Pain* 23(1):54-64.

Rauck, R.L., J. North, and J.C. Eisenach. 2015. Intrathecal clonidine and adenosine: Effects on pain and sensory processing in patients with chronic regional pain syndrome. *Pain* 156(1):88-95.

Reiter, E., S. Ahn, A.K. Shukla, and R.J. Lefkowitz. 2012. Molecular mechanism of beta-arrestin-biased agonism at seven-transmembrane receptors. *Annual Review of Pharmacology and Toxicology* 52:179-197.

Reuben, D.B., A.A. Alvanzo, T. Ashikaga, G.A. Bogat, C.M. Callahan, V. Ruffing, and D.C. Steffens. 2015. National Institutes of Health Pathways to Prevention Workshop: The role of opioids in the treatment of chronic pain. *Annals of Internal Medicine* 162(4):295-300.

Reyna, V.F., and F. Farley. 2006. Risk and rationality in adolescent decision making: Implications for theory, practice, and public policy. *Psychological Science in the Public Interest* 7(1):1-44.

Reyna, V.F., and B.A. Mills. 2014. Theoretically motivated interventions for reducing sexual risk taking in adolescence: A randomized controlled experiment using fuzzy-trace theory. *Journal of Experimental Psychology: General* 143(4):1627-1648.

Reyna, V.F., S.M. Estrada, J.A. DeMarinis, R.M. Myers, J.M. Stanisz, and B.A. Mills. 2011. Neurobiological and memory models of risky decision making in adolescents versus young adults. *Journal of Experimental Psychology: Learning, Memory, and Cognition* 37(5):1125-1142.

Reynolds, D.V. 1969. Surgery in the rat during electrical analgesia induced by focal brain stimulation. *Science* 164(3878):444-445.

Rigg, K.K., and S.M. Monnat. 2015. Urban vs. rural differences in prescription opioid misuse among adults in the United States: Informing region specific drug policies and interventions. *International Journal on Drug Policy* 26(5):484-490.

Robinson, J.P., E.J. Dansie, H.D. Wilson, S. Rapp, and D.C. Turk. 2015. Attitudes and beliefs of working and work-disabled people with chronic pain prescribed long-term opioids. *Pain Medicine* 16(7):1311-1324.

Rolyan, H., S. Liu, J.G. Hoeijmakers, C.G. Faber, I.S. Merkies, G. Lauria, J.A. Black, and S.G. Waxman. 2016. A painful neuropathy-associated $Na_v1.7$ mutant leads to time-dependent degeneration of small-diameter axons associated with intracellular Ca2+ dysregulation and decrease in ATP levels. *Molecular Pain* 12:1744806916674472.

Romer, D., and M. Hennessy. 2007. A biosocial-affect model of adolescent sensation seeking: The role of affect evaluation and peer-group influence in adolescent drug use. *Prevention Science* 8(2):89-101.

Rosenblum, A., H. Joseph, C. Fong, S. Kipnis, C. Cleland, and R.K. Portenoy. 2003. Prevalence and characteristics of chronic pain among chemically dependent patients in methadone maintenance and residential treatment facilities. *Journal of the American Medical Association* 289(18):2370-2378.

Ross, S., and E. Peselow. 2009. The neurobiology of addictive disorders. *Clinical Neuropharmacology* 32(5):269-276.

Ross-Durow, P.L., S.E. McCabe, and C.J. Boyd. 2013. Adolescents' access to their own prescription medications in the home. *Journal of Adolescent Health* 53(2):260-264.

Rudd, R.A., N. Aleshire, J.E. Zibbell, and R.M. Gladden. 2016a. Increases in drug and opioid overdose deaths—United States, 2000–2014. *Morbidity and Mortality Weekly Report* 64(50-51):1378-1382.

Rudd, R.A., P. Seth, F. David, and L. Scholl. 2016b. Increases in drug and opioid-involved overdose deaths—United States, 2010–2015. *Morbidity and Mortality Weekly Report* 65(50-51):1445-1452.

Rudolph, M., O. Miranda-Dominguez, A. Cohen, K. Breiner, L. Steinberg, R.J. Bonnie, E.S. Scott, K. Taylor-Thompson, J. Chein, K.C. Fettich, J.A. Richeson, D.V. Dellarco, A. Galván, B.J. Casey, and D. Fair. 2017. At risk of being risky: The relationship between "brain age" under emotional states and risk preference. *Developmental Cognitive Neuroscience* 24:96-106.

SAMHSA (Substance Abuse and Mental Health Services Administration). 2013. *Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings*. NSDUH Series H-46, HHS Publication SMA 13-4795. Rockville, MD: SAMHSA.

SAMHSA. 2014. *2014 National Survey on Drug Use and Health (NSDUH)*. Rockville, MD: SAMHSA.

Sarlani, E., and J.D. Greenspan. 2005. Why look in the brain for answers to temporomandibular disorder pain? *Cells, Tissues, Organs* 180(1):69-75.

Sarlani, E., E.G. Grace, M.A. Reynolds, and J.D. Greenspan. 2004. Evidence for up-regulated central nociceptive processing in patients with masticatory myofascial pain. *Journal of Orofacial Pain* 18(1):41-55.

Schenkel, L.B., P.R. Olivieri, A.A. Boezio, H.L. Deak, R. Emkey, R.F. Graceffa, H. Gunaydin, A. Guzman-Perez, J.H. Lee, and Y. Teffera. 2016. Optimization of a novel quinazolinone-based series of transient receptor potential A1 (TRPA1) antagonists demonstrating potent in vivo activity. *Journal of Medicinal Chemistry* 59(6):2794-2809.

Schmelzer, K.R., L. Kubala, J.W. Newman, I.H. Kim, J.P. Eiserich, and B.D. Hammock. 2005. Soluble epoxide hydrolase is a therapeutic target for acute inflammation. *Proceedings of the National Academy of Sciences of the United States of America* 102(28):9772-9777.

Schneider, S., D. Provasi, and M. Filizola. 2016. How oliceridine (TRV-130) binds and stabilizes a μ opioid receptor conformational state that selectively triggers G protein signaling pathways. *Biochemistry* 55(46):6456-6466.

Schrepf, A., D.E. Harper, S.E. Harte, H. Wang, E. Ichesco, J.P. Hampson, J.K. Zubieta, D.J. Clauw, and R.E. Harris. 2016. Endogenous opioidergic dysregulation of pain in fibromyalgia: A PET and fMRI study. *Pain* 157(10):2217-2225.

Schumacher, M.A. 2010. Transient receptor potential channels in pain and inflammation: Therapeutic opportunities. *Pain Practice* 10(3):185-200.

Segall, S.K., A.G. Nackley, L. Diatchenko, W.R. Lariviere, X. Lu, J.S. Marron, L. Grabowski-Boase, J.R. Walker, G. Slade, J. Gauthier, J.S. Bailey, B.M. Steffy, T.M. Maynard, L.M. Tarantino, and T. Wiltshire. 2010. Comt1 genotype and expression predicts anxiety and nociceptive sensitivity in inbred strains of mice. *Genes, Brain, and Behavior* 9(8):933-946.

Sehgal, N., J. Colson, and H.S. Smith. 2013. Chronic pain treatment with opioid analgesics: Benefits versus harms of long-term therapy. *Expert Reviews in Neurotherapeutics* 13(11):1201-1220.

Shcherbatko, A., A. Rossi, D. Foletti, G. Zhu, O. Bogin, M. Galindo Casas, M. Rickert, A. Hasa-Moreno, V. Bartsevich, A. Crameri, A. R. Steiner, R. Henningsen, A. Gill, J. Pons, D. L. Shelton, A. Rajpal, and P. Strop. 2016. Engineering highly potent and selective microproteins against nav1.7 sodium channel for treatment of pain. *Journal of Biological Chemistry* 291(27):13974-13986.

Sherman, K.J., D.C. Cherkin, R.D. Wellman, A.J. Cook, R.J. Hawkes, K. Delaney, and R.A. Deyo. 2011. A randomized trial comparing yoga, stretching, and a self-care book for chronic low back pain. *Archives of Internal Medicine* 171(22):2019-2026.

Shippenberg, T.S. 2009. The dynorphin/kappa opioid receptor system: A new target for the treatment of addiction and affective disorders. *Neuropsychopharmacology* 34:247.

Shippenberg, T.S., C. Stein, A. Humer, M.J. Millan, and A. Herz. 1988. Motivational effects of opioids in an animal model of prolonged inflammatory pain: Alteration in the effects of kappa- but not of mu-receptor agonists. *Pain* 35(2):179-186.

Shirayama, Y., H. Ishida, M. Iwata, G.I. Hazama, R. Kawahara, and R.S. Duman. 2004. Stress increases dynorphin immunoreactivity in limbic brain regions and dynorphin antagonism produces antidepressant-like effects. *Journal of Neurochemistry* 90(5):1258-1268.

Singhal, A., Y. Tien, and R.Y. Hsia. 2016. Racial-ethnic disparities in opioid prescriptions at emergency department visits for conditions commonly associated with prescription drug abuse. *PLoS One* 11(8):e0159224.

SIS (Spine Intervention Society). 2014. *Practice guidelines for spinal diagnostic and treatment procedures*. 2nd ed., edited by N. Bogduk. San Rafael, CA: SIS.

Siuda, E.R., B.A. Copits, M.J. Schmidt, M.A. Baird, R. Al-Hasani, W.J. Planer, S.C. Funderburk, J.G. McCall, R.W. Gereau, and M.R. Bruchas. 2015. Spatiotemporal control of opioid signaling and behavior. *Neuron* 86(4):923-935.

Skarke, C., N. Alamuddin, J.A. Lawson, X. Li, J.F. Ferguson, M.P. Reilly, and G.A. FitzGerald. 2015. Bioactive products formed in humans from fish oils. *Journal of Lipid Research* 56(9):1808-1820.

Sommer, C. 2016. Exploring pain pathophysiology in patients. *Science* 354 (6312):588-592.

Stagg, N.J., H.P. Mata, M.M. Ibrahim, E.J. Henriksen, F. Porreca, T.W. Vanderah, and P. Malan. 2011. Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: Role of endogenous opioids. *Anesthesiology* 114(4):940-948.

Staud, R., M.E. Robinson, C.J. Vierck, and D.D. Price. 2003. Diffuse noxious inhibitory controls (DNIC) attenuate temporal summation of second pain in normal males but not in normal females or fibromyalgia patients. *Pain* 101(1-2):167-174.

Steinberg, L., G. Icenogle, E. Shulman, K. Breiner, J. Chein, D. Bacchini, L. Chang, N. Chaudhary, L. DiGuinta, K.A. Dodge, K.A. Fanti, J.E. Landsford, P.S. Malone, P. Oburu, C. Pastorelli, A.T. Skinner, E. Sorbring, S. Tapanya, L.M.U. Tirado, L.P. Alampay, S.M. Al-Hassan, and H. Takash. 2017. Around the world, adolescence is a time of heightened sensation seeking and immature self-regulation. *Developmental Science*:e12532.

St-Jacques, B., and W. Ma. 2014. Peripheral prostaglandin E2 prolongs the sensitization of nociceptive dorsal root ganglion neurons possibly by facilitating the synthesis and anterograde axonal trafficking of EP4 receptors. *Experimental Neurology* 261:354-366.

Sugita, R., H. Kuwabara, K. Sugimoto, K. Kubota, Y. Imamura, T. Kiho, A. Tengeiji, K. Kawakami, and K. Shimada. 2016. A novel selective prostaglandin E2 synthesis inhibitor relieves pyrexia and chronic inflammation in rats. *Inflammation* 39(2):907-915.

Sun, E.C., A. Dexit, K. Humphreys, B.D. Darnall, L.C. Baker, and S. Mackey. 2017. Association between concurrent use of prescription opioids and benzodiazepines and overdose: Retrospective analysis. *British Medical Journal* 356:j760.

Takeuchi, O., and S. Akira. 2010. Pattern recognition receptors and inflammation. *Cell* 140(6):805-820.

Tan, Y.H., K. Li, X.Y. Chen, Y. Cao, A.R. Light, and K. Fu. 2012. Activation of SRC family kinases in spinal microglia contributes to formalin-induced persistent pain state through p38 pathway. *The Journal of Pain* 13(10):1008-1115.

Taylor, A.M.W., A. Castonguay, A.J. Taylor, N.P. Murphy, A. Ghogha, C. Cook, L. Xue, M.C. Olmstead, Y. DeKoninck, C.J. Evans, and C.M. Cahill. 2015. Microglia disrupt mesolimbic reward circuitry in chronic pain. *Journal of Neuroscience* 35(22):8442-8450.

Tegeder, I., M. Costigan, R.S. Griffin, A. Abele, I. Belfer, H. Schmidt, C. Ehnert, J. Nejim, C. Marian, J. Scholz, T. Wu, A. Allchorne, L. Diatchenko, A.M. Binshtok, D. Goldman, J. Adolph, S. Sama, S.J. Atlas, W.A. Carlezon, A. Parsegian, J. Lötsch, R.B. Fillingim, W. Maixner, G. Geisslinger, M.B. Max, and C.J. Woolf. 2006. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nature Medicine* 12(11):1269-1277.

Teixeira, J.M., F. Bobinski, C.A. Parada, K.A. Sluka, and C.H. Tambeli. 2016. P2X3 and P2X2/3 receptors play a crucial role in articular hyperalgesia development through inflammatory mechanisms in the knee joint experimental synovitis. *Molecular Neurobiology* [Epub ahead of print].

Tennessen, J.A., A.W. Bigham, T.D. O'Connor, W. Fu, E.E. Kenny, S. Gravel, S. McGee, R. Do, X. Liu, G. Jun, H.M. Kang, D. Jordan, S.M. Leal, S. Gabriel, M.J. Rieder, G. Abecasis, D. Altshuler, D.A. Nickerson, E. Boerwinkle, S. Sunyaev, C.D. Bustamante, M.J. Bamshad, and J.M. Akey. 2012. Evolution and functional impact of rare coding variation from deep sequencing of human exomes. *Science* 337:64-69.

Tepper, J.M., and C.R. Lee. 2007. GABAergic control of substantia nigra dopaminergic neurons. *Progress in Brain Research* 160:189-208.

Thayer, J.F., and R.D. Lane. 2009. Claude Bernard and the heart-brain connection: Further elaboration of a model of neurovisceral integration. *Neuroscience and Biobehavioral Reviews* 33(2):81-88.

Tracey, I. 2010. Getting the pain you expect: Mechanisms of placebo, nocebo and reappraisal effects in humans. *Nature Medicine* 16(11):1277-1283.

Tracey, I., and P.W. Mantyh. 2007. The cerebral signature for pain perception and its modulation. *Neuron* 55(3):377-391.

Trigeiro, A.A., K.L. Kirsh, and S.D. Passik. 2016. Scope of the problem: Intersection of chronic pain and addiction. In *Controlled substance management in chronic pain*, edited by P.S. Staats and S.M. Silverman. Switzerland: Springer International Publishing. Pp. 13-27.

Tsai, H.C., F. Zhang, A. Adamantidis, G.D. Stuber, A. Bonci, L. de Lecea, and K. Deisseroth. 2009. Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. *Science* 324(5930):1080-1084.

Turk, D.C., R.H. Dworkin, R.R. Allen, N. Bellamy, N. Brandenburg, D.B. Carr, C. Cleeland, R. Dionne, J.T. Farrar, B.S. Galer, D.J. Hewitt, A.R. Jadad, N.P. Katz, L.D. Kramer, D.C. Manning, C.G. McCormick, M.P. McDermott, P. McGrath, S. Quessy, B.A. Rappaport, J.P. Robinson, M.A. Royal, L. Simon, J.W. Stauffer, W. Stein, J. Tollett, and J. Witter. 2003. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 106(3):337-345.

Turk, D.C., K.S. Swanson, and R.J. Gatchel. 2008. Predicting opioid misuse by chronic pain patients: A systematic review and literature synthesis. *Clinical Journal of Pain* 24(6):497-508.

Turner, B.J., and Y. Liang. 2015. Drug overdose in a retrospective cohort with non-cancer pain treated with opioids, antidepressants, and/or sedative-hypnotics: Interactions with mental health disorders. *Journal of General Internal Medicine* 30(8):1081-1096.

Ubbink, D.T., and H. Vermeulen. 2013. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. *Cochrane Database of Systematic Reviews* 2:CD004001.

Van't Veer, A., and W.A. Carlezon. 2013. Role of kappa-opioid receptors in stress and anxiety-related behavior. *Psychopharmacology* 229(3):435-452.

Veinante, P., I. Yalcin, and M. Barrot. 2013. The amygdala between sensation and affect: A role in pain. *Journal of Molecular Psychiatry* 1(1):9.

Viatchenko-Karpinski, V., N. Novosolova, Y. Ishchenko, M.A. Azhar, M. Wright, V. Tsintsadze, A. Kamal, N. Burnashev, A.D. Miller, N. Voitenko, R. Giniatullin, and N. Lozovaya. 2016. Stable, synthetic analogs of diadenosine tetraphosphate inhibit rat and human P2X3 receptors and inflammatory pain. *Molecular Pain* 12:1744806916637704.

Vijayaraghavan, M., J. Penko, D. Guzman, C. Miaskowski, and M.B. Kushel. 2011. Primary care providers' judgments of opioid analgesic misuse in a community-based cohort of HIV-infected indigent adults. *Journal of General Internal Medicine* 26(4):412-418.

Volkow, N.D., and F.S. Collins. 2017. The role of science in addressing the opioid crisis. *New England Journal of Medicine* 377:391-394.

Volkow, N.D., G.F. Koob, and A.T. McLellan. 2016. Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine* 374:363-371.

Von Korff, M., S. Dublin, R.L. Walker, M. Parchman, S.M. Shortreed, R.N. Hansen, and K. Saunders. 2016. The impact of opioid risk reduction initiatives on high-dose opioid prescribing for patients on chronic opioid therapy. *The Journal of Pain* 17(1):101-110.

Vorspan, F., W. Mehtelli, G. Dupuy, V. Bloch, and J.P. Lépine. 2015. Anxiety and substance use disorders: Co-occurrence and clinical issues. *Current Psychiatry Reports* 17(2):4.

Wadachi, R., and K.M. Hargreaves. 2006. Trigeminal nociceptors express TLR-4 and CD14: A mechanism for pain due to infection. *Journal of Dental Research* 85(1):49-53.

Wade, C.L., P. Krumenacher, K.F. Kitto, C.D. Peterson, G.L. Wilcox, and C.A. Fairbanks. 2013. Effect of chronic pain on fentanyl self-administration in mice. *PloS One* 8:e79239.

Wadley, A.L., Z. Lombard, C.L. Cherry, P. Price, and P.R. Kamerman. 2012. Analysis of a previously identified "pain protective" haplotype and individual polymorphisms in the GCH1 gene in Africans with HIV-associated sensory neuropathy: A genetic association study. *Journal of Acquired Immune Deficiency Syndrome* 60(1):20-23.

Wagner, K.J., T. Sprenger, E.F. Kochs, T.R. Tolle, M. Valet, and F. Willoch. 2007. Imaging human cerebral pain modulation by dose-dependent opioid analgesia: A positron emission tomography activation study using remifentanil. *Anesthesiology* 106(3):548-556.

Wagner, K., K.S.S. Lee, S.H. Hwang, and B.D. Hammock. 2016. Novel inhibitors of the soluble epoxide hydrolase block pain in multiple models. *The FASEB Journal* 30(1).

Walter, C., and J. Lotsch. 2009. Meta-analysis of the relevance of the OPRM1 118A>G genetic variant for pain treatment. *Pain* 146:270-275.

Wang, C., C.H. Schmid, M.D. Iversen, W.F. Harvey, R.A. Fielding, J.B. Driban, L.L. Price, J.B. Wong, K.F. Reid, R. Rones, and T. McAlindon. 2016. Comparative effectiveness of tai chi versus physical therapy for knee osteoarthritis: A randomized trial. *Annals of Internal Medicine* 165(2):77-86.

Warner, L.A., R.C. Kessler, M. Hughes, J.C. Anthony, and C.B. Nelson. 1995. Prevalence and correlates of drug use and dependence in the United States. Results from the National Comorbidity Survey. *Archives of General Psychiatry* 52(3):219-229.

Wasan, A.D., S.F. Butler, S.H. Budman, K. Fernandez, R.D. Weiss, S.F. Greenfield, and R.N. Jamison. 2009. Does report of craving opioid medication predict aberrant drug behavior among chronic pain patients? *Clinical Journal of Pain* 25(3):193-198.

Watabe-Uchida, M., L. Zhu, S.K. Ogawa, A. Vamanrao, and N. Uchida. 2012. Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron* 74(5):858-873.

Webster, L.R., and R.M. Webster. 2005. Predicting aberrant behaviors in opioid treated patients: Preliminary validation of the Opioid Risk Tool. *Pain Medicine* 6(6):432-442.

Weissman-Fogel, I., E. Sprecher, Y. Granovsky, and D. Yarnitsky. 2003. Repeated noxious stimulation of the skin enhances cutaneous pain perception of migraine patients in-between attacks: Clinical evidence for continuous sub-threshold increase in membrane excitability of central trigeminovascular neurons. *Pain* 104(3):693-700.

Wendel, B., and M.R. Hoehe. 1998. The human mu opioid receptor gene: 5' regulatory and intronic sequences. *Journal of Molecular Medicine (Berlin)* 76:525-532.

Westanmo, A., P. Marshall, E. Jones, K. Burns, and E.E. Krebs. 2015. Opioid dose reduction in a VA health care system—implementation of a primary care population-level initiative. *Pain Medicine* 16(5):1019-1026.

White, K.L., A.P. Scopton, M.L. Rives, R.V. Bikbulatov, P.R. Polepally, P.J. Brown, T. Kenakin, J.A. Javitch, J.K. Zjawiony, and B.L. Roth. 2014. Identification of novel functionally selective κ-opioid receptor scaffolds. *Molecular Pharmacology* 85(1):83-90.

Wiech, K. 2016. Deconstructing the sensation of pain: The influence of cognitive processes on pain perception. *Science* 354(6312):584-587.

Williams, F.M., S. Scollen, D. Cao, Y. Memari, C.L. Hyde, B. Zhang, B. Sidders, D. Ziemek, Y. Shi, J. Harris, I. Harrow, B. Dougherty, A. Malarstig, R. McEwen, J.C. Stephens, K. Patel, C. Menni, S.Y. Shin, D. Hodgkiss, G. Surdulescu, W. He, X. Jin, S.B. McMahon, N. Soranzo, S. John, J. Wang, and T.D. Spector. 2012. Genes contributing to pain sensitivity in the normal population: An exome sequencing study. *PLoS Genetics* 8:e1003095.

Wise, R.A., P. Newton, K. Leeb, B. Burnette, D. Pocock, and J.B. Justice. 1995. Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. *Psychopharmacology* 120(1):10-20.

Wise, R.G., R. Rogers, D. Painter, S. Bantick, A. Ploghaus, P. Williams, G. Rapeport, and I. Tracey. 2002. Combining fMRI with a pharmacokinetic model to determine which brain areas activated by painful stimulation are specifically modulated by remifentanil. *Neuroimage* 16(4):999-1014.

Woolf, C.J. 2010. Overcoming obstacles to developing new analgesics. *Nature Medicine* 16(11):1241-1247.

WTCCC (Wellcome Trust Case Control Consortium). 2010. Genome-wide association study of CNVs in 16,000 cases of eight common diseases and 3,000 shared controls. *Nature* 464:713-720.

Wu, Y., X. Na, Y. Zang, Y. Cui, X. Xin, R. Pang, L. Zhou, X. Wei, Y. Li, and X. Liu. 2014. Upregulation of tumor necrosis factor-alpha in nucleus accumbens attenuates morphine-induced rewarding in a neuropathic pain model. *Biochemical and Biophysical Research Communications* 449(4):502-507.

Xiao, C., and J.H. Ye. 2008. Ethanol dually modulates GABAergic synaptic transmission onto dopaminergic neurons in ventral tegmental area: Role of mu-opioid receptors. *Neuroscience* 153(1):240-248.

Xu, Z.Z., T. Berta, and R.R. Ji. 2013. Resolvin E1 inhibits neuropathic pain and spinal cord microglial activation following peripheral nerve injury. *Journal of Neuroimmune Pharmacology* 8(1):37-41.

Yaksh, T.L. 1987. Opioid receptor systems and the endorphins: A review of their spinal organization. *Journal of Neurosurgery* 67(2):157-176.

Yalcin, I., and M. Barrot. 2014. The anxiodepressive comorbidity in chronic pain. *Current Opinion in Anaesthesiology* 27(5):520-527.

Yang, G., and L. Chen. 2016. An update of microsomal prostaglandin E synthase-1 and PGE2 receptors in cardiovascular health and diseases. *Oxidative Medicine and Cellular Longevity* 2016:5249086.

Yarnitsky, D. 2015. Role of endogenous pain modulation in chronic pain mechanisms and treatment. *Pain* 156(Suppl. 1):S24-S31.

Yarnitsky, D., Y. Crispel, E. Eisenberg, Y. Granovsky, A. Ben-Nun, E. Sprecher, L.A. Best, and M. Granot. 2008. Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain* 138(1):22-28.

Yarnitsky, D., M. Granot, H. Nahman-Averbuch, M. Khamaisi, and Y. Granovsky. 2012. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. *Pain* 153(6):1193-1198.

Young, A., S.E. McCabe, J.A. Cranford, P. Ross-Durow, and C.J. Boyd. 2012. Nonmedical use of prescription opioids among adolescents: Subtypes based on motivation for use. *Journal of Addictive Diseases* 31(4):332-341.

Zádor, F., and M. Wollemann. 2015. Receptome: Interactions between three pain-related receptors or the "triumvirate" of cannabinoid, opioid and TRPV1 receptors. *Pharmacological Research* 102:254-263.

Zavala, K., J. Lee, J. Chong, M. Sharma, H. Eilers, and M.A. Schumacher. 2014. The anticancer antibiotic mithramycin-A inhibits TRPV1 expression in dorsal root ganglion neurons. *Neuroscience Letters* 578:211-216.

Zedler, B., L. Xie, L. Wang, A. Joyce, C. Vick, F. Kariburyo, P. Rajan, O. Baser, and L. Murrelle. 2014. Risk factors for serious prescription opioid related toxicity or overdose among Veterans Health Administration patients. *Pain Medicine* 15(11):1911-1929.

Zhang, G., K. Sean, and B.D. Hammock. 2014. Stabilized epoxygenated fatty acids regulate inflammation, pain, angiogenesis and cancer. *Progress in Lipid Research* 53:108-123.

Zheng, Y., L. Qin, N.V. Zacarias, H. de Vries, G.W. Han, M. Gustavsson, M. Dabros, C. Zhao, R.J. Cherney, P. Carter, D. Stamos, R. Abagyan, V. Cherezov, R.C. Stevens, A.P. IJzerman, L.H. Heitman, A. Tebben, I. Kufareva, and T.M. Handel. 2016. Structure of CC chemokine receptor 2 with orthosteric and allosteric antagonists. *Nature* 540(7633):458-461.

Zorina-Lichtenwalter, K., C.B. Meloto, S. Khoury, and L. Diatchenko. 2016. Genetic predictors of human chronic pain conditions. *Neuroscience* 338:36-62.

Zubieta, J.K., M.M. Heitzeg, Y.R. Smith, J.A. Bueller, K. Xu, Y. Xu, R.A. Koeppe, C.S. Stohler, and D. Goldman. 2003. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science* 299(5610):1240-1243.

Zygmunt, P.M., and E.D. Högestätt. 2014. TRPA1. In *Mammalian transient receptor potential (TRP) cation channels*, Vol. 1, edited by B. Nilius and V. Flockerzi. Berlin Heidelberg: Springer. Pp. 583-630.

PART II

ADDRESSING THE OPIOID EPIDEMIC

4

Trends in Opioid Use, Harms, and Treatment

Not since the HIV/AIDS epidemic has the United States faced as devastating and lethal a health problem as the current crisis of opioid misuse and overdose and opioid use disorder (OUD). Current national trends indicate that each year more people die of overdoses—the majority of which involve opioid drugs—than died in the entirety of the Vietnam War, the Korean War, or any armed conflict since the end of World War II. Each day 90 Americans die prematurely from an overdose that involves an opioid (Rudd et al., 2016b), leaving families and friends bereft. The opioid epidemic's toll is felt across the life span and in every sociodemographic group, but more heavily burdens vulnerable populations, such as those in economically depressed areas of the country. This chapter updates key statistics regarding use and misuse of prescription opioids, identifies risk factors for opioid-related harms, describes the recent increase in use of heroin and illicitly manufactured synthetic opioids and its relation to the prescription opioid epidemic, describes the impact of prescription opioids on illicit markets, reviews the current state of surveillance systems, and summarizes recent trends in treatment of OUD and use of naloxone to prevent overdose deaths. The committee selected these topics to discuss in particular for their relevance to the U.S. Food and Drug Administration's (FDA's) exercise of its authority to regulate pharmaceutical opioid products (analgesics, agonists, and antagonists). Each aspect of this chapter identifies considerations that should be taken into account when weighing the societal perspective and public health impact relevant to these products when they are being considered for new drug approval or during post-market surveillance.

TRENDS IN PRESCRIPTION OPIOID USE AND MISUSE

Medical prescriptions for opioids started to increase sharply in the mid- to late 1990s (NIDA, 2014). Shortly thereafter, nonmedical opioid use also started to increase markedly, reaching a peak of 2.7 million new users in 2002 (Kolodny et al., 2015). The annual number of new nonmedical users slowly declined to about 1.8 million in 2012 (SAMHSA, 2013b), but the overall pool of people continuing to use nonmedically is very large. From 1999 to 2011, hydrocodone use increased more than two-fold, oxycodone use more than five-fold (Jones, 2013b), and the mortality rate of opioid-related overdose almost four-fold (Chen et al., 2014). Overdose mortality is the most dramatic consequence of increased opioid use, but it is not the only one; rates of emergency room visits for nonmedical opioid use (SAMHSA, 2013a), neonatal abstinence syndrome (NAS) (Patrick et al., 2012), and OUD treatment admissions all have soared since 2002 (SAMHSA, 2010).

While death rates associated with opioid overdose have increased for virtually every population group, the rates are highest among males under age 50 (CDC, 2015a). In Massachusetts during the period 2013–2014, 76 percent of opioid overdose deaths occurred among people under the age of 50, and men aged 18 to 34 had opioid-related death rates nearly three times higher than those of women of the same age (Massachusetts Department of Public Health, 2016). Opioid-related death rates also were higher among those who had recently been released from prison, those who obtained opioid prescriptions from multiple pharmacies, and those who obtained prescription opioids in combination with other scheduled medications.

The age group with the greatest past-year nonmedical use of opioids is young adults aged 18 to 25, yet the greatest use (i.e., exposure) of prescription opioids is among adults aged 26 and older. Substance Abuse and Mental Health Services Administration (SAMHSA) data indicate that most people who report prescription opioid misuse in current cohorts initiated use in their early to late 20s, which may explain why prescription opioid mortality disproportionately affects adults aged 25 to 54 (CDC, 2016c). More recent data show an overlap in these age-related demographics with respect to current use of heroin and, more disturbingly, the coincident increase in overdose deaths caused by heroin and synthetic opioids other than methadone among people aged 15 and older (Rudd et al., 2016). It is important to acknowledge that data on overdose deaths may be subject to misclassification with respect to intent (i.e., whether the overdose was intentional or unintentional), especially for older, medically ill patients prescribed medications, whose deaths may not be followed up with toxicology testing and may not be referred to a medical examiner as a drug-involved or suspicious death. Misuse and aberrant opioid use behaviors also may manifest differently in older adults (Beaudoin et al., 2016; Henderson et

al., 2015), and given the aging U.S. population, the role of suicidal intent in prescription opioid poisoning in older adults is an area of active inquiry (Rocket et al., 2010; West et al., 2015).

The full extent of the public health consequences of prescription opioids is further complicated by the increased availability of heroin, which is less expensive than prescription opioids in the black market (DEA, 2013), and by the fact that so many who develop OUD from prescription opioids switch to heroin. In one study, about 80 percent of current heroin users reported that they began with prescription opioids (Muhuri et al., 2013). Therefore, the public health effects of prescription opioids and heroin are intertwined (Kolodny et al., 2015). Between 2001 and 2011, the rate of admission to treatment for OUD involving heroin doubled among non-Hispanic whites aged 20 to 34 (it stayed relatively constant for all other age groups among whites and for all age groups among non-Hispanic blacks), and the rate of heroin overdose deaths increased more than 2.5-fold among whites aged 18 to 44 (CDC, 2014; SAMHSA, 2013a). The cumulative effect is a 200 percent increase in opioid-involved overdoses from 2000 to 2014 (Rudd et al., 2016) concordant with increases in nonmedical prescription opioid use (Calcaterra et al., 2013; Cerdá et al., 2013; Kenan et al., 2013). In more recent years, national initiatives to reduce opioid prescribing have modestly decreased the number of prescription opioids dispensed (Dart et al., 2015). However, many people who otherwise would have been using prescription opioids have transitioned to heroin use, with a resulting three-fold increase in heroin-involved overdose deaths from 2010 to 2014 (Compton et al., 2016). Indeed, the overall frequency of heroin deaths has been accelerating since 2010 (see Figure 1-2 in Chapter 1).

Risk Factors for Prescription Opioid Misuse and Overdose

Despite the unsettling trends described above, a more nuanced examination indicates that not all prescription opioid medications confer similarly heightened risk. The causal pathways from the onset of pain to opioid exposure and to potential negative consequences such as misuse, drug seeking related to undertreatment of pain (Green and Chambers, 2015; Vadivelu et al., 2017), OUD, and overdose are difficult to disentangle, and represent an area of active research and investigation (Stumbo et al., 2017). Multiple post-marketing studies currently under way for extended-release (ER)/long-acting (LA) opioids (see Annex Table 6-1 in Chapter 6) may shed light on the timing and sequence of and precursors to the development of problem use and OUD and the incidence of nonfatal and fatal overdose among patients prescribed opioids for the treatment of chronic noncancer pain.

Characteristics of opioid medication and how they are prescribed can affect the risk of nonmedical use and other harms. Three key characteristics

of opioid medications that have been found to influence the risk of harms include the chemical compound, the formulation, and the intended route of administration. Also salient are the number of pills prescribed and dosage, as well as other prescribing patterns.

Chemical Compound

Neuropsychological experiments demonstrate that "likability," and therefore "abuse liability," is greater for some compounds than others. In seminal work by Comer and colleagues (2008) among a sample of patients dependent on heroin, laboratory experiments compared the likability of oxycodone, fentanyl, buprenorphine, and morphine with that of heroin. Findings indicated that across several validated subjective scales, oxycodone scored most favorably among participants, while buprenorphine scored lowest. Translating data from laboratory-based, controlled abuse liability studies to the community and clinic to examine possible increased risk is more challenging. However, several studies provide insight into "real-world" abuse liability and risk variation by compound. One means by which demand for a compound can be deduced is through street price. Taking availability into account, one recent study found that the street price of buprenorphine/naloxone was lower than that of buprenorphine single-entity and of methadone (Larance et al., 2015). Interestingly, these findings are congruent with those of the laboratory-based abuse liability studies noted earlier.

Another indicator of a compound's risk is seen in mortality data. Unless the chemical entity is a novel one, it is difficult to differentiate branded from generic products as causal in an unintentional opioid poisoning death. Nevertheless, overdose death data show key compound-level trends, taking methadone as an example. Ray (2015) reports high overdose risk associated with use of methadone medications (for pain), and a 2017 analysis of methadone deaths and prescribing from 2007 to 2014 conducted by the U.S. Centers for Disease Control and Prevention (CDC) found that although methadone accounted for about 1 percent of all opioid prescriptions, overall methadone-related deaths accounted for 22.9 percent of all opioid-related mortality in 2014 (Faul et al., 2017). These findings have been replicated in other studies, suggesting that certain compounds are more likely to be misused and potentially lead to greater health consequences in the absence of preventive measures. Novel compounds, such as tapentadol (Nucynta), designed specifically to avoid tampering and reduce risk while achieving pain control, exhibit promising post-marketing epidemiologic data across a number of misuse and risk indicators (Butler et al., 2015; Dart et al., 2016; McNaughton et al., 2015), findings that warrant further examination in longitudinal studies.

Formulation

Another characteristic of a medication that may influence the risk of harm is its formulation, specifically whether it is an ER/LA or immediate-release (IR) formulation. The FDA's Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioids anticipated that greater risks would be associated with opioids that increased the possible time of exposure through longer-time-release formulations. In fact, while further research is needed, available data show that ER/LA and IR formulations are associated with different types of elevated risk. ER/LA formulations are associated with increased risks of diagnosis of substance use disorder (SUD) and nonfatal and fatal opioid overdose (Braden et al., 2010; Miller et al., 2015; Zedler et al., 2014). However, limited data suggest that IR, short-acting opioid medications also may be associated with various morbidities and nonmedical use. Relative to ER/LA formulations, for example, these medications have been found to be indicated more often in poison center data as medications of misuse, and are associated with higher rates of nonfatal injury, including motor vehicle and pedestrian crashes and falls (Iwanicki et al., 2016). Moreover, an IR medication may be the first opioid of exposure over the course of one's lifetime (SAMHSA, 2016a), given the routine use of these drugs following dental and surgical procedures, as discussed in Chapter 2. These data suggest that both ER/LA and IR opioids warrant measures to reduce risks that can arise with their use. Indeed, the FDA plans to expand its REMS program for opioids to include IR formulations (FDA, 2017b).

Combination opioid products, especially those coformulated with naloxone (e.g., Targaniq [oxycodone/naloxone] and Suboxone [buprenorphine/naloxone]) may be associated with lower rates of misuse and nonmedical use by other than intended routes of administration (i.e., by injection or insufflation) compared with their single-entity counterparts (Davis et al., 2013; Larance et al., 2015; Walsh et al., 2016). Although coformulations may help prevent misuse and OUD (Raffa et al., 2014), epidemiologic studies to explore these differences further are needed, and some such studies are under way (Degenhardt et al., 2015).

Route of Administration

A final characteristic that may elevate the risk of an opioid medication is its intended route of administration. Many preparations are used in ways other than prescribed and may be manipulated to extract the active pharmaceutical ingredient. For instance, pills may be crushed in the mouth, insufflated, smoked, or injected with few physical barriers to use, and a transdermal patch's active pharmaceutical ingredients may be chewed, sucked, or extracted and prepared for injection. It is well substantiated that

drugs used by insufflation and injection, in particular, enter the bloodstream and hasten the opioid's crossing of the blood–brain barrier, generating a faster onset of action, which in turn is associated with a greater risk of overdose and of developing OUD (EMCDDA, 2016).

Some prescription opioid preparations approved in recent years make crushing the pill more difficult or may be formulated to deter tampering. These abuse-deterrent formulations (ADFs) are reviewed more extensively in Chapter 5, but it is worth noting here that the level of tampering and prevalence of use by unintended routes associated with an opioid will influence its public health consequences. For example, a new and comprehensive analysis by Alpert and colleagues (2017) shows that the reformulation of OxyContin from a non-ADF to an ADF prescription opioid was linked to higher-than-expected rates of subsequent heroin use, especially in places with persistently high rates of opioid misuse. The authors estimate that up to 80 percent of the increase in heroin use could be attributed to the formulation change. Likewise, the ADF Opana ER (oxymorphone ER) has been associated with several injection-related harms, linked to the same ADF preparation applied to OxyContin. Because of these injection-related harms, in June 2017 the FDA requested that Opana ER be removed from the market by its manufacturer (FDA, 2017a).

In a retrospective 24-month cohort study based on National Poison Data System data, Copelan and colleagues (2017) found intentional misuse and suspected suicidal intent to be significantly lower among patients using a 7-day buprenorphine transdermal system/patch than among those taking other ER/LA opioid analgesics examined. On the other hand, data from a recent Australian study showed that, 2 years after the introduction of a buprenophine-naloxone film, levels of injection and diversion were comparable between the film and methadone and buprenorphine-naloxone tablets among out-of-treatment people who inject drugs (PWID), but levels of injection and diversion were lower for mono-buprenorphine than for the film, after adjusting for availability (Larance et al., 2015). The ADF film was found to be easier to administer, which impacted clinician time and workflow. These data suggest a need for caution in reliance on ADF products as a regulatory strategy for improving opioid safety and the importance of weighing the public health impacts of all decisions. Tracking the prevalence of the intended and unintended routes of administration of a drug can provide signals of compromised safety and harmful consequences at the individual and societal levels.

Number of Pills Prescribed and Dosage

Emerging literature since the Institute of Medicine (IOM) report *Relieving Pain in America* was issued (IOM, 2011) also suggests that potentially

modifiable features of the prescription itself are associated with harm. The greater the number of days for which a prescription is written and the higher the dosage, the greater is the risk exposure. Unfortunately, the literature lacks clear consensus on the number of days after which risk increases (i.e., the threshold). The CDC's Guideline for Prescribing Opioids for Chronic Pain, released in 2016 (Dowell et al., 2016), urges prescribers to provide the lowest effective dosage and prescribe "no greater quantity than needed for the expected duration of pain severe enough to require opioids" (stating that "three days or less will often be sufficient"). Some states (e.g., Maine and Massachusetts) have recently legislated a supply limit for opioids prescribed for the treatment of noncancer pain, with far-reaching applications. (In Maine, the law limits the number of pills that can be prescribed to a 7-day supply within a 7-day period for acute pain and a 30-day supply within a 30-day period for chronic pain [Smith, 2016; Traynor, 2016], while Massachusetts imposes a 7-day supply limit for first-time prescriptions for adults and a 7-day limit at any time for minors.[1]) More research in this area could better inform policy makers, patients, and providers.

A concept related to that of number of days' supply is daily morphine milligram equivalent (MME) dosing. Unlike the days' supply literature, the literature on this topic presents a clear and consistent finding that risk of overdose increases as dose increases (i.e., a dose-response relationship) (Baumblatt et al., 2014; Bohnert et al., 2011, 2016; Dunn et al., 2010; Gomes et al., 2011; Liang and Turner, 2015; Paulozzi, 2012; Zedler et al., 2014). Based on several early findings, some authors concluded—erroneously—that a specific threshold or MME cutpoint value (e.g., >100, >50, or >20 MME) could signify the point of elevated risk, below which opioids are safe but above which risk rises. Based on the existing literature and analysis of large clinical datasets, however, the risk of overdose and OUD increases as a function of dose (i.e., dose-response relationship) at any given level of exposure greater than none.

The FDA's required "abuse liability" studies attempt to anticipate and measure many of these drug-specific characteristics before a drug is approved. However, these studies are not designed to predict a fuller range of potentially harmful effects that one may want to consider in deciding whether to approve an opioid or other drug, such as unforeseen allergies, unanticipated side effects, co-use with other licit and illicit drugs, and ease of manipulation to prepare the product for misuse. For these effects, the current approach is to rely on post-marketing surveillance to capture, in a proactive, preventive way, the cumulative effects of drug-specific characteristics as the drugs are actually used or misused in the population. Given

[1]See https://malegislature.gov/Bills/189/House/H4056 (accessed May 15, 2017).

heightened concerns about opioid misuse, OUD, overdose, and diversion, involving people who use drugs (or their representative organizations) in the review and discussion of post-marketing data may be informative.

Other Prescribing Patterns

Other patterns of prescribing and dispensing suggest additional risks for OUD and overdose. The timing of risk exposure, for instance, may contribute to iatrogenic overdose. Similar to the patterns of elevated risk of overdose mortality during the first 2 weeks after release from incarceration, circumstances defined by loss of tolerance (such as during hospitalization [Bird et al., 2016] or following detoxification [Strang et al., 2003]) or the establishment of tolerance, such as at the onset of treatment with opioid analgesics (Miller et al., 2015), all suggest that the timing of opioid exposure can affect patient safety and overdose risk. In addition to timing, obtaining opioids from multiple prescribers or multiple pharmacies and overlapping prescriptions have been associated with greater risk of overdose (Baumblatt et al., 2014; Hall et al., 2008; Yang et al., 2015). These patterns may ultimately reflect poor coordination of care for people with pain and OUD in the community rather than causal drivers of the epidemiology of nonmedical use of prescription opioids. In addition, a large body of health services literature indicates that a number of opioid analgesic prescribing behaviors contribute greatly to patient risk and prolonged opioid exposure. These include errors in MME calculations (e.g., during opioid rotation or conversion) (Paulozzi et al., 2009; Rich and Webster, 2011), underutilization of prescription drug monitoring programs (Starrels et al., 2011), and inconsistencies in monitoring of opioid use (Becker et al., 2011; Khalid et al., 2015), among others.

While the FDA-approved indications for use and labeling of opioids specify for whom and under what conditions the medications are intended to be used, prescribing and patient use patterns may differ from those envisioned at the time of approval. For instance, many opioid medications, such as IR products, are intended to be used to treat acute pain, such as postsurgical pain, over a short duration. However, a large proportion of patients continue to be treated with IR opioids far beyond the expected duration of healing (Bartels et al., 2016; Clarke et al., 2014), a phenomenon that could indicate failure to heal from an injury or surgery, progression or persistence of pain to a chronic state, opioid dependence, onset of OUD, poor product labeling, or something else entirely. Still other patients may be prescribed an ER/LA opioid to treat an acute pain condition, a practice that runs counter to recommendations of the CDC guideline and from professional organizations.

With respect to chronic pain, ER/LA opioids are approved for use

in the treatment of moderate to severe pain as may be needed to treat instances of failure to heal from injury or surgery or progression of acute to chronic pain, or in instances of treatment of other chronic conditions when moderate to severe pain occurs. As discussed in Chapter 2, however, there is a lack of long-term evidence (>1 year) from rigorous studies that opioid therapy is effective for improving pain and function for people with chronic noncancer pain (Dowell et al., 2016), while there is evidence that opioid therapy for chronic pain is associated with increased risk of OUD, overdose, and other adverse outcomes (Baldini et al., 2012; Chou et al., 2015; Dowell et al., 2016). For example, rates of iatrogenic OUD in studies in which OUD has been carefully diagnosed have averaged about 8 percent, while rates of iatrogenic misuse, OUD, and aberrant behaviors thought to be indicative of OUD have ranged from 15 to 26 percent (Volkow and McClellan, 2016). While the FDA does not regulate the practice of medicine, the committee recognizes the importance of prescribing practices in helping to curb opioid-related harms, and in Chapter 5 describes several interventions designed to promote more judicious prescribing.

One key aspect of opioid prescribing safety overseen by the FDA is drug–drug interactions, whereby concurrent use of certain medications may alter a patient's risk. Certain medications are coprescribed more frequently based on the co-occurrence of pain with other conditions, and it is also widely observed that patients may co-use other drugs with opioids to achieve heightened or prolonged analgesic or euphoric effects.

The co-use of opioid medications with one class of drugs, benzodiazapines, has been well established in preclinical, clinical, and epidemiologic studies, and contributes to up to one-third of fatal opioid overdoses in the United States (Jones and McAnich, 2015). Biological data indicate that these two drug classes have synergistic effects in producing sedation and respiratory depression, increasing the risk of overdose and death. Studies of opioid and benzodiazepine co-use in humans have demonstrated an elevated risk of overdose, especially in the context of misuse (Park et al., 2015; Sun et al., 2017). A large case-cohort study of U.S. veterans treated for chronic pain with long-term opioid analgesics, for example, showed that the risk of death from drug overdose increased in a synergistic, dose-response fashion as daily benzodiazepine dose increased, with risk being independent of dosing schedule (Park et al., 2015; see Figure 4-1). The safety concerns related to co-use of opioids and benzodiazepines led the FDA to require boxed warnings and patient-focused medication guides providing information about the risks associated with the concurrent use of these medications for more than 400 opioid and benzodiazepine products (FDA, 2016). These concerns also led to a recommendation in the CDC guideline urging caution in co-use or mitigation of the risk of respiratory

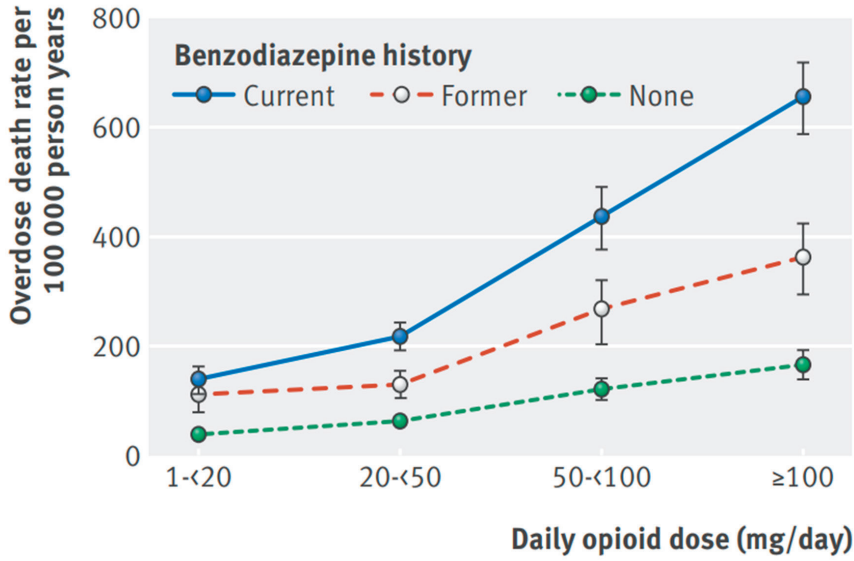


FIGURE 4-1 Benzodiazepine prescribing patterns and deaths from drug overdose among U.S. veterans receiving opioid analgesics: Case-cohort study. Overdose deaths rise sharply when opioid dose is 50 mg or greater and benzodiazepine is also used.
SOURCE: Park et al., 2015.

depression with naloxone for patients coprescribed benzodiazepines and opioids (Dowell et al., 2016).

Summary

The level and type of risk to a patient from a given opioid are influenced by specific features of the medication iself, including the compound, formulation (whether the medication is an ER/LA, IR, and/or combination product), and route of administration. How opioids are prescribed (e.g., with other medications, days for which prescribed) also may influence the risk of overdose. Available studies consistently demonstrate that the risk of overdose increases in a dose-response fashion with increasing MME. While the FDA abuse liability studies capture several features of drugs that influence the risk of harm, including mechanisms of misuse and diversion, post-marketing studies and surveillance data could help to identify a comprehensive range of potentially harmful effects.

Vulnerable Populations

This section reviews recent trends in OUD among three especially vulnerable populations—pregnant women and neonates, persons involved with the criminal justice system, and injection drug users.

Pregnant Women and Neonates

According to a study by Patrick and colleagues (2015), the proportion of babies born with NAS in the United States increased five-fold from 2000 to 2012, concurrently with a significant increase in opioid use and misuse among pregnant women. Subsequent studies have found that the incidence of NAS varies significantly among states, that the geographic variations in NAS are consistent with the variations in opioid pain prescriptions, and that the incidence of NAS and maternal opioid use increased disproportionately in rural relative to urban counties (Ko et al., 2016; Villapiano et al., 2017). Recent years have seen an unprecedented focus on NAS in the media; among policy makers; and among medical specialists in neonatology, pediatrics, and obstetrics. Strong disagreement among these interested groups is not uncommon as a result of poor understanding of and differences in opinion about the contexts and factors that affect NAS (Kaltenbach and Jones, 2016).

Recently the FDA has used the term "neonatal opioid withdrawal syndrome" on warning labels when referring to maternal use of opioids during pregnancy. It is understandable why this term is used on an FDA label pertaining to an opioid; however, the committee believes it is inappropriate for use in a clinical setting. When NAS occurs as a result of prenatal exposure to an opioid, it does so in various different contexts, and the presentation and severity are related to a number of factors in addition to maternal use of opioids. Accordingly, the discussion here uses the customary NAS terminology.

Although NAS was initially reported in 1865 as congenital morphism, with the first case of treatment reported in 1903, the focus of treatment and assessment over the past 50 years is based on work in the 1970s that established the definition of NAS and developed an instrument for measuring neonatal withdrawal. This work took place in response to the heroin epidemic and the resultant implementation of methadone pharmacotherapy for OUD (Jones and Fielder, 2015).

NAS generally is described as the occurrence of opioid withdrawal at birth after the discontinuation of prenatal opioid exposure. It is characterized by signs and symptoms of central nervous system irritability, including excessive crying, increased muscle tone, tremors, and sleep disturbances; gastrointestinal dysfunction, including poor feeding, vomiting,

and diarrhea; respiratory distress; and autonomic symptoms, including sweating, sneezing, and mottling (McQueen and Murphy-Oikonen, 2016). It is a temporary phenomenon that may or may not require treatment. In general, available data do not suggest an association between NAS in particular and long-term adverse developmental outcomes, regardless of whether the NAS was severe enough to require treatment.[2] There is also no conclusive evidence that maternal dose is related to the severity of NAS (Cleary et al., 2010; Kaltenbach and Finnegan, 1986). In addition to factors discussed below, the presentation and severity of NAS are related to genetics (Wachman et al., 2013, 2014, 2015), maternal physiology (Jansson et al., 2007), and gestational age (Dysart et al., 2007; Gibson et al., 2017; Ruwanphthirana et al., 2015).

The current public focus on NAS does not take into account the context in which it occurs. The context encompasses whether the opioid is a medication taken under the care of a health care provider (e.g., a woman receiving medication under the care of a physician for pain management, or a woman being treated by a physician for OUD with methadone or buprenorphine), or whether the woman is misusing pain medications with or without a prescription and/or using illicit opioids such as heroin. Even though the risk of NAS is comparable across contexts, the overall risk to the fetus and neonate differ between women taking medications under the care of a qualified health care provider and those misusing medications and/or using illicit drugs. In particular, in contrast with diverted medications and illicit drugs of unknown purity, source, and quantity, the treatment of pain or OUD with opioid medications occurs within the safety of known doses of FDA-approved medications that have been rigorously tested for safety and efficacy and obtained legally from a qualified pharmacy or dispensary. In the case of misuse and OUD involving black market prescription or illicit opioids such as heroin, in addition to the uncontrolled dose, quantity, and purity of the drugs, the pregnancy may be affected by stress, violence, and trauma surrounding illegal activity. Indeed, research shows that prenatal stress, depression, and trauma can influence birth outcomes and later development (Fatima et al., 2017; Su et al., 2015). Thus, although not altering the probability of NAS occurrence, shifting the opioid-exposed pregnancy from one that is untreated to one that is treated may improve overall health outcomes for both mother and baby.

The national and state data that have been used to report significant increases in NAS are based on hospital codes that do not differentiate between NAS occurring as a result of maternal opioid misuse and that due

[2]Although some babies with NAS may have other risks, such as low birth weight and/or parents with suboptimal caregiving capacity due to SUD, which are known to be associated with increased risk for adverse developmental outcomes.

to the appropriate use of an opioid prescription. Additionally, the codes do not indicate whether an infant required treatment for NAS.

Complicating the understanding of NAS is that there are other medications that produce withdrawal symptoms similar to those associated with opioids and, when taken in conjunction with opioids, exacerbate NAS. When pregnant women receiving methadone or buprenorphine take selective serotonin reuptake inhibitors (SSRIs, i.e., antidepressants), for example, the SSRIs have been found to be related to both the presentation and treatment of NAS, with higher peak scores of NAS and higher doses of medication required for treatment (Jansson et al., 2010; Kaltenbach et al., 2012). A number of studies also have found that when pregnant women receiving methadone or buprenorphine take benzodiazepines, such concomitant use is related to prolonged length of treatment for NAS (Pritham et al., 2012; Seligman et al., 2008; Wachman et al., 2011). In addition, as noted earlier, this co-use of opioids and benzodiazepine increases the risk of overdose. Cigarette smoking also has been found to adversely affect NAS, including the total amount of medication required to treat it and the length of treatment (Jones et al., 2013).

With the exception of methadone and buprenorphine, no attention has been given to whether the incidence of signs and symptoms of NAS may differ by opioid. One study comparing the NAS profile before treatment or in the absence of treatment in infants exposed prenatally to methadone or buprenorphine found that the incidence of nasal stuffiness, sneezing, and loose stools was greater in the buprenorphine-exposed infants, whereas the methadone-exposed infants were found to have higher mean scores for hyperactive Moro reflex, disturbed and undisturbed tremors, failure to thrive, and excessive irritability (Gaalema et al., 2012). Such findings may explain reported differences in NAS incidence, severity, and treatment duration between methadone and buprenorphine. No information is available for other opioid pain medications regarding signs and symptoms of NAS, its incidence and severity, and the length of treatment. Importantly, little to no information is available regarding exposure to illicitly manufactured fentanyl or fentanyl analogs in pregnant women and its effect on the risk of fatal overdose; responsiveness to OUD treatment; the maternal medication-assisted treatment (MAT) dose; or NAS incidence, severity, or treatment duration.

The issue of assessment, which determines the diagnosis and severity of NAS and thus directs the course of treatment, is another area of misunderstanding. No objective, biological index or marker exists for the determination of NAS. Neonatal metabolic alterations such as hypocalcemia, hypoglycemia, hypomagnesemia, and hypothermia can mimic NAS and need to be ruled out before treatment for NAS is initiated. The most widely used assessment tool consists of 21 items with 31 possible scores (e.g.,

"mild tremors when disturbed" and "marked tremors when disturbed," "loose stools" and "watery stools," "hyperactive Moro reflex and markedly hyperactive Moro reflex") (Finnegan and Kaltenbach, 1992). Making such distinctions requires extensive reliability training, and even with such training, it can be difficult to score some items with a high degree of accuracy. Additionally, neither the incremental validity of the differential weighting of the tool nor its sensitivity and specificity have been examined. Such limitations have led to calls to reexamine the assessment of NAS and the need for an objective measure derived from a rigorous psychometric approach (Jones and Fielder, 2015).

Although a standard of care for NAS has been developed over the past 50 years, aggregate data across several hospital/fellowship program surveys suggest significant variability in both diagnosis and treatment protocols (Jones and Fielder, 2015). Effectiveness evidence for medications used to treat NAS is limited. Currently, oral morphine solution and methadone are recommended by the American Academy of Pediatrics for the treatment of NAS (Hudak and Tan, 2012). Morphine has been found to have shortcomings under some dosing and weaning regimens, and no data from randomized controlled trials comparing methadone with morphine are currently available. Although not yet used in clinical settings, randomized controlled trial data comparing buprenorphine and morphine show buprenorphine to be more effective than morphine, requiring less medication and shorter length of treatment (Kraft et al., 2011). In a recent randomized trial involving 63 infants with NAS, those treated with buprenorphine had significantly shorter treatment duration compared with those treated with morphine. The median between-group difference in treatment duration was 13 days (Kraft et al., 2017).

Medication dose regimens for NAS are traditionally determined by the infant's weight, but some institutions and research protocols use a symptom-based approach in which the dose is based on the severity of the infant's symptoms. To date, no systematic studies have evaluated these differing regimens.

The lack of protocols has recently been identified as impacting the duration of NAS treatment, the length of inpatient stay, and the rate of adjunctive therapy. Other recent changes in hospital practices, such as supporting breastfeeding and integrating mothers as partners in care, have been found to decrease the need to treat NAS and reduce the length of hospital stay (Holmes et al., 2016).

It should be reemphasized that these data are specific to women maintained on methadone or buprenorphine for OUD. To the committee's knowledge, no data specific to other opioid pain medications are available. Infants undergoing NAS would be assessed and treated the same, but mothers receiving opioids for chronic pain who wished to breastfeed would

require a safety evaluation, including type of medication, length of time on medication, and rapid increases in dose (Sachs, 2013).

The incidence of NAS in relation to the opioid epidemic has been identified as a major concern. Regrettably, strategies to address NAS are often punitive and excessive and applied disproportionately to vulnerable populations. The identification of NAS as fetal harm calls into question the ability to adequately parent their children for both women who use opioid medications as prescribed by their health care providers and those who misuse opioid medications or use illicit opioids (Terplan et al., 2015). Some state legislatures have required surveillance of NAS prevalence for both prescribed and illicit drugs. Judges and prosecutors have implemented punitive approaches with women who use both prescribed and nonprescribed opioids during pregnancy, including arrest, civil commitment, detention, prosecution, and loss of custody. The Child Abuse Prevention and Treatment Act of 2010[3] requires states to have policies and procedures in place for notifying child protective services about children affected by withdrawal symptoms from exposure to prenatal drugs, and the Comprehensive Addiction and Recovery Act of 2016 requires that a plan of safe care be implemented. Neither law differentiates among the highly varied contexts in which NAS occurs. While there may be situations that call for action to prevent child abuse and neglect, caution is warranted in designating NAS as a proxy for risk of abuse and neglect.

In summary, only by disentangling NAS due to the use of an opioid medication as prescribed by a health care provider from that due to misuse of these medications and/or the use of illicit opioids can prevention and treatment approaches for NAS be better refined. A more comprehensive response to NAS and treatment of OUD in pregnant women would be enabled by better understanding of the signs and symptoms of NAS for specific opioid medications and illicitly manufactured fentanyl and its analogs, including the development of an objective diagnostic tool, better understanding of the effectiveness of various medications and protocols for treatment of NAS, and the development of treatment protocols specifically for pregnant women using fentanyl.

Persons Involved with the Criminal Justice System

Another population heavily affected by the opioid epidemic and with unique risks consists of people within the criminal justice system. Drug-related crimes and seizures of illicit drugs point to a sharp rise in the opioid crisis. As the opioid epidemic shifts rapidly from prescription opioids to heroin, illicitly manufactured fentanyl, and other illicit drugs, more indi-

[3]Public Law 93-247.

viduals, many of whom live with OUD, are coming into contact with the criminal justice system. Authors of a 2006 study analyzing data on arrests, incarcerations, and heroin use estimate that 24 to 36 percent of all people with OUD involving heroin pass through U.S. prisons and jails each year (Boutwell et al., 2006), although this figure may be different today owing to changes in the heroin-using population. People recently released from incarceration experience the highest risk of fatal opioid overdose of any subpopulation (Binswanger et al., 2007, 2011, 2013; Farrell and Marsden, 2008; Merrall et al., 2010) because of their loss of tolerance, social isolation, and extraordinarily high relapse rates. Examining data from the Arrestee Drug Abuse Monitoring II Program, Hunt and colleagues (2015) found that those with a history of heroin use had higher drug use and severity and higher rates of treatment utilization relative to those reporting use of other drugs. Only one-third (34 percent) of arrestees with drug use histories had received SUD treatment during their lifetime, and only 14 percent had obtained such treatment during the year prior to their arrest. Receipt of mental health treatment services also was extremely low in this population despite a high prevalence of mental health problems (Hunt et al., 2015).

As is the case for pregnant women with OUD, there are important opportunities to identify and treat people in the criminal justice system who are at risk of progressing to more severe OUD and overdose. However, the most effective evidence-based approaches for addressing OUD and reducing overdose risk (Connock et al., 2007) have historically been inaccessible to people who are incarcerated in the United States. The social, medical, and economic benefits of providing MAT in correctional settings have been well documented (Deck et al., 2009; Dolan et al., 2003; Heimer et al., 2006; Kerr et al., 2007; Kinlock et al., 2009; MacArthur et al., 2012; Mattick et al., 2009; McKenzie et al., 2012; Rich et al., 2015; Zaller et al., 2013). Although the World Health Organization (WHO, 2009) and SAMHSA (Miller and Hendrie, 2008) have strongly endorsed the use of MAT to treat OUD in criminal justice settings, there has been little to no implementation or routine use of MAT in U.S. jail and prison settings (Lee et al., 2015; Vestal, 2016).

National household-based surveys exclude people who are incarcerated and other institutionalized populations. Thus, trends in the epidemiology of opioid use and misuse, OUD, and overdose in this large, underserved, and particularly vulnerable population often are missed, as is the chance to provide lifesaving treatment and medications to a high-risk population at a high-risk point in time. When new medications are approved for the treatment of OUD and overdose, it will be important for those drugs to be made available to individuals who are incarcerated. In addition to the enormous potential public health benefit of doing so, people involved in the criminal justice system are in contact with community corrections and

thus could provide key surveillance data points, thereby improving post-marketing surveillance and public health data capacity.

In summary, OUD is prevalent in criminal justice settings, and improved access to effective treatments and collection of surveillance data with which to track opioid use and associated harms in these settings are needed. The status of surveillance systems for collecting data on drug use among individuals involved in the criminal justice system and other populations is discussed later in this chapter.

People Who Inject Drugs

PWID are subject not only to the harms related to the drug itself but also to the harms related to injection. In particular, PWID are at risk of abscesses, tissue infections, ulcers at the site of injection, and endocarditis (Smith et al., 2014), and those who share syringes and other injection equipment also are at risk of contracting bloodborne infections such as hepatitis C virus (HCV) and HIV.

HCV, which can cause liver scarring and liver cancer, is spread primarily through blood contact, with the primary risk factor in the United States being injection drug use. In 2014, there were an estimated 30,500 cases of acute HCV infection in the United States and an estimated 2.7 to 3.9 million people living with chronic HCV (CDC, 2016a). HCV is now responsible for nearly 20,000 deaths annually in the United States—more than the number due to 60 other infectious conditions combined (Ly et al., 2016). The number of acute HCV infections had been declining steadily in the United States but reversed course and began to increase in the mid-2000s; since 2005, the estimated number of acute infections has more than doubled (CDC, 2016b). This increase in infections has been particularly pronounced among young, nonurban white people (Suryaprasad et al., 2014). Between 2006 and 2012, there was an estimated 364 percent increase in HCV infection among people under age 30 in Kentucky, Tennessee, Virginia, and West Virginia, for a total of 1,377 reported cases (Zibbel et al., 2015). Among the 265 cases for which risk information was available, 73 percent of infected persons reported injection drug use (Zibbel et al., 2015). The authors of this study note that during the same period, there was a surge in the number of young people in these states seeking treatment for OUD related to use of prescription opioids and heroin, suggesting that "the increase in acute HCV infections in central Appalachia is highly correlated with the region's epidemic of prescription opioid abuse and facilitated by an upsurge in the number of persons who inject drugs in these four states" (Zibbel et al., 2015, p. 457). An analysis of national surveillance data showed similar trends, with 75 percent of young persons newly infected with HCV reporting that they had ever injected drugs and 75 percent report-

ing that they had ever misused prescription opioids (Suryaprasad et al., 2014). The authors conclude that all "available information indicates that early prescription opioid abuse and addiction, followed by initiation to IDU [injection drug use], is fueling increases in HCV infection among young persons" (Suryaprasad et al., 2014, p. 1417).

HIV attacks a person's immune system and can lead to infections, cancers, and death. It is spread primarily through sexual activity, but 6 percent (2,392) of new diagnoses in the United States in 2015 were attributable to injection drug use, and another 3 percent (1,202) were due to injection drug use in addition to male-to-male sexual contact (CDC, 2017a). It is estimated that more than 171,000 people in the United States are living with HIV that is attributable to injection drug use (CDC, 2017a). In general, HIV diagnoses among PWID are on the decline, down 48 percent between 2008 and 2014 (CDC, 2017a). However, an increase in injection drug use in nonurban areas and in new populations has created new challenges in monitoring and preventing HIV transmission. High-risk practices—sharing needles, syringes, and other injection equipment—have declined among black and Hispanic PWID, but have not declined among their white counterparts. Young (under 30 years) and new (injecting less than 5 years) PWID are more likely than other PWID to share equipment (CDC, 2017a). High-profile HIV outbreaks have been seen in areas that were previously considered low-risk for HIV. In southeast Indiana, for example, a region that normally saw about 5 new cases of HIV annually, 169 people were diagnosed with HIV in the first half of 2015 (Strathdee and Beyrer, 2015). Most of these people were young and white and lived in rural communities, and the infections were linked directly to the preparation of the newly reformulated ADF Opana ER (oxymorphone ER) for injection (Strathdee and Beyrer, 2015). This development represents a major shift. Since the beginning of the HIV epidemic in the United States, most PWID who became infected with HIV were black men older than 35 who lived in urban areas, and most infections were associated with the injection of street drugs, not prescription medications (Strathdee and Beyrer, 2015). Effective interventions for reducing harm associated with bloodborne disease have a strong evidence base and include the provision of new syringes and needles through syringe access programs and point-of-sale pharmacy access to this equipment (CDC, 2015b; Hagan et al., 2011; Logan and Deutsch, 2015); however, many states recently affected by HIV and HCV increases, including Indiana, do not provide legal access to safe injection equipment. Further discussion on policies related to injection equipment is included in Chapter 5.

New data presented by the CDC at a March 13–14, 2017, advisory committee meeting reviewing ADF Opana ER (oxymorphone ER) suggest that ADF strategies and specific formulation components common to the

ADF versions of OxyContin and Opana ER had harmful effects on PWID and drove outbreaks of HIV, HCV, and thrombotic thrombocytopenic purpura-like illness (TPP)[4] in this population (Brooks, 2017). Data from quantitative (case-control) and qualitative (focus group and interview) studies were analyzed to understand how the characteristics of drugs—and their subsequent use—influenced risks of infection and TPP. Findings indicated that in these communities, which had endemic prescription opioid misuse (with little heroin use), diverted prescription opioids were used in multiple injection events per day. Oxymorphone (the active ingredient in Opana), which is 10 times more potent than the equivalent morphine dose, led to more intense withdrawal in people who had developed OUD involving use of the drug. Opana ER—like OxyContin ER—is formulated with a crush-resistant coating, which drove many users who had been snorting their Opana to inject the drug. The reformulation, however, required multiple steps to be prepared for injection, and the preparation methods used involved the use of more solvents, which ultimately diluted the injection so that more injections occurred during the same injection episode. Also unique to preparation of Opana ER ADF (compared with injection use of other prescription opioids or heroin, for instance) was the use of "rinse shots" to extract all possible drug from the leftover materials. The increased street cost of Opana ER in the community incentivized cooperation and collaboration among people injecting the drug, creating more opportunities for transmission of HIV and HCV (Brooks, 2017). Additional data reported from a 2011 outbreak of HCV in New York State traced transmission to injection of prescription opioids, and in this case, Opana ER and OxyContin ER were the two most frequently injected opioids. These three instances illustrate well the risks of specific drug characteristics and drugs developed to treat pain that can be expected to be misused, diverted, and repurposed.

In summary, PWID are vulnerable to harms related to drug use. It is predictable that new medications with abuse liability will be used by people with established patterns of injecting drugs. Tracking the toll of expected nonmedical use of specific products on the health of people who inject drugs is of public health importance. For new formulations of opioids and other drugs that may be manipulated and injected, it is prudent to anticipate and fully examine the possible harms to health that might occur via injection routes. Data on harms can be collected through surveillance, but ethnographic and qualitative research also is required to understand use behaviors. When harm arises, involving PWID and their health advocates

[4]TPP is a rare but serious blood disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia (low blood platelet count). Intravenous drug use is a known risk factor for TPP (CDC, 2013).

in interventions that affect them can improve public health outcomes. Harm to this population can be minimized and treatment entry improved through safe access to injection materials.

HEROIN USE AND ITS RELATION TO PRESCRIPTION OPIOID USE

It is now abundantly clear that heroin use and trends in illicit drug markets have a substantial influence on the public health impact of prescription opioid use and misuse and OUD. One cannot weigh the importance of new therapeutics without taking full account of unintended harm from diversion and transition to illicit opioid use.

Trends in Heroin Use

Heroin, also known as diamorphine, is a synthetic derivate of the opium plant that can produce intense feelings of euphoria. Its use by humans traces to 1874, when it was synthesized from morphine and subsequently marketed as a medication. Now considered an illegal drug with no medical applications in the United States, diamorphine is currently used in some countries in palliative care or as medication treatment for people with OUD who have not responded successfully to other opioid agonist therapies (Strang et al., 2015).

Data indicate that heroin use has been rising in the United States in recent years among both men and women, in most age groups, and across all income levels (see Figure 4-2). The CDC notes that some of the greatest increases have occurred in demographic groups with historically low rates of heroin use, including women, the privately insured, and people with higher incomes. Of note, heroin use among people aged 18 to 25 more than doubled in the past decade (Jones et al., 2015).

Concomitant with increased heroin use over the past decade have been increases in heroin-related overdose deaths, heroin-related emergency department visits, and help seeking through treatment admission for OUD. Heroin-related overdose deaths have more than quadrupled since 2010, totaling more than 12,989 in 2015. Demographically, the highest rate for heroin overdose death (7.0 per 100,000) in 2013 was among non-Hispanic whites aged 18 to 44, a demographic that one decade earlier had been heavily affected by nonmedical use of prescription opioids, as reviewed earlier in this chapter. Importantly, there are geographic differences in heroin overdose rates, with the greatest burden being exhibited in the Northeast (6.3 per 100,000) and Midwest (6.1 per 100,000) (see Figure 4-3).

Trends in heroin use among those entering treatment have changed radically and quickly. A study of patients entering SUD treatment programs for OUD involving heroin nationwide examined retrospective reports on

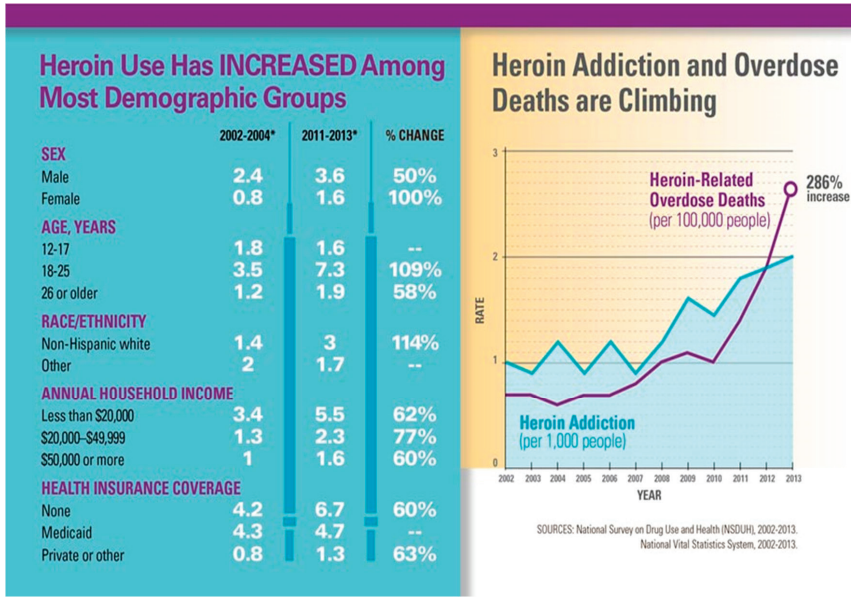


FIGURE 4-2 Public health impact of heroin use.
SOURCE: CDC, 2015c.

past drug use patterns (Cicero et al., 2014). Findings indicate significant changes in the profile of heroin users over the past several decades, from a previously predominantly inner-city, minority-centered problem to one that has more widespread geographic distribution. Users now comprise white men and women in their late 20s living outside of large urban areas who were introduced to opioids through prescription drugs and progressed to heroin in part because of its lower cost and greater availability (Cicero et al., 2014).

Interactions and Transitions from Prescription Opioids to Heroin

One of the most urgent concerns posed by the widespread increase in prescription opioid use and consequent misuse beginning around 2000 is how this epidemic is influencing current trends in the use of heroin and fentanyl and mortality due to overdose involving these drugs. A number of studies have yielded evidence strongly supporting the conclusion that the recent prescription opioid epidemic has resulted in a significant increase in domestic heroin use and associated overdose deaths (Al-Tayyib et al., 2017; Jones, 2013a; Muhuri et al., 2013). The rate of heroin overdose

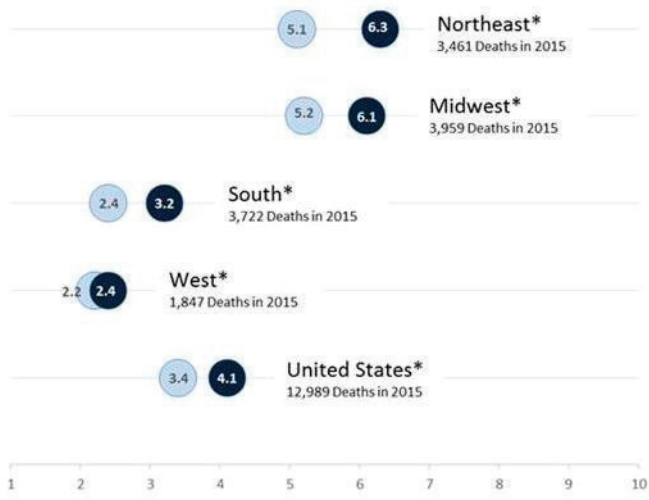


FIGURE 4-3 Age-adjusted heroin overdose death rates per 100,000 population from 2014 (light blue) to 2015 (dark blue), by census region of residence.
*Statistically significant at $p < 0.05$ level.
SOURCE: Adapted from Rudd et al., 2016.

increased moderately from 2006 to 2010 but more than tripled from 2010 to 2014 for all age groups (see Figure 4-4), with the greatest increase occurring among those aged 25–34 (CDC, 2017b). Data for 2015 indicate that the rate of heroin overdose continued to climb, reaching a rate of 4.1 per 100,000 population, more than four times the rate in 2010 (Rudd et al., 2016). Furthermore, from 2007 to 2013, rates of past-year nonmedical use of or OUD involving heroin increased nearly 150 percent (Jones et al., 2015). While societal factors have certainly contributed to this trend, a major concern is how prescription opioids contributed to this problem both by serving as "gateway" drugs to heroin use (Muhuri et al., 2013) and by "squeezing the balloon" through focused efforts to reduce their misuse (e.g., the development of ADFs), leading to illicit sources and drugs such as heroin (Unick et al., 2013).

One issue to keep in mind in this discussion is the relative size of the heroin and prescription opioid epidemics. Heroin historically has attracted only a small number of chronic users in the United States. In terms of the number of people regularly using opioid medications (for pain or nonmedical reasons), the prescription opioid epidemic is many orders of magnitude larger than the endemic level of heroin use. This means that an unprecedented number of people are potentially vulnerable to meeting their

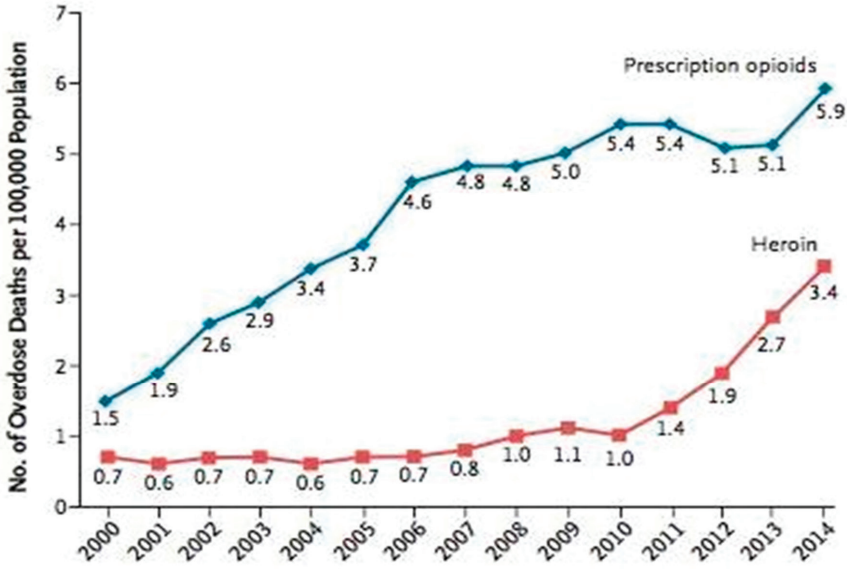


FIGURE 4-4 Age-adjusted rates of death related to prescription opioids and heroin drug poisoning in the United States, 2000–2014.
SOURCE: Adapted from Compton et al., 2016.

opioid use needs with heroin. Understanding how the dynamics of these two current epidemics overlap and the motives of people switching from pills to heroin is a critical challenge.

Prescription Opioids as a Gateway

The gateway theory of the movement of prescription opioid users to heroin is predicated on the fact that opioid medications produce the same neuropharmacologic effects as heroin, so the substances are natural substitutes. Use of both heroin and prescription opioids involves tolerance, cross-tolerance, and withdrawal. Yet heroin is, on balance, more potent than the most common low-dose prescription opioids (e.g., codeine, Vicodin, Percocet). This is true of even fairly low-purity (<30 percent) heroin, but has become even more evident with recent increases in heroin purity rates in some cities (Gray, 2014). The implication is that as people become tolerant to a dose (i.e., level) of opioid medication and no longer feel the desired effects of the drug, they may use heroin and thereby feel more intensely and rapidly effects that pills once may have produced. As discussed in Chapter 3, anyone consistently using these medications is likely to experi-

ence tolerance, which may lead to taking opioid medications in amounts greater than prescribed (Webster and Webster, 2005).

Moreover, initial use of opioids to treat pain may shift to chronic use. In an analysis of linked health care claims, Shah and colleagues (2017) found that the probability of long-term prescription opioid use increased markedly in the initial period of therapy, especially after 5 days or 1 month. Over this initial course of care, tolerance develops and can, if the patient is not tapered off the drug and cared for safely, lead to dependence and OUD. While other factors may influence the transition to heroin use, the point is that the risk of this transition is great for people prescribed opioids, and those initially prescribed the drugs for longer periods or in larger doses (i.e., ER opioids) tend to stay on opioids.

For many people who misuse opioids, switching to heroin also involves an associated transition to a more potent route of administration—e.g., injecting—either before or in conjunction with initiation of heroin use. It is true that most prescription opioids are swallowed, but depending on their formulation (and the knowledge of the person misusing) they also can be sniffed, smoked, chewed, sucked, or injected. In the United States, heroin is most commonly injected—the fastest route of administration—which introduces a host of additional public health consequences (discussed earlier regarding PWID). Heroin (along with fentanyl) is more potent than opioid analgesics (NIDA, 2016), and the potency of opioid analgesics is influenced by the route of administration. The differences in potency and onset of effects among orally ingested opioid medications, snorted or injected prescription opioids, and injected heroin places a person making the switch away from oral routes at much higher risk for overdose. Moreover, to someone tolerant to and misusing prescription opioids, ER opioid formulations and heroin offer a much more rapid onset of effects relative to prescription IR formulations. In this manner, ER opioids and heroin can reset the reward pathway, giving people who make this switch a powerful incentive to continue using them. Efforts to make ER opioid formulations less accessible and/or "abuse-deterrent" and black market efforts to make heroin more readily available, then, may tilt the reward mechanism in favor of seeking heroin.

It is important to acknowledge that an overwhelming majority of people who use prescription opioids do not continue to use them chronically (Shah et al., 2017), and so are not at risk of switching to using heroin. However, for those that do use chronically and then move to heroin through this pathway, the movement is typically one-way. Once a person has begun using heroin consistently, returning to a pattern of primary use of prescription opioids is unlikely for a variety of reasons, including heightened scrutiny by health care providers and the relative expense (see below for discussion of opioid markets) (DEA, 2013). Chronic users of heroin seldom

consume prescription opioids and typically do so only to delay withdrawal when heroin is episodically unavailable; when informally seeking to reduce their heroin intake; or, more recently, when protecting themselves against fentanyl-contaminated heroin.

Further promoting such transitions to heroin among persons previously using prescription opioids is the financial incentive for switching, since heroin is considerably cheaper than street-available pain medications (DEA, 2013). In locations where both illicit prescription opioids and heroin are available, drug users consistently report that prices are lower for heroin. This price difference has always existed. Heroin also has a much lower initial market entry price than that of opioid pills for new users (e.g., a bag of heroin sells for $10, while a pill might cost $20), but few people start with heroin because its use is stigmatized.

Market Effects and the Transition to Heroin

Differences in drug prices are complex and often a consequence of how the markets operate. For instance, the supply of legal prescription opioids is controlled and can therefore be restricted—for example, when a pill mill is shut down or an opioid is reformulated with abuse-deterrent properties (see discussion on OxyContin reformulation below and related discussion in Chapter 5). These medications also are sold in what can be described as a secondary market, meaning the drug is first diverted from some legitimate source to be resold illegally, which is costly and raises the price. As discussed further in the next section, these markets are now growing. Even within expanding markets for counterfeit opioid medications and illicitly manufactured synthetic opioids, moreover, the latter products remain less expensive to purchase than most opioid analgesics, both diverted and counterfeit.

Part of the reason for the price difference between illicit prescription opioids and heroin is that heroin supplies coming into the United States are largely unrestricted (other than by the sorts of supply-related control measures that may restrict opioid medications). In many places where heroin is sold, sales are well-organized and have the support of an established black market infrastructure. Therefore, all other things being equal, once a person starts using heroin, acquiring it consistently may become easier and less expensive relative to pills. As tolerance increases and if OUD progresses, evidence-based treatment may be the only intervention able to disrupt this cycle.

The important regional variations in the numbers of people switching to injection use and to heroin from prescription opioids noted earlier reflect such market factors. One reason especially high rates of prevalence of prescription opioid use did not immediately lead to extensive heroin use

in rural communities may be that heroin was not yet as entrenched and available in these locations. For instance, consistently low rates of heroin use have been seen in a cohort of rural Appalachian injectors in Hazard, Kentucky, even after reformulation of OxyContin and Opana (Havens et al., 2014). But more recent state and local data on overdose deaths, treatment entry, and arrests indicate that heroin is now surging in these same areas. The substantial delay in heroin uptake in these areas may be linked to shifts in drug trafficking patterns, localized interventions to reduce the supply of diverted opioid medications, or changes in the social structure created alongside the pill-based economy (Jonas et al., 2012).

Quantifying the Degree of Overlap

Although a number of factors have prompted people to move from use of opioid medications to use of heroin, quantifying precisely how many people have made this switch is difficult. Yet a number of studies suggest that an alarming overlap has occurred, and is still occurring, between these two epidemics. Authors of a national study of people who use heroin (Cicero et al., 2014) note that an important demographic shift has occurred in recent years. Over the past 50 years, the population of people using heroin has transformed to mirror the population of people using and misusing prescribed opioids. People who use heroin now are primarily younger and non-Hispanic white. Those who have an OUD involving heroin today are very different from their counterparts only 10 years ago, but much more like the people affected by the prescription opioid epidemic. In asking whether people who use heroin begin doing so before or after using prescription opioids, these authors identified a complete reversal from the 1960s: almost all people who initiated heroin use in the 1960s started with heroin, whereas almost all those who began using heroin in the 2000s began with the use of prescription opioids (Cicero et al., 2014).

One large cohort study and a number of regional studies confirmed that a majority of people who had recently started using heroin began by misusing opioid medications. In the first published study on this topic, Siegal and colleagues (2003) found that 50 percent of young persons (aged 18–33) in Ohio who had recently started using heroin reported first having misused opioid medications, primarily OxyContin. A number of similar studies yielded a similar finding, although rates of prior opioid misuse varied. A large study of illicit and prescription drug misuse in young urban people in New York and Los Angeles in 2008 and 2009 found that 73 percent had a lifetime history of obtaining a prescription for opioids and initiated prescription misuse at a younger age relative to use of heroin, suggesting that nonmedical opioid misuse may serve as a gateway to initiation of heroin use (Lankenau et al., 2012). Studies of heroin users in San Diego (Pollini et

al., 2011), Seattle (Peavy et al., 2012), and New York City (Mateu-Gelabert et al., 2015) found that 40 percent, 39 percent, and 77 percent of heroin users, respectively, were users of nonmedical opioids before initiating heroin use. In a more recent sample of PWID in Denver, 32 percent reported being "hooked" on prescription opioids before injecting, and the primary drug they injected was heroin (Al-Tayyib et al., 2017). Finally, in a large, matched cohort of aging U.S. veterans who reported no previous history of nonmedical prescription opioid or illicit opioid use, Banerjee and colleagues (2016) found that nonmedical use of prescription opioids was associated positively and independently with subsequent initiation of heroin use.

An analysis of data from the National Survey on Drug Use and Health (NSDUH), the only nationally representative study of self-reported drug use behavior in the United States, supports the conclusions of the above cohort and regional studies, although it is important to note that household surveys have unavoidable limitations for use in assessing high-frequency use of drugs such as heroin (Caulkins et al., 2015b). Using NSDUH data pooled from 2002 through 2011, Muhuri and colleagues (2013) noted that, among individuals aged 12–49, four of every five recent heroin initiates (79.5 percent) (i.e., those who had initiated heroin use within the past 12 months) were previous self-reported users for purposes of nonmedical pain relief (NMPR) (see Figure 4-5).

The analysis by Muhuri and colleagues (2013), which included approximately 609,000 respondents at risk for heroin initiation and 524,000 respondents at risk for NMPR use, is notable because it found that only a small percentage (3.9 percent) of NMPR users initiated heroin within 5 years after first using NMPR. The NSDUH, however, is a household-based sample that excludes institutionalized populations, homeless individuals, and others, and thus likely underestimates these outcomes. The small incidence rate also is deceptive because of the large annual number of new heroin users it represents. As others have noted, "given the large number of nonmedical users, even a small percentage who initiate heroin use translates into several hundred thousand new heroin users" (Compton et al., 2016, p. 158). Applying the 3.9 percent incidence rate to the 25 million Americans who ever initiated NMPR use between 2002 and 2011 (SAMHSA, 2012) indicates that the prescription opioid epidemic created nearly 1 million new heroin users in this 10-year time frame, or roughly 100,000 annually. Given underreporting, the correct number may be considerably higher still.[5]

[5]It is important to note that until 2015, the NSDUH instrument posed questions regarding "misuse" in terms of two behaviors: using the medication in ways other than prescribed and using it for the way it makes one feel. In 2015 the latter query was eliminated. Because of this change, estimates of misuse from the NSDUH before and after the change was made are not entirely comparable.

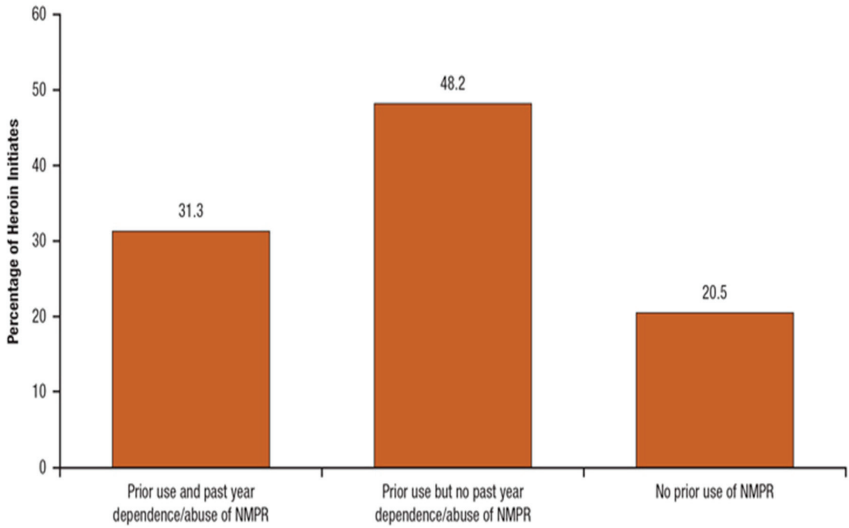
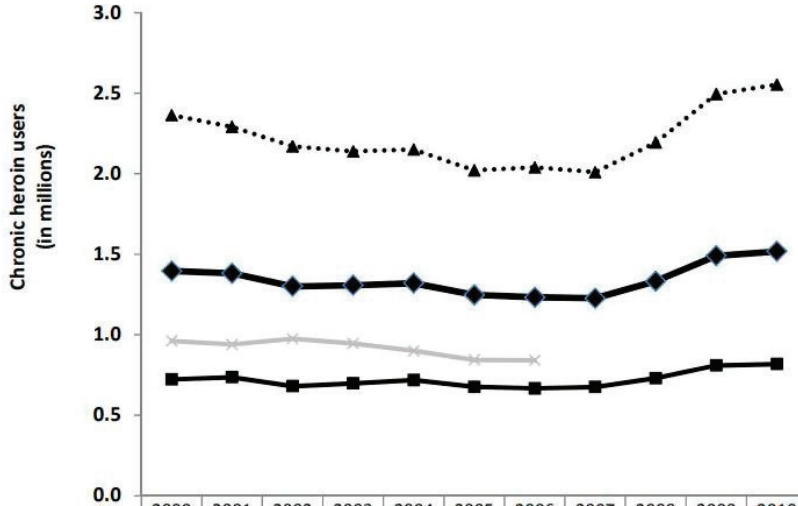


FIGURE 4-5 Percentage of heroin initiates among persons aged 12–49, by prior and past-year dependence on/abuse of nonmedical pain relievers (NMPRs), 2002–2011.
NOTES: Past-year NMPR users are those who had initiated NMPR use prior to initiation of heroin use in the past 12 months. Past-year NMPR users who initiated NMPR use subsequent to initiation of heroin use in the past 12 months are not included. Dependence or abuse is based on self-reported problems and definitions found in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV).
SOURCE: Muhuri et al., 2013.

Alarmingly, data from other sources are consistent with this projection. The most recent estimate from a RAND Corporation report prepared for the Office of National Drug Control Policy (ONDCP) suggests there were 1.5 million chronic heroin users in the United States in 2010 (the latest year estimated) (Kilmer et al., 2014). Based on this "high" projection, 400,000 more chronic heroin users existed in 2010 than in 2002. The estimated number of chronic heroin users remained fairly stable between 2000 and 2007, but from 2007 to 2010 increased 25 percent (see Figure 4-6). During 2007–2010, the rate of new chronic heroin users was >100,000 annually, keeping in mind that these calculations are conservative because they are based on the noted underestimates of the rate of initiation of heroin use from the NSDUH. Based on these estimates, starting from 2010 and assuming 100,000 new heroin users annually, the prescription opioid epidemic could at least double the number of heroin users in the United States by 2025.



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Middle	1.4	1.4	1.3	1.3	1.3	1.2	1.2	1.2	1.3	1.5	1.5
Lower	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.8	0.8
Higher	2.4	2.3	2.2	2.1	2.1	2.0	2.0	2.0	2.2	2.5	2.6
ONDCP (2012)	1.0	0.9	1.0	0.9	0.9	0.8	0.8				

FIGURE 4-6 Estimated number of chronic heroin users, 2000–2010 (in millions).
NOTE: ONDCP = Office of National Drug Control Policy.
SOURCE: Kilmer et al., 2014.

A preponderance of evidence suggests that the major increase in prescription opioid use beginning in the late 1990s has served as a gateway to increased heroin use. Two questions remain: How costly, in terms of heroin mortality, has this connection been? and What does this mean if prescription opioid supplies are curtailed? As in the findings cited above, the year 2010 is an important turning point for addressing these issues.

Marketed aggressively in a campaign that began in 2000, OxyContin—developed by Purdue Pharma in 1996 and the most popular opioid medication in history—is widely regarded as the drug that initiated the current opioid medication misuse epidemic. A critical factor in the initial epidemic was that many people were able to misuse OxyContin by crushing, dissolving, and injecting the drug. All routes of administration were available, and presumably, early in this epidemic, many individuals who misused the drug were particularly vulnerable to using heroin (if locally or regionally available) because they had progressed beyond barriers posed by injection. This trend in OxyContin misuse progressed unabated until August 2010, when at the request of the FDA, an ADF of OxyContin was introduced, after which it became more difficult for people to crush, snort, and inject

the drug. Yet the reformulation of OxyContin to an ADF led some users to abandon the drug entirely (e.g., for treatment), while others moved to other drugs or routes of administration and still others switched to heroin. Cicero and Ellis (2015) found that 33 percent of nonmedical OxyContin users had adapted to the OxyContin ADF by using other drugs, and 70 percent of that group had switched to heroin.

The importance of OxyContin and the change to its ADF formulation offered Alpert and colleagues (2017) an opportunity to conduct a unique analysis to assess how this policy influenced both opioid medication misuse and heroin mortality. Notably, using NSDUH data (again noting the limitations of this household survey described earlier) and comparing states with high and low rates of OxyContin misuse, the authors found that before 2010, no correlation existed between trends in heroin mortality and opioid misuse; death rates for heroin during this time period were stable. By contrast, in the years after the reformulation (2010–2013), "each additional percentage point of pre-reformulation OxyContin misuse is associated with a relative decrease in OxyContin misuse of 0.8 percentage points and an additional 2.5 heroin deaths per 100,000 through 2013" (Alpert et al., 2017, p. 5). In other words, the reformulation decreased opioid medication misuse as intended but substantially increased heroin mortality. This finding led the authors to conclude that for each percentage point reduction in misuse of OxyContin generated by its reformulation, there was an increase in heroin-related deaths of 3.1 per 100,000. When the authors applied their calculation to increased heroin mortality rates between 2010 and 2014, 80 percent of the increase in those rates was explained by OxyContin's reformulation. As noted by the authors, the reformulation of OxyContin to an ADF had different short- and long-term outcomes. In the short term, the change increased heroin-related overdose deaths, while in the long term it reduced (or at least leveled) prescription opioid misuse, which could potentially reduce heroin deaths down the road (Alpert et al., 2017).

Finally, increases in the numbers of individuals who use heroin over the past decade of the prescription opioid epidemic entail important independent dynamics. With more new heroin users entering the market every year, it has become much easier for people to start using heroin directly, without first using prescription opioids. Thus, in addition to individuals who formerly misused prescription opioids, individuals whose heroin use began recently include those who were not influenced by the gateway effect of prescription opioid medications. As a result, heroin may become much more mainstream, appearing to have crossed a threshold that has historically restricted its popularity, so that the movement to direct use of heroin is occurring in the context of a social contagion fueled by the many heroin users produced by the prescription opioid epidemic. In short, the demographic shift in heroin use among persons who are rural, white, and

geographically isolated as well as those who are suburban, young, white, more educated, and from middle-class backgrounds may be facilitating the popularity of heroin by slowly eroding long-standing stigmas that have prevented people from using this drug in the past. The potential waves of new heroin users naïve to opioids are particularly alarming and may explain why heroin and synthetic opioids (fentanyl) have been increasing exponentially the numbers of heroin-related overdose deaths since 2010. Thus, in addition to initiating and continuing to directly feed the current heroin epidemic by facilitating people's switch to heroin, the prescription opioid epidemic may have mutated into a new and independent heroin epidemic.

Summary

The prescription opioid and heroin epidemics are intertwined. One of the consequences of increased prescribing of opioid analgesics has been increases in the use of heroin; in associated overdose deaths; and in the incidence of HIV, HCV, and other injection-related harms. In addition to prescription opioids serving as a gateway to use of heroin, market forces and efforts designed to reduce harms associated with use of prescription opioid medications (e.g., ADFs) may be contributing to increased heroin use. And given the comparatively small population of heroin users relative to that of prescription opioid users, there is currently an unprecedented potential market for heroin use.

ILLICIT OPIOID MARKETS

While it is reasonable to presume for many prescription medicines that consumption is limited substantially to those to whom the drugs were prescribed, this is not the case for all medications, including prescription opioids. Prescription opioids may be diverted (e.g., through resale, theft, or other means) to illicit markets that are the proximate cause of considerable harm (OUD and overdose). Furthermore, these markets for diverted prescription opioids interact with purely illegal markets for opioids that are not supplied through the U.S. health care system (Unick et al., 2013), as well as with the dark web of vibrant online drug cryptomarkets (Aldridge and Décary-Hétu, 2016). Traditionally, markets for purely illegal opioids pertained primarily to heroin, but they have been expanding to encompass new psychoactive substances, most recently and infamously synthetic opioids such as fentanyl and its analogs (e.g., acetyl fentanyl, ocfentanil, carfentanyl) that are packaged and sold in bulk from abroad to drug trafficking organizations or even as counterfeit pills made to look like popularly diverted prescription opioid medications. Thus, part and parcel of creating the supply of prescription opioids for treatment of chronic

pain are increases in the supply to and demand for black markets for opioids, with all of their attendant harms, including violence, corruption, and incarceration.

History of Illicit Opioid Markets

Prescription opioids did not create the black markets for illegal opioids. The illicit opioid markets already had a long history in the United States. In fact, their prominence is reflected in the very names of such institutions as the Bureau of Narcotics and Dangerous Drugs (the predecessor of today's U.S. Drug Enforcement Administration [DEA]) and in the fact that "narc" is a slang term for a drug enforcement officer. However, large-scale misuse of prescription opioids created new demand that substantially reinvigorated, expanded, and diversified those markets.

The illegal opioid markets saw ebbs and flows before the expansion of prescription opioid misuse. A surge of use occurred after World War II, but it had been largely contained by the 1960s (President's Commission on Law Enforcement and Administration of Justice, 1967). Another, larger epidemic of heroin use took place in the late 1960s and early to mid-1970s, but that, too, was quelled by a combination of interventions on the demand side (early deployment of methadone) and supply side (Turkish poppy ban and breaking of the "French Connection") (DuPont, 1971, 1973, 1974; DuPont and Greene, 1973; Kaplan, 1983).

The heroin market was not completely stable between the mid-1970s and mid-1990s. The source of supply shifted markedly, from Mexico to Southwest Asia to Southeast Asia to South America (DEA, 2016b, p. 47). Heroin purity rose between the 1980s and 1990s, and purity-adjusted prices fell sharply (DEA, 2016c). But initiation was low, and use had remained substantially confined to an aging group of mostly men in major urban centers, predominantly in the Northeast and Southwest. Notably, availability was quite limited in most small cities and rural areas.

The heroin market was revived in the mid-1990s by a new source of initiation in the form of people whose opioid misuse had started with prescription opioids who transitioned to cheaper, and riskier, black market opioids (see Figure 4-7). This influx changed the demographic composition of the user base (Cicero et al., 2014; Muhuri et al., 2013), roughly doubled initiation into heroin use, and much more than doubled demand because all of these new initiates were experienced opioid users.

The effects can be seen not only on initiation but also on the ages of those seeking treatment. Among those in the Treatment Episodes Data Set (TEDS) records as seeking treatment for heroin as their primary drug of use, in 1993 two-thirds were between the ages of 30 and 44. Twenty years later, in 2012, that proportion had fallen to one-third. The absolute numbers had

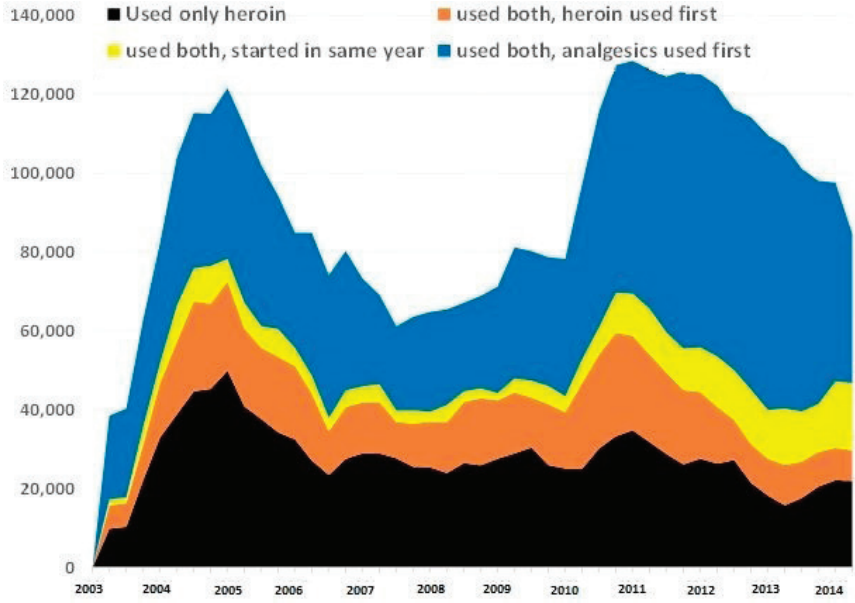


FIGURE 4-7 Heroin initiation reported in the 2003–2014 National Survey on Drug Use and Heroin (NSDUH), broken down by whether analgesics were used nonmedically before heroin.
SOURCE: Committee analysis of 2003–2014 National Survey on Drug Use and Health (NSDUH) data.

declined by 20 percent (from 124,000 to 98,000), whereas the corresponding numbers for those under the age of 30 had grown by 150 percent (from 49,000 to 124,000) (SAMHSA, 2013b).

A further shift in supply occurred as well, with heroin produced in Mexico eclipsing that produced in South America. Seizures of heroin along the Southwest border of the United States began to increase sharply after 2007 (DEA, 2016b, p. 46). Importantly, retail distribution expanded into smaller cities and rural areas and to parts of the country, such as the Midwest, that previously had had lower availability. It is unclear whether that expansion in availability was demand-driven (supply reached out to where the new users lived), supply-driven (heroin distribution from other countries piggy-backing on networks that already had broad geographic reach for the delivery of cocaine and methamphetamine), or both.

In the past few years, two "new" and potentially very important product forms—fentanyl and counterfeit opioid pills—have proliferated in North American black markets for illegal opioids. The word "new" is in quotes

because little that happens in black markets is truly unprecedented (Baum, 1985). Rather, what is new is that these products are becoming common, not exceptional. For example, the DEA (2016a) reports that before 2014, the National Forensic Laboratory Information System (NFLIS) recorded more than 1,000 fentanyl exhibits only in a single year—2006, when a fentanyl "crisis" was associated with production tracked primarily to a clandestine lab in Toluca, Mexico. Yet by 2015, NFLIS recorded 13,002 fentanyl exhibits, more than 8 times the 1,594 exhibits observed during the 2006 crisis.

Present-Day Illicit Opioid Markets

Today's illicitly manufactured fentanyl may have multiple sources that are diversifying and expanding. Much illicitly manufactured fentanyl is reputedly produced in the same areas (and perhaps even the very same factories) that produce legal medications for distribution by pharmaceutical companies (DEA, 2016a). Black market drugs often move through complex pathways, but the DEA believes a common pathway is bulk shipments from China to drug trafficking organizations in Mexico and thence across the Southwest border, although some of the drugs may also be produced in Mexico. The fentanyl may be sold straight up at retail, but also is mixed into heroin as an extender and increasingly into other drugs such as cocaine. This practice is facilitated because trafficking organizations now distribute various powdered forms of heroin, not just the traditional "black tar" heroin, which cannot as easily be adulterated with fentanyl.

An economic incentive exists for trafficking organizations to "extend" heroin with fentanyl or to sell fentanyl outright. Fentanyl is thought to be 25 to 50 times more potent than heroin (DEA, 2016d). As a synthetic opioid, it is more economically appealing than natural opioids such as heroin. The Western States Information Network (WSIN) (2016) reports kilogram prices of heroin ranging from $17,000 to $30,000 for Mexican brown and $20,000 to $46,000 for Colombian white (which is also distributed by Mexican drug trafficking organizations), two forms that can readily be cut with fentanyl (Southeast Asian heroin is somewhat more expensive, but has a very minor market share in the United States, especially in the West). While fentanyl manufactured in a lab could be purchased at prices below that of heroin per kilo (DEA, 2016a), fentanyl's potency allows it to be diluted more and still deliver a dangerous dose. In this way, a kilo of drug can be multiplied into 10 to 20 kilos or more of drug for street sale with the addition of fentanyl products. There exist at present only anecdotal reports of wholesale fentanyl prices, but the DEA (2016a, p. 8) cites instances of a distributor selling fentanyl for $3,500 per kilogram, while the DEA's Miami Field Division reports that fentanyl could be purchased for $1,700 per kilogram (DEA, 2016a, p. 8).

The other factor that affects relative price is competition and the presence of substitute products. As with many new synthetic psychoactive products, manipulation of fentanyl contributes to the creation and proliferation of fentanyl analog products in the illegal drug trade and cryptomarkets (Quintana et al., 2017) and a ready source of replacement chemicals.

If fentanyl in wholesale markets costs about one-tenth as much as heroin but is 10–25 times as potent on a pure milligram basis, then heroin "per unit of intoxication" from the customer's perspective is 10–25 times more expensive for drug traffickers. Thus, there is an incentive to adulterate heroin (and other drugs) with fentanyl to reduce the costs of materials.

Prices in illegal markets adjust slowly, perhaps because of poor information flows, but they are competitive, and in the long run prices tend to fall in parallel with production costs, at least if one understands costs broadly to include compensation for the various risks involved in distributing drugs (Caulkins and Reuter, 2010; Reuter and Kleiman, 1986). One should not be surprised, then, if over the next half-dozen years, fentanyl continues to displace heroin in illegal opioid markets, and its prices continue to fall, perhaps very substantially.

A related phenomenon is the selling of counterfeit prescription opioid pills, often laced with or containing only fentanyl. The logic for the fentanyl adulteration is compelling. Fentanyl, as noted, is cheaper than heroin, and heroin is cheaper than prescription opioids, so fentanyl-laced counterfeit pills are markedly cheaper than are diverted pharmaceuticals. That this is so is not really surprising, given that production costs for many pharmaceuticals are just a tiny fraction of their sales price in the United States.

Pressing pills is not difficult. Pill presses are not regulated and can be purchased openly in some countries. (It is illegal to bring presses into the United States without notifying the DEA, but criminal organizations ignore that law or do the pressing in other countries.) The DEA (2016a, p. 9) cites prices of under $1,000 for a press that can produce 5,000 pills per hour and die molds selling for a little over $100, so the equipment costs are negligible given that pills often sell for $20 apiece at retail, and perhaps $6.50 per counterfeit pill in bulk. And while it may be difficult to meet the exacting standards for legal pharmaceutical pills, it is not difficult to make counterfeit pills that are potent and indistinguishable from true pharmaceutical pills to the casual observer. Moreover, the street-based purchase environment for the illicit drug consumer often is not conducive to thorough inspection of pills to verify indicia, color, weight, and shape (Green et al., 2015a). Counterfeit pills may serve a purpose for suppliers as well: they may be a relatively safe means of transporting some of the most potent fentanyl analogs (e.g., carfentanyl), and may be perceived as a more economically efficient and controlled dosing mechanism than powdered fentanyl or contaminated illicit powder drugs (if the fentanyl quantity contained in the pill is known to the

supplier or purchaser) (Green and Gilbert, 2016). The proliferation of a counterfeit prescription opioid market into the foreseeable future is likely.

Whether the trafficker is pressing it into pills, dividing it to sell outright, or using it to adulterate other powdered illicit drugs, fentanyl's chemical properties leave little room for error. Its potency means that very small quantities can be lethal, and it is sometimes difficult for black market producers to mix and dilute powders with sufficient precision to avoid inadvertently selling quantities that contain a lethal dose. (It is easier to reliably dilute and prepare fentanyl solutions, which can be delivered via metered dose, either intranasally or intravenously, as is typically performed by anesthesiologists in hospitals.)

Again, while prices in illegal markets do not always arbitrage away price gaps swiftly, they tend to do so over time. So as with fentanyl displacing heroin, one can envision counterfeit pills displacing diverted pharmaceutical pills in the coming years, at least for those who have developed OUD. It will be important to track the public health implications of the fentanyl and counterfeit market displacements on the symptoms, prevalence, and severity of OUD.

Smaller-Scale Diversion to Illicit Markets

Thus far, this section has been addressing traditional black markets that involve long distribution chains through which organized criminal groups connect users to (mostly) overseas production. There exists another form of illegal market in which smaller quantities of prescribed medications are diverted and sometimes even sold. This is a sort of retail-to-retail distribution more akin to heavy cannabis users growing their own and selling to other users on the side.

It has long been understood that prescription drugs get diverted into illegal markets in multiple ways (Inciardi et al., 2007), but solid estimates of the relative magnitude of these channels are lacking, for reasons that also have long been understood (Inciardi et al., 2009). It appears that most of the diversion is carried out by individuals who receive prescriptions lawfully rather than through robberies of pharmacies or delivery trucks and other diversion from the legal, wholesale supply chain.

To understand why, it is important to get a sense of scale. It has been estimated that the United States consumes 39,487 defined daily doses (DDDs)[6] of opioids per million inhabitants per day (Häuser et al., 2016).

[6]DDD refers to "the assumed average maintenance dose per day for a drug used for its main indication in adults." It does not necessarily correspond to the recommended or prescribed daily dose for a given patient, which will often differ from the DDD based on such characteristics as age and weight, as well as pharmacokinetic considerations (WHO, 2003).

Multiplying by the U.S. population of 320 million and by 365 days per year indicates that there are approximately 4.6 billion DDDs of opioids per year in the United States.

Respondents to the 2014 NSDUH self-reported 564 million days of use of prescription pain relievers that were not prescribed for them or were taken "for the experience or feeling it caused." As an aside, the majority (61 percent) of those days was among respondents who self-reported enough problems with drugs or alcohol to be judged as meeting the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV), for abuse or dependence on drugs or alcohol, and 43 percent was among respondents who met those criteria specifically for "abuse or dependence on prescription pain relievers."

Surveys, moreover, can underestimate drug consumption as a result of respondents' social desirability concerns or inability to recall, among other reasons. Even for alcohol, it has been found that survey self-reports account for only about half of the alcohol known to be sold based on tax records (Cook, 2007). Thus, the 564 million self-reported days in the NSDUH may correspond to more like 1 billion actual days. If the average dose per day for NSDUH respondents equals the DDDs underpinning the 39,487 DDDs per million figure, then dividing that 1 billion by the 4.6 billion DDDs posited above, one might speculate that very roughly 20 to 25 percent of prescription opioids in the United States are used nonmedically.

The DEA (2016b, p. 34) reports that in recent years, distributors in the United States disbursed 12–15 billion dosage units of opioid narcotics to retail-level purchasers, suggesting that total diversion is on the order of 2.5–4.0 billion dosage units. By contrast, the DEA (2016b) reports that in the entire country in 2015, only 9.1 million dosage units of opioid narcotics were lost to diversion from the supply chain (e.g., from robberies of pharmacies), while another 1.9 million dosage units were "lost in transit." Those are small numbers compared with the 12–15 billion dosage units disbursed to the retail level and the speculation of something like 2.5–4.0 billion units diverted.

A small number of high-volume, corrupt prescribers can provide substantial supply. ProPublica, for example, reported on Medicare's top 20 OxyContin prescribers for 2010.[7] The 12 prescribers who were charged, were fined, and/or had their medical licenses revoked wrote 17,000 OxyContin prescriptions and more than 56,000 prescriptions for narcotics of all kinds in 2010. Those are prescriptions, not dosage units, and there are many more than just a dozen corrupt doctors. Still, it is not clear that a handful of extreme prescribers can account for a number of dosage units in the billions.

[7]See https://projects.propublica.org/checkup/oxycontin (accessed January 30, 2017).

There is slightly better information from the other direction on where people obtained the analgesics they used nonmedically. It is clear from the NSDUH and other sources that many people who use prescription analgesics nonmedically obtain them for free from friends or family, and it is believed that in turn, most of those friends and family obtained those drugs from a single doctor (DEA, 2016b; Hughes et al., 2016; Kennedy-Hendricks et al., 2016). However, for drugs, and for that matter many other consumer goods, a minority of heavy users account for a disproportionate share of consumption. In the 2014 NSDUH, two-thirds of those answering the question about where they most recently had obtained pain relievers for nonmedical use reported use on 50 or fewer days in the past year (i.e., less than weekly), and those users accounted for just 14 percent of the self-reported days of use. To the extent that frequent users also tend to use more per day of use, their share of market demand was even smaller. Conversely, the 8 percent of those respondents who said they had used on 180 or more days in the past year (so every other day or more often) accounted for almost half of the days of use, and presumably well more than half of the consumption. This means that statistics based on numbers of users can differ sharply from those based on a measure related more closely to market demand. For example, people who reported in the 2014 NSDUH that they had obtained nonmedical analgesics most recently by purchasing them—whether from a friend, relative, dealer, or other stranger—tended to be heavy users. So even though they represented just 14 percent of respondents who had used analgesics for nonmedical reasons, they accounted for 25 percent of the self-reported days of use (SAMHSA, 2014).[8]

It is worth noting as well that some people who had acquired the drugs most recently by some relatively innocuous means may also have purchased them or obtained them by fraud at other times. Respondents who reported use within the past 30 days account for the majority of days of use, and the NSDUH asks respondents to "Please enter all of the ways that you got the prescription pain relievers you used in the past 30 days." In 2014, fully 39 percent of those individuals reporting days of use indicated that they had bought the drugs at some point in the past month, from a dealer, friend or relative, or the Internet. Another 5 percent denied purchasing but admitted to other illegal behavior (stealing, obtaining fake prescriptions, or taking from a friend or relative without asking), and a further 5 percent had neither bought nor scammed, but had obtained from multiple doctors. Based on these findings, perhaps roughly half of current nonmedical consumption is among people who engage in such tactics at least some of the time. To be clear, this does not mean that half of nonmedical analgesics are obtained using these tactics. Even among the 500,000 respondents who reported

[8]Committee calculations. Variable ANLLTS2 = 6 or 8.

buying from drug dealers, 20 percent said they also had obtained in the past month from a single doctor.

This pattern is not new. Figure 4-8 shows that if anything, the proportion of current demand attributable to people who buy analgesics for nonmedical use at least occasionally has been greater in previous years.

Furthermore, all of these statistics apply to those who responded to the questions on this household survey, and household surveys fail badly at capturing the behavior of most problematic users. Caulkins and colleagues (2015a), for example, observe that the NSDUH suggests there were only 60,000 daily or near-daily heroin users in the United States, whereas Kilmer and colleagues' (2014) more comprehensive estimate, drawing on the Arrestee Drug Abuse Monitoring (ADAM) system, among other sources, puts the figure closer to 1,000,000.

If the people who fell outside the NSDUH's sampling frame were unwilling to complete the survey, skipped these questions, or did not respond truthfully were more heavily involved in diversion relative to those who answered the survey questions forthrightly, then the extent of diversion may be even greater than is suggested by this discussion. Omitted and

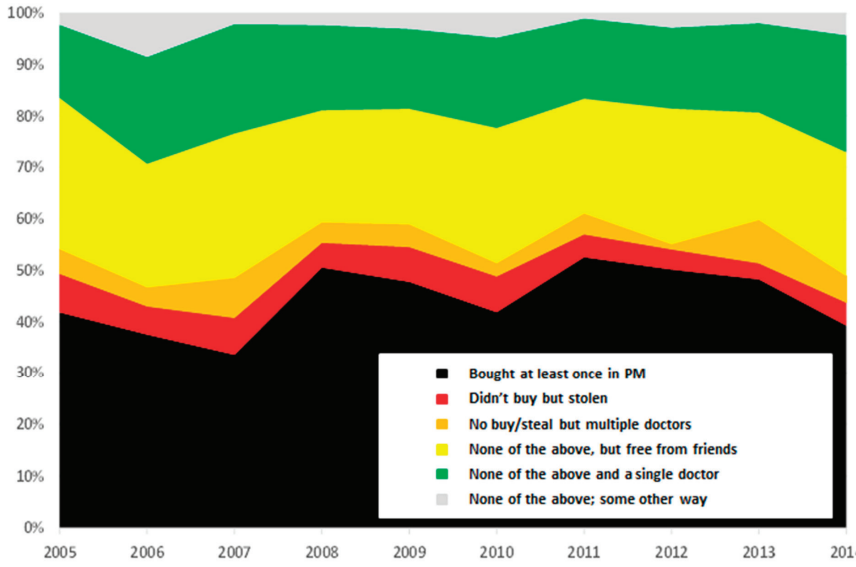


FIGURE 4-8 Proportion of past-month (PM) users' days of use, broken down by whether those individuals reported ever participating in diversion.
SOURCE: Committee analysis of 2005–2014 National Survey on Drug Use and Health (NSDUH) data.

untruthful responses by individuals within the NSDUH's sampling frame also are a potential source of bias. What is clear is that the scale of diversion is sufficient to enable such organizations as StreetRx.com (Dasgupta et al., 2013) and WSIN (2016, p. 27) to quote black market prices with high geographic specificity not only for such staples as oxycodone, methadone, and hydromorphone (Dialaudid) tablets, but also for buprenorphine (with and without naloxone) and 25, 50, 75, and 100 mcg/hour fentanyl patches.

Trends indicate that for more than a decade, opioid-related harms, including OUD and unintentional overdose, have been growing problems across the country (Calcaterra et al., 2013; Paulozzi, 2012) and the world (EMCDDA, 2015a,b), and are now negating indicators of public health advances and altering both life expectancy (Olshansky et al., 2012) and the very demography of the American populace. The implications of these extensive illicit markets for the evaluation of post-marketing or other policy interventions for prescription opioids, given the current paucity of surveillance capacities (discussed in the section on surveillance below), cannot be overstated.

Summary and Recommendation

Several distinct, well-established markets for opioids exist with overlapping demand in the United States that are likely to persist for the foreseeable future. The products they supply include opioids prescribed, dispensed, and used by patients as medically intended; those prepared as a prescription but not used as intended, including opioids dispensed and misused, as well as those that are diverted before being dispensed (i.e., diverted from lawful channels of commercial distribution, such as wholesalers and pharmacies); and those supplied by drug trafficking organizations, mostly from international sources. Conditions appear ripe for fentanyl and counterfeit prescription pills to continue to spread, with potential effects not only on heroin and other illicit drug markets but also on markets for diverted prescription drugs. These markets are both well established and likely to persist for the foreseeable future. **The committee recommends that, in designing and implementing policies and programs pertaining to prescribing of, access to, and use of prescription opioids, the U.S. Food and Drug Administration, other agencies within the U.S. Department of Health and Human Services, state agencies, and other stakeholders consider the potential effects of these interventions on illicit markets—including both the diversion of prescription opioids from lawful sources and the effect of increased demand for illegal opioids such as heroin among users of prescription opioids—and take appropriate steps to mitigate those effects (Recommendation 4-1).**

THE CURRENT STATE OF SURVEILLANCE SYSTEMS

Since the IOM report *Relieving Pain in America* (IOM, 2011) was issued, a remarkable loss of publicly available data sources on drug-related trends has occurred. Four major publicly funded data sources (discussed later in this section) were phased out during this period, and only one has been replaced with a new system; still others remain in validation stages for redesign. In the void created by the defunding of these data sources, proprietary and specialized post-marketing surveillance systems have gained immense importance. The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System and the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) are two such multimodal data systems. They provide product-level real-time post-marketing surveillance at cost to the pharmaceutical industry, which then uses these data to respond to the FDA REMS and other FDA-related post-marketing reports and inquiries.

RADARS originated as part of Purdue Pharma's risk management activities and was subsequently incorporated into the Rocky Mountain Poison and Drug Center, a division of the Denver Health and Hospital Authority. Its real-time, product-specific data collection includes a survey of key informants across the country, a survey of methadone treatment program attendees, analysis of news and social media mentions, drug diversion investigator surveys, a college student survey, street price analysis, and poison control reports. NAVIPPRO operates a similar system, with real-time data collection via a version of the well-known Addiction Severity Index (ASI), amended to collect product-level information about misuse, route of administration, and drug source. NAVIPPRO is a proprietary dataset owned by Inflexxion, Inc., which created the system through a series of Small Business Innovation Research (SBIR) grants from the National Institute on Drug Abuse (NIDA). NAVIPPRO includes data collected from a national sample of both adults and young adults attending substance use treatment centers. The data are compiled for analysis together with poison control data and text-based analysis of drug-related online message boards and chatter from drug-use discussion forums. Although both systems have published extensively on their creation, validation, and product-level analyses and are used by pharmaceutical companies, they have not been widely used by public health practitioners and researchers. Sources that report drug-related data are catalogued in Appendix C; those no longer operating since 2011 to date are discussed immediately below.

The Drug Abuse Warning Network (DAWN) was a public health surveillance system created in 1972 that monitored drug-related hospital emergency department visits (DAWN-ED) in order to report on the impact of drug use in metropolitan areas and nationally. While DAWN was never

designed to be nationally representative, the system generated estimates at the metropolitan area level and was later used to produce nationwide estimates. In addition, the system was expanded to encompass drug-related deaths investigated by medical examiners or coroners (DAWN-ME) in a selected sample of metropolitan areas. After 2003, DAWN included a real-time data access portal called DAWN Live. The site facilitated quicker access to data for participating sites and public health organizations, with clear indicators of reporting completeness and attendant caveats.

The agent (i.e., product and compound)-level specificity of the data reported in DAWN meant that the pharmaceutical industry and the public had access to product-level information and could compare product impacts, including morbidity and mortality trends, interactively. DAWN was initially overseen by the DEA, then NIDA, and finally SAMHSA, but both DAWN-ED and DAWN-ME were discontinued in 2011 (SAMHSA, 2016b). Thus, this resource was unavailable as the opioid epidemic unfolded. In retrospect, the product-level detail in DAWN could have informed decision makers across institutions of the nature and challenge of the prescription opioid and illicit drug crises.

In researching the reasons for the defunding of DAWN, the committee learned of several factors, including frustrations with the sampling frame, incompleteness of data, concerns among industry about the product-level data, cost, and the lack of representation of small-town and suburban communities. In the absence of DAWN, it has become more difficult to track drug-related emergency department visits (Rowe et al., 2016). SAMHSA's new Emergency Department Surveillance System (SEDSS) is intended to serve as the new source of data on drug-related emergency department visits, and will combine aspects of DAWN with the National Center on Health Statistics' (NCHS's) National Hospital Care Survey. The timeliness of reporting, geographic specificity, and product-level details of the new system are unknown.

In 2014, two additional key data sources were phased out. First, funding for the Arrestee Drug Abuse Monitoring survey (ADAM II), which had been funded since 2007 by ONDCP, was cut for budgetary reasons (before 2007, an earlier version of the system had been housed in the National Institute of Justice) (Kilmer and Caulkins, 2014; NIJ, 2014). ADAM collected self-reported data and biological samples from arrestees admitted to booking facilities, inquiring about drug use trends and street prices and examining their urinalysis results. The value of the ADAM data was evident in information on trends of illicit drugs other than marijuana, which generated strikingly different estimates from those extrapolated from the NSDUH (Caulkins, 2015a; Kilmer et al., 2014). These data were useful for policy makers, law enforcement, and treatment resource planners. To date, this data source has not been replaced or reinvigorated.

Also phased out was NIDA's Community Epidemiology Work Group (CEWG), a network of local experts in drug-related topics, which had met semiannually to report on drug trends and emerging issues in sentinel sites from 1976 to 2014. The CEWG experts created metrics and indicators of drug use trends, collaborated on annual reports, and conducted field research on emerging trends. The CEWG was replaced by the National Drug Early Warning System (NDEWS) (NIDA, 2015), which coordinates a listserv, hosts webinars, tracks online media mentions of various drug-related terms and trends, and convenes a virtual network of sentinel sites that conduct local area data collection as requested. Only 3 years into its existence, the NDEWS is not equal to its predecessor in terms of representation, participation, and reach; however, its role and purpose continue to evolve, providing a crucial platform for questions and discussion related to drug use trends for its online and invited membership.

Notably, few of the public and proprietary datasets that have collected self-reported data from people who use drugs have asked respondents about their overdose history. Those that have inquired about overdoses have tended to employ wording that conflates unintentional and intentional (i.e., suicide attempt) overdose or failed to specify or ask separately about overdose on opioids (heroin, pain medication, or MAT medications). More recent efforts to better apply and report emergency department *International Classification of Diseases* (ICD) E-codes in order to standardize and improve the reporting of hospital-treated overdoses are laudable, but will underestimate the true rate of nonfatal overdose in a community. Capturing the many nonfatal overdose experiences in which the person is not transported to the hospital requires a valid and reliable direct inquiry encompassing all people who use these drugs.

It has been said that one cannot see what one does not count. The absence of agent-specific, real-time, drug-related data has contributed to the severity of the current opioid crisis. The timing of these data losses exacerbated the inability to detect changes in misuse and mortality driven by prescription opioids, and it continues to hinder the nation's capacity to track illicit drug trends and their public health consequences. Cost-effective and nimble data collection systems may be reliable and even timely, but need to be examined rigorously for validity. More critically, the pervasiveness and lethality of illicit synthetic drugs heighten the need to capture agent-level information and concurrent and subsequent drug-using behaviors.

As discussed in Chapters 2 and 3, gaps exist in the reporting of data that can be used to accurately describe the epidemiology of pain and OUD in the United States, including how these conditions relate to one another and how often they co-occur. This chapter has reviewed the interrelated nature of the prescription and illicit opioid epidemics and the limitations of current salient surveillance systems. Closing these data gaps would improve

understanding of pain, OUD, and overlapping illicit use, and enable more effective and measurable policy interventions. **The committee recommends that the Substance Abuse and Mental Health Services Administration, the U.S. Food and Drug Administration, the National Institutes of Health, and the U.S. Centers for Disease Control and Prevention collaborate to identify best practices and reporting formats that portray the epidemiology of both pain and opioid use disorder accurately, objectively, and in relation to one another (Recommendation 4-2).**

The committee recommends that the National Institute on Drug Abuse and the U.S. Centers for Disease Control and Prevention invest in data collection and research relating to population-level opioid use patterns and consequences, especially nonmedical use of prescription opioids and use of illicit opioids, such as heroin and illicitly manufactured fentanyl (Recommendation 4-3). The research proposed in Recommendation 4-3 could include transitions to and cessation of use of heroin and fentanyl; motivations for use; social determinants underpinning misuse and illicit use; and differences arising by sex, gender, race, and ethnicity.

RECENT DEVELOPMENTS IN PHARMACEUTICAL TREATMENT OF OPIOID USE DISORDER

This section highlights the use of pharmacotherapies in the treatment of OUD, with an emphasis on new research and treatment approaches that have emerged since the 2011 IOM report was issued. A review of current trends in access to, utilization of, and outcomes of treatment services is presented in Chapter 5.

The Centrality of Pharmacotherapies in Treatment of Opioid Use Disorder

Medications are central to the treatment of OUD. The three medications approved by the FDA for treatment of OUD are methadone, buprenorphine, and naltrexone (see Table 4-1). There continues to be some debate in the field regarding whether, and under what circumstances, use of these medications should be regarded as necessary or sufficient, a debate that is reflected in the terms used to refer to treatment with these medications. For example, recovery community advocates encourage the use of the term "medication-assisted recovery" to describe the combination of pharmacotherapy and counseling and/or recovery work that they believe patients should undergo. They argue that remission of SUD achieved through use of medication alone is not genuine because without counseling, the person may not have achieved the interpersonal and spiritual changes deemed necessary for lasting recovery. The assumption is that only by participating

TABLE 4-1 Characteristics of Medications for the Treatment of Opioid Use Disorder

Characteristic	Methadone	Buprenorphine	Naltrexone
Selected Brands	Dolophine, Methadose	Subutex,* Suboxone, Zubsolv	Depade, Revia, Vivitrol
Class	Agonist (fully activates opioid receptors)	Partial agonist (activates opioid receptors but produces a diminished response even with full occupancy)	Antagonist (blocks the opioid receptors and interferes with the rewarding and analgesic effects of opioids)
Use and Effects	Taken once per day orally to reduce opioid cravings and withdrawal symptoms	Taken orally or sublingually (usually once per day) to relieve opioid cravings and withdrawal symptoms	Taken daily orally or monthly by injection to diminish the reinforcing effects of opioids (potentially extinguishing the association between conditioned stimuli and opioid use)
Advantages	High strength and efficacy as long as oral dosing (which slows brain uptake and reduces euphoria) is adhered to; excellent option for patients who have no response to other medications	Eligible to be prescribed by certified physicians, nurse practitioners, and physician assistants, which eliminates the need to visit specialized treatment clinics and thus widens availability; lower risk of overdose	Not addictive or sedating and does not result in physical dependence; a recently approved depot injection formulation, Vivitrol, eliminates the need for daily dosing
Disadvantages	Mostly available through approved outpatient treatment programs, which patients must visit daily; respiratory depression; abuse liability	Subutex* has measurable abuse liability; Suboxone diminishes this risk by including naloxone, an antagonist that induces withdrawal if the drug is injected; for Subutex and Suboxone, withdrawal in patients dependent on methadone or short-acting prescription opioids	Poor patient compliance with the oral form (but Vivitrol should improve compliance); initiation requires attaining prolonged (e.g., 7-day) abstinence, during which withdrawal, relapse, and early dropout may occur; overdose fatality due to self-discontinuation and hypersensitized μ opioid receptors

*Subutex (a single-agent buprenorphine product) is no longer on the market in the United States. However, multiple other generic single-agent buprenorphine products are available.
SOURCE: Adapted from Volkow et al., 2014.

in regular counseling and adjunctive treatment services can people attain signficant recovery achievements. As an alternative, WHO uses the term "psychosocially assisted" pharmacotherapy, to capture the central role of medications in the treatment of OUD (WHO, 2009). It is both critical and convenient for the purposes of this report that the most effective approaches for treating OUD are those within the purview of the FDA.

The committee has chosen to use the acronym MAT to refer to the use of pharmacotherapies in treatment of OUD. As explained in Box 1-2 in Chapter 1, MAT may be defined to refer either to "medically assisted treatment" (use of medications in combination with counseling and behavior therapies to treat OUD) or to "medication for addiction treatment" (implying that medication may be used alone, but need not be). The committee has chosen to use MAT to embrace this ambiguity instead of opting for one definition or the other. For purposes of this report, the only material scientific conclusion is that medications should play a central (if not exclusive) role in treatment of OUD, a view strongly supported by the scientific literature.

A 2009 Cochrane systematic review found that opioid agonist treatment without counseling is more effective than being waitlisted for treatment or receiving psychosocial treatment with or without placebo (Mattick et al., 2009). These findings were affirmed by recent results from the NIDA Clinical Trials Network's Prescription Opioid Addiction Treatment Study (POATS), in which a randomized controlled trial examined buprenorphine-naloxone treatment of varying durations and counseling of varying intensities among patients dependent on prescription opioids. It was found that patients receiving individual counseling for OUD in conjunction with the medication (weekly 45- to 60-minute sessions with a trained mental health or substance abuse professional) showed no additional benefit over those receiving standard medical management (15- to 20-minute visits with a physician certified to prescribe the medication) (Weiss et al., 2011). Similarly, a study of more intensive counseling in the setting of office-based buprenorphine prescribing compared with medication only showed no superior patient outcomes (Fiellin et al., 2006). On the other hand, one study in a veteran population showed superior outcomes for patients receiving methadone coupled with counseling compared with medication-only treatment (McLellan et al., 1993).

The central importance of medication treatment is further affirmed for patients with prescription OUD in a recent evidence synopsis by Nielsen and colleagues (2017, p. 967), who found that "long-term maintenance of opioid agonists is associated with less prescription opioid use and better adherence to medication and psychological therapies for opioid dependence compared with opioid taper or psychological treatments alone." In addition, no differences in efficacy were observed between methadone and

buprenorphine maintenance therapies (Nielsen et al., 2017). While the studies across this literature were not exhaustive in the psychological therapies tested, and therefore should not be construed as suggesting that all such approaches are ineffective, the data consistently indicate clinical utility and improvements in quality of life for people with OUD who receive medication treatment.

Instistence on provision of counseling is an important factor in access to buprenorphine. According to state regulations and accrediting standards, opioid treatment programs are required to provide a minimum of counseling services each month. Yet the literature shows that counseling may help engage people in their recovery, but may not be necessary or effective beyond the provider–patient clinical sessions. The inability to provide the recommended OUD treatment services alongside prescription buprenorphine does not indicate inferior treatment, and withholding prescription buprenorphine from a patient with OUD if these services are unavailable, as may be the case as a result of insurance companies' prior authorization requirements for buprenorphine, may be lethal.

Data from studies of methadone treatment programs provide a compelling rationale for medication-only treatment when this is the only available option. Schwartz and colleagues (2012), for example, compared mortality rates among patients with OUD treated with methadone in a treatment program providing counseling services with similar patients on a waitlist for the program treated only with medication (i.e., interim dosing) and with waitlisted patients not receiving interim dosing. Mortality rates were comparably reduced for patients receiving MAT with or without supportive counseling, but were significantly higher among patients who received no medication (Schwartz et al., 2012). In a randomized trial, patients receiving MAT without counseling also showed lower HIV risk behaviors, suggesting that this approach could reduce the risk of bloodborne virus transmission (Wilson et al., 2010). A recent systematic review of interim methadone dosing studies concluded that this approach helped bridge gaps due to treatment shortages, improved patient outcomes, and warranted expansion to assess generalizability (Sigmon, 2015). And in a small randomized pilot study, participants assigned to interim dosing with buprenorphine combined with technology-assisted components to support adherence showed a statistically significant reduction in the use of illicit opioids and intravenous drugs compared with waitlist controls, indicating that interim therapy may be suitable when treatment options are limited. The authors note that additional studies with larger samples and longer follow-up periods are needed (Sigmon et al., 2016).

Notably, other countries that provide pharmacotherapies to treat patients with OUD do not impose counseling and psychotherapy as a requirement for receipt of treatment; indeed, the provision of medication

in combination with counseling is not common. In the United Kingdom, for example, pharmacotherapies are dispensed daily or less frequently to patients through community pharmacies, and patients with OUD are managed by general practitioner–assisted teams of SUD treatment specialists (NICE, 2007). Counseling and psychological therapies may be used, but are not a condition or expectation for receipt of medication.

The literature is consistent in finding that the longer a person with OUD is treated and maintained on medication for the disorder, the better are their health outcomes. This consistent finding argues against the application of a tapering approach, a detoxification model, and the expectation that short-term courses of therapy can treat OUD effectively. It further supports a long-term, maintenance model of provision of pharmacotherapy and the need for a more diverse product environment for FDA-approved medications for treatment of OUD. In fact, short-term treatment for OUD, especially in the case of abstinence-based treatment, but also with medications, is associated with increased mortality risk (Woody et al., 2008).

The following subsections briefly describe the medications available for treatment of OUD, whose characteristics are summarized in Table 4-1.

Methadone

Response to methadone appears to be dose related. Mean response at 1 year is approximately 60 percent, but differs based on a host of patient factors and adherence to evidence-based dosing practices (Bart, 2012). Methadone is a full opioid agonist that was invented in Germany in the late 1930s for use during World War II as a cheaper and easier-to-manufacture analgesic alternative to the opioids available at the time (Strang and Tober, 2003). It was approved for use in the United States shortly after the end of the war and started being used to treat opioid withdrawal within 1 year (Isbell et al., 1947). A few decades later, in the 1960s, it began to be investigated for maintenance therapy for OUD (Dole and Nyswander, 1965). For reasons that may have to do with its antagonism at the NMDA (*N*-methyl-D-aspartate) receptor, tolerance does not increase for methadone the way it often does for other opioids (Davis and Inturrisi, 1999). This feature, along with its low cost, makes methadone an ideal medication for long-term maintenance therapy for OUD.

In the 50 years since first being used to treat OUD, methadone has been the subject of hundreds of studies evaluating its efficacy and safety. Several large-scale studies in the 1970s and 1980s showed that 25–45 percent of people with OUD who were treated with methadone remained drug-free after 1 year (Hubbard and Marsden, 1986; IOM, 1995; Sells et al., 1979). Modern reviews confirm these findings, and observe further that retention

in treatment is greater for people on methadone than for those in treatment who are not receiving pharmacotherapy (Mattick et al., 2009).

Methadone's safety also has been well established, having been documented extensively for at least 40 years (Kreek, 1973). While methadone can, like all opioids, lead to respiratory depression, most cases of overdose involving methadone stem not from its use to treat OUD but its less tightly regulated use as a pain medication (SAMHSA, 2007). Among patients with OUD, it has been shown that more intensive monitoring of medication dosing is associated with decreased mortality (Bart, 2012; Strang et al., 2010).

Buprenorphine

Buprenorphine was the first opioid medication to become available in the United States since 1914 that could be used for OUD maintenance treatment in primary care settings. FDA approval of buprenorphine came in 2002. Since that time, several forms of buprenorphine have been approved, as a single entity or formulated in combination with naloxone to protect against tampering (see Box 4-1), in pill form and as sublingual film, and in varying flavors. A systematic review of 16 randomized controlled trials on the efficacy of buprenorphine found that it is associated with improved outcomes compared with placebo for individuals and pregnant women with OUD (Thomas et al., 2014).

The Drug Addiction Treatment Act of 2000 (DATA 2000) broadened the types of clinical settings where MAT for OUD could be provided. In the two decades prior to its passage, only opioid treatment programs could dispense Schedule III–V medications used to treat OUD. DATA 2000 specified that qualified providers are permitted to dispense or prescribe specifically approved Schedule III, IV, and V narcotic medications (medications with a lower risk for misuse, such as buprenorphine) in settings other than an opioid treatment program (SAMHSA, 2017b).

While expanding the types of health professionals and the places where people with OUD could find treatment, DATA 2000 also specified a cap on the number of patients per prescriber who could be treated, as well as the requirements of providers who opted to provide office-based treatment. Providers must apply to SAMHSA to provide buprenorphine treatment beyond a 30-patient limit for up to 100 patients with OUD (SAMHSA, 2017a). In 2016, two changes aimed at improving access to buprenorphine treatment were announced. First, providers who have prescribed buprenorphine to 100 patients for at least 1 year can apply to increase their patient limit to 275 (SAMHSA, 2017a). Second, the 2016 Comprehensive Addiction and Recovery Act extended buprenorphine prescribing privileges to physician assistants and nurse practitioners for 5 years (until October

BOX 4-1
Buprenorphine-Naloxone

Buprenorphine-naloxone (Suboxone) is an effective treatment for opioid use disorder (OUD). Accessing the drug, however, has proven problematic. For example, a 2003 survey revealed that 31 percent of 814 private health plans did not cover it. Of those that did, 80 percent placed it in tier three of their formulary, requiring the highest level of patient copayment. One reason for this was the drug's high price, set initially by Reckitt Benckiser at almost $300 per month.

In addition, using a combination of tactics, Reckitt kept the price of buprenorphine-naloxone artificially high over time by forestalling generic competition. First, as the end of market exclusivity approached for the original tablet formulation, the company introduced a sublingual film version of the drug. Following the U.S. Food and Drug Administration's (FDA's) approval of this modified formulation in 2010, Reckitt ceased producing the tablets. With Abbreviated New Drug Applications (ANDAs) for generic buprenorphine-naloxone tablets pending before the FDA, Reckitt then submitted a Citizen Petition requesting that the agency reject such products, claiming that tablets were less safe than film. The FDA denied the petition 5 months later but was forced to delay its approval of the ANDAs over this time.

Finally, Reckitt capitalized on a relatively new FDA post-market safety program: Risk Evaluation and Mitigation Strategies (REMS). Possible REMS components include medication guides for patients; communication plans for physicians; and—for drugs raising the most serious safety concerns—elements to assure safe use (ETASU), such as mandatory prescriber or pharmacy certification and patient follow-up testing. Brand-name and generic manufacturers of a drug must generally use a shared ETASU REMS. However, in the case of the ETASU REMS for buprenorphine-naloxone, Reckitt refused to cooperate on a shared system. As alleged in a complaint filed by 37 states in 2016, Reckitt "merely feigned cooperation with the shared REMS development process and used deceptive tactics for months to hide its true intent, which was to delay the generic industry from obtaining" approvals.

These strategies effectively forestalled generic competition for several years, keeping the drug's price artificially elevated and reducing access to this OUD treatment.

SOURCE: Sarpatwari et al., 2017.

of 2021) (ASAM, 2017), with rigorous training requirements in place to ensure consistent and careful prescribing.

Importantly, DATA 2000 did not require prescribers with a waiver to prescribe buprenorphine for OUD to provide other treatment services (i.e., counseling, group therapy) as well. Rather, the act states only that it is recommended that such services be provided or coordinated. While many providers prescribing buprenorphine are SUD specialists, and many oth-

ers recognize the importance of ensuring coordination of SUD treatment services, many do no more than prescribe medication. As discussed earlier, many believe that optimal care for OUD involves providing medication accompanied by supportive counseling and other treatment services.

Since buprenorphine may be dispensed within an office-based practice and methadone can be dispensed only within an opioid treatment facility, buprenorphine has the potential to provide better access to treatment. Many areas of the country have limited numbers of opioid treatment facilities or facilities that lack the capacity to meet demand (see Figure 4-9). Additionally, although methadone regulations require that opioid treatment facilities give priority to pregnant women, facilities are not always compliant. Preference for an office-based system of care also often makes buprenorphine preferable since the requirements for onsite dosing differ significantly from those for an opioid treatment facility. However, the delivery system for buprenorphine functions well below capacity. A recent study found that the majority of physicians with waivers to prescribe buprenorphine were doing so well below the limits allowed by law, with fewer than 10 percent prescribing to at least 75 patients (Stein et al., 2016). How this gap impacts special populations such as pregnant women is unknown, but anecdotally,

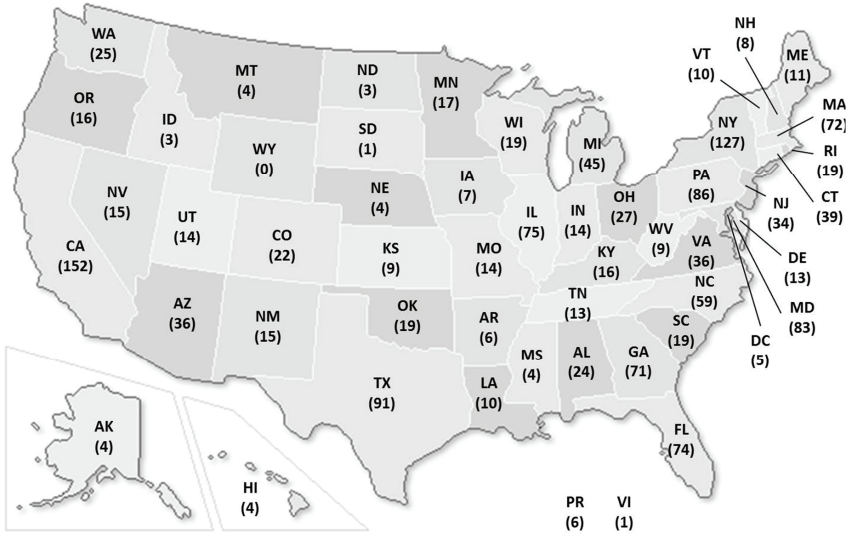


FIGURE 4-9 Number of opioid treatment programs certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) by state, 2016.
SOURCE: SAMHSA, 2016b.

many pregnant women report they were discharged from care for OUD upon becoming pregnant, and many prescribers report being unwilling to provide care to pregnant women. It is possible that for many pregnant women with OUD, the context and structural challenges of receiving MAT contribute substantially to the severity of NAS. (See the section below on pharmacotherapies for treatment of pregnant women with OUD.)

In addition, significant disparities in the use of buprenorphine have been documented. A recent review of the literature found that buprenorphine patients are largely white, are employed full time, are seeking treatment for heroin or prescription OUD, are treated in private physician practices, and pay out of pocket or are privately insured (Duncan et al., 2015). Furthermore, a study in New York City found neighborhood-level disparities, with the highest buprenorphine prescription rates being in high-income residential areas with low percentages of African American and Hispanic residents (Hansen et al., 2016). The authors note that these disparities may be attributable to buprenorphine marketing to the private sector (primary care physicians represent 65 percent of buprenorphine maintenance providers) and perceptions that this form of treatment is most appropriate for employed patients. Despite increased numbers of buprenorphine providers, moreover, 43 percent of U.S. counties had no buprenorphine-waivered physicians as of 2011 (Stein et al., 2015). The authors argue that because of buprenorphine's greater effectiveness relative to methadone in the treatment of OUD; its suitability for varying therapeutic settings, including public health care systems; and its additional advantages (e.g., less required oversight, potential to reduce stigma, increase in treatment of comorbid health and psychiatric conditions), its accessibility in such settings should be promoted as a first line of treatment.

Naltrexone

Naltrexone is a μ opioid receptor antagonist, and when formulated as naltrexone ER has been shown to be safe and effective in treating OUD. Accordingly, the FDA approved the naltrexone ER product in 2011. The evidence for oral naltrexone's effects on craving in OUD is less clear than that for its effects on craving in alcohol addiction (Bart, 2012), and the oral formulation is not recommended or widely used for treating OUD. However, the long-acting form of naltrexone, which is implanted under the skin, is more effective than a daily pill because it eliminates problems with adherence (Comer et al., 2006; Krupitsky and Blokhina, 2010; Krupitsky et al., 2012). Patients using long-acting naltrexone are three times more likely than those using oral naltrexone to remain relapse-free after 6 months (Krupitsky et al., 2012).

Some have questioned the findings of pivotal efficacy studies of naltrexone and raised additional safety concerns about naltrexone ER related to overdose (Wolfe et al., 2011). A meta-analysis of cost and utilization outcomes between naltrexone ER and other pharmacotherapies for treatment of OUD found that patients with OUD taking naltrexone ER had lower inpatient substance misuse–related utilization relative to those taking other agents, and had $8,170 lower total costs relative to those taking methadone (Hartung et al., 2014). With respect to clinical outcomes, however, it is unclear whether naltrexone ER is as effective as methadone and buprenorphine in reducing the risk of fatal overdose and other drug-related health and quality-of-life outcomes. Lee and colleagues' (2015) study of outcomes in jail-initiated naltrexone ER found reductions in opioid use and increased abstinence, while findings on secondary outcomes suggested lower risk of overdose compared with controls. Another trial examined naltrexone ER compared with treatment as usual for the prevention of opioid relapse among individuals in the criminal justice system. No overdoses occurred in the naltrexone group compared with seven in the usual treatment group. Individuals assigned to naltrexone ER also had significantly lower rates of relapse than those in the usual treatment group (43 percent versus 64 percent) (Lee et al., 2015). While promising, these findings have not been replicated in other populations and settings.

Other Alternatives

In Europe, Canada, and Australia, other opioids have been used successfully for opioid maintenance treatment to reduce the risks of injection of illicit opioids. For example, several trials using slow-release morphine (Ferri et al., 2013), heroin (Ferri et al., 2011), and hydromorphone (Oviedo-Joekes et al., 2016) for patients who had not done well with methadone showed positive outcomes (Strang et al., 2015).

Prescription of heroin also is integrated into the treatment systems of several European countries (Uchtenhagen, 2010). Supervised injectable heroin (SIH, or diamorphine) may be an effective treatment for heroin dependence refractory to standard treatment, although it is less safe than methadone maintenance treatment and therefore requires more clinical attention to manage safety issues (Strang et al., 2015). A systematic review and meta-analysis identified six randomized clinical trials of SIH and concluded that among patients with OUD involving heroin, those receiving SIH compared with control groups (most often receiving methadone maintenance treatment) demonstrated better outcomes with respect to greater reduction in use of illicit heroin (Strang et al., 2015).

Pharmacotherapies for Treatment of Women with Opioid Use Disorder Who Are Pregnant

The use of MAT for the treatment of women with OUD who are pregnant has a long history, beginning with the implementation of methadone pharmacotherapy in the late 1960s. Initially, the FDA mandated methadone-assisted withdrawal for pregnant women, but it quickly reversed this decision following the occurrence of adverse pregnancy events (Blinick et al., 1969; Jones et al., 1999). Currently, questions often arise about exposure of the fetus to the medication as the newborn may experience withdrawal that requires treatment, and there have been calls recently for pregnant women wth OUD to be withdrawn from all opioids, including treatment medications. However, the risk of withdrawal is deemed much less important than the benefits of treatment. The 1993 and 2004 SAMHSA Treatment Improvement Protocols for OUD, the 1997 National Institutes of Health Consensus Panel on Effective Medical Treatment of Opioid Addiction, the 2012 American College of Obstetricians and Gynecologists and American Society of Addiction Medicine Joint Opinion, the WHO 2014 Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy, and the 2016 SAMHSA Collaborative Approach to the Treatment of Pregnant Women with Opioid Use Disorders all recommend MAT for pregnant women as the standard of care. The underlying principle behind the use of MAT during pregnancy is that it prevents erratic maternal opioid levels and protects the fetus from repeated episodes of withdrawal. In addition, it ensures that the woman is engaged in the health care system and promotes prenatal care, which results in healthier outcomes for both mother and infant (Kaltenbach et al., 1998).

The emergence of the implementation of methadone pharmacotherapy for pregnant women with OUD coincided closely with the creation of NIDA. One of NIDA's first endeavors was to fund a number of research demonstration projects in 1974 implementing treatment programs for pregnant women with OUD. This research provided the foundation for the model of care that emerged in the 1980s. Another major contributor to the development of treatment for this population was the funding source created by SAMHSA's Pregnant and Postpartum Women's project, initiated in the early 1990s, which is still part of the agency's portfolio.

The treatment options that exist today are an extension of the original model, which began with the premise that services for pregnant women must be comprehensive, to include not only treatment of OUD but also obstetrical, medical, and psychiatric care. Research has shown that women with SUD, including OUD, have a complex array of biopsychosocial problems that must be addressed if treatment is to be successful and recovery sustained (Comfort and Kaltenbach, 1999).

The framework for treatment is grounded in the premise that the treatment should be woman-centered (i.e., responsive to the specific needs of the individual); trauma-informed (i.e., recognizing the role of trauma and violence in the lives of women); strengths-based (i.e., focusing on strengths rather than deficits); and culturally competent (i.e., acknowledging the role of culture, ethnicity, race, racism, and sexual orientation) (SAMHSA, 2009). The treatment approach should be multidisciplinary and include pharmacotherapy with methadone, buprenorphine, or buprenorphine-naloxone. Initiation of naltrexone currently is not recommended in pregnant women.

At present, the field is waiting for existing recommendations to reflect new data. The current recommendation that the combination product buprenorphine-naloxone not be used was published in 2004 and was based on a lack of data on infant exposure to naloxone. And although there have been no salient randomized controlled trial data to date, several studies have shown no difference in infant outcomes between the single-entity and combination products, with the latter being used by many providers (Debelak et al., 2013; Lund et al., 2013; Wiegand et al., 2015). In addition to pharmacotherapy supports, a multidisciplinary approach would involve not only obstetrical, medical, and psychiatric services but also individual and family therapy, trauma services, case management, parent–child services, and liaison relationships with the department of human services. Treatment modalities encompass traditional levels of care, including outpatient, intensive outpatient, and women and children residential care.

Although the efficacy of comprehensive treatment for pregnant women with OUD has been well established, the number of programs available to provide such services is extremely limited. Nationally, there exist only 20 residential treatment programs for pregnant and parenting women funded under the SAMHSA portfolio, and of those, only three provide treatment specific to OUD. Among the 1,450 opioid treatment programs (see Figure 4-9), it is estimated that no more than 12 programs provide specialized treatment for pregnant women. Moreover, treatment for pregnant women often is fragmented and may be impeded when collaboration is lacking among the opioid treatment facility, obstetrician, pediatrician, and hospital.

In light of these limited services, newer models of collaboration among multiple systems of care have emerged within the past few years to provide comprehensive care to pregnant women with OUD. Excellent examples of collaboration among the state, medical providers, and treatment providers are the Vermont Children and Recovering Mothers (CHARM) Collaborative and the Ohio Maternal Opiate Medical Support (MOMS) project. CHARM involves 10 organizations, including hospitals, treatment providers, state agencies, maternal and child health programs, and the visiting nurse association aimed at providing comprehensive care coordination for

pregnant women with OUD.[9] The MOMS project, funded by the state of Ohio, employs a maternity care home (MCH) model in four sites across the state. Each site is unique, but all utilize the MCH team-based care delivery model, which emphasizes coordination of community services and treatment for OUD, including pharmacotherapy, case management, and prenatal care.[10] Additionally, a new model based on Project ECHO (Extension for Community Healthcare Outcomes)[11] is currently being examined to provide support and improve care in treatment programs for pregnant and postpartum women with SUD. Project ECHO is based on an approach in which telemonitoring utilizes case-based learning to focus on best practices. The ECHO model is based on a hub-and-spoke knowledge-sharing network led by a team of "experts" using video conferencing to conduct virtual clinics with community providers.

Other treatment matters to be addressed for this vulnerable population are centered on the medications used. Since the FDA approved buprenorphine in 2002, there have been two medications to use in treating pregnant women with OUD. The two have different benefits and disadvantages, but the basic tenets of treatment are the same.

The efficacy criterion for the choice of medication for pregnant women with OUD (i.e., methadone or buprenorphine) has not yet been established. However, data from a multisite randomized controlled trial that compared maternal and infant outcomes among women maintained on methadone with those of women maintained on buprenorphine often are cited as a determining factor. The study found that, although there was no difference in the number of infants that required treatment for NAS, infants exposed prenatally to buprenorphine required 89 percent less morphine to treat NAS, spent 58 percent less time in the hospital being medicated for NAS, and spent 43 percent less time in the hospital overall relative to infants exposed prenatally to methadone (Jones et al., 2010).

A systematic review and meta-analysis of 12 studies, including the above-cited randomized controlled trial, found that infants explosed prenatally to buprenorphine had better outcomes than methadone-exposed infants with respect to treatment duration, morphine dose, birth weight, length, and head circumference (Brogley et al., 2014). These findings have led some practitioners to recommend always that buprenorphine rather than methadone be used for pregnant women. Ideally, however, treatment

[9]See SAMHSA's Collaborative Approach to the Treatment of Pregnant Women with Opioid Use Disorders (SAMHSA, 2016c) for a detailed description.

[10]See www.momsohio.org for further information.

[11]Project ECHO, developed at the University of New Mexico to address hepatitis C, is now used throughout the United States and other countries to address 40 different subject areas. There are 14 institutions in the United States conducting pain management ECHOs. See http://echo.unm.edu for more information.

will be based on what is best for both the mother and child; each woman's medical, psychological, and substance use history must be considered in any treatment decision. As a partial agonist, for example, buprenorphine may not be as effective as methadone for certain women. Without data to guide decisions, however, the current recommendation is that women with OUD who are naïve to agonist treatment may be good candidates for buprenorphine. If women do not respond to buprenorphine, transfer to methadone can easily be initiated. In any case, it is recommended that women successfully stabilized on methadone or buprenorphine who become pregnant remain on their current medication (Jones et al., 2012). And the 2012 Joint Opinion of the American College of Obstetricians and Gynecologists and American Society of Addiction Medicine recommends the use of either methadone or buprenorphine.

Although withdrawal often is cited as a way to reduce NAS, there is no evidence based on an intention-to-treat analysis that withdrawal without medication is beneficial to the mother, fetus, or infant. In addition, limited data suggest that infant treatment outcomes with buprenorphine may be similar to those of withdrawal. A long history of concern regarding withdrawal during pregnancy also merits consideration. Adverse fetal events that occurred in the 1970s as a result of withdrawing pregnant women from methadone led to recommendations that withdrawal be initiated only in the second trimester because of safety concerns, such as fetal demise in the first trimester of pregnancy and prematurity in the third trimester. In the 1990s, however, research indicated that with appropriate fetal monitoring, women could be withdrawn safely at anytime during pregnancy (Jarvis and Schnoll, 1994). Yet the question is not whether withdrawal can be done safely but whether it should be done at all. A summary of the recent literature on medication-assisted withdrawal during pregnancy indicates that it can be safe and may be associated with less NAS and improved birth weights. When given a choice, however, approximately 50 percent of women choose medication treatment rather than withdrawal, and among those who are undergoing withdrawal, the risk of relapse is high (Bell et al., 2016; Dashe et al., 1988; Jones et al., 2008; Lund et al., 2012; Stewart et al., 2013). A recent commentary by Jones and colleagues (2017) speaks to the lack of evidence supporting a clear benefit of medication-assisted withdrawal for the maternal–infant dyad, as it increases the risk of poor treatment engagement and relapse for the mother and does not improve the health of or significantly reduce the occurance of NAS in the infant. The WHO 2014 *Guidelines for the Identification and Management of Substance Use and Substance Use Disorders in Pregnancy,* the 2012 American College of Obstetricians and Gynecologists and American Society of Addiction Medicine *Opinion No. 524: Opioid Abuse, Dependence, and Addiction in Pregnancy*, and SAMHSA's 2016 *A Collaborative Approach to the Treatment*

of Pregnant Women with Opioid Use Disorders all recommend treatment rather than withdrawal because of the high rate of relapse that places the fetus at additional risk.

Access to care for pregnant women with OUD also is driven by state policies. Office-based provision of buprenorphine is covered by Medicaid in all states and the District of Columbia, but provision of methadone is covered only in 31 states and the District of Columbia. A recent study by Angelotta and colleagues (2016) found that fewer than 50 percent of pregnant women with OUD received MAT. The most important factors associated with lack of MAT were referral source, geographic location, Medicaid funding for methadone, and state laws permitting child abuse charges for illicit drug use in pregancy. Pregnant women referred to treatment by the criminal justice system were the least likely to receive MAT, especially in states with prenatal child abuse laws (Angelotta et al., 2016). As might be expected, lack of Medicaid coverge also was a factor, but there was a high correlation as well between lack of Medicaid funding for methadone and state prenatal child abuse laws. Absent better coordination between medical standards of care and public policy at both the national and state levels, the provision of effective treatment for this at-risk population will continue to be fragmented at best.

Summary

Three underutilized, efficacious medications are available for the treatment of OUD. Few new products for treatment of OUD have entered the market, although several new modes of medication delivery have emerged. Even for special populations such as pregnant and postpartum women, medication therapy is the standard of care. Expected side effects of opioid exposure in utero, such as NAS, can be treated and symptoms abated with no current evidence of long-term effects.

TRENDS IN TREATMENT OF OPIOID OVERDOSE WITH NALOXONE

The term "overdose" is used to describe the poisoning event that occurs when opioid exposure results in respiratory depression, morbidity, or mortality. The onset of respiratory depression caused by exposure to opioids may progress to severe, life-threatening symptoms within a matter of minutes to hours depending on a number of factors, including the drug involved (e.g., rapid-onset medications such as fentanyl), the presence of other drugs in the individual's system, the route of administration (i.e., injection hastens delivery of opioids to the bloodstream and speeds crossing of the blood–brain barrier, bringing on respiratory depression, among

other physiological reactions), and the individual's health condition (e.g., a respiratory condition or metabolic distrubance can worsen symptoms more rapidly) (EMCDDA, 2016). Therefore, although a single large dose can cause severe respiratory depression and death, overdoses occur at varying opioid doses in individuals with compromised breathing, metabolic conditions, or altered opioid tolerance (Sporer, 1999), and even at therapeutic levels when used in combination with other central nervous system depressants such as benzodiazepines (as reviewed above) or alcohol.

Use of Naloxone to Treat Overdose

Naloxone, a synthetic N-allyl derivative of oxymorphone and an opioid antagonist, was first synthesized in 1961 by Jack Fishman and investigated by Harold Blumberg. The discovery was the first of its kind, an antagonist with the ability to avoid agonistic activity through prevention or elimination of agonistic narcotic binding. Also related to its antagonistic activity, naloxone uniquely reverses opioid-induced respiratory depression and may precipitate withdrawal. Naloxone was approved by the FDA in 1971 as a diagnostic and therapeutic agent for the treatment of opioid-induced respiratory depression and is currently on the WHO Model List of Essential Medicines (WHO, 2015).

Adverse reactions and consequential events associated with naloxone are well established in the literature. Serious complications (seizure, pulmonary edema, asystole, cardiac arrest) following naloxone administration are reportedly rare (occurring in between 0.3 and 1.6 percent of individuals) (Buajordet et al., 2004; Osterwalder, 1996; Yealy et al., 1990) and could be related to the overdose itself as opposed to the naloxone. Opioid withdrawal symptoms (confusion, headache, nausea or vomiting, aggressiveness, tachycardia, sweating, and tremor) are expected in opioid-dependent persons (Buajordet et al., 2004; Osterwalder, 1996; Terman, 2012; Yealy et al., 1990). Also reported in postoperative patients are hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema. Naloxone is light-sensitive, is recommended to be stored at room temperature, and typically has a shelf life of 18 to 24 months. It is safe, effective, and nonaddictive and lacks contraindications except for a possible rare allergic reaction (Hardmann et al., 2001; Sporer, 1999, 2003).

While use of naloxone over the past 40 years has been primarily by trained health professionals in research, hospital, and prehospital settings, community activism since the late 1990s on the part of harm reduction organizations and people who use drugs has moved it to the forefront of efforts to address the opioid crisis. As of 2014, 136 opioid overdose prevention and response programs collectively managed 644 naloxone distribution sites throughout the United States, distributing naloxone kits to 152,283 lay-

persons and reporting 26,463 overdose reversals (between 1996 and 2014) (Wheeler et al., 2015). In addition to the pharmacologic and extensive clinical application literature, the evidence base for expanded community access to naloxone is growing. Data show that educating and providing naloxone to people who are at risk of witnessing or experiencing overdose is associated with reduced heroin consumption (Seal et al., 2005), fewer opioid-related emergency department visits (Coffin et al., 2016), and a 30–45 percent decrease in opioid overdose death rates at the community and individual levels (Bird et al., 2016; Walley et al., 2013). Increasing the availability of naloxone, therefore, is a central component of population-level efforts to prevent opioid overdose deaths, as illustrated by the U.S. Department of Health and Human Services having identified access to naloxone as one of three main strategies for addressing the national opioid epidemic (HHS, 2016).

In the United States, naloxone is available only by prescription, although many states and locales have implemented innovative models of expanded community access to naloxone, such as standing orders (whereby pharmacists are permitted to offer the medication broadly under a prescriber's order and according to the prescriber's stipulations); collaborative pharmacy practice agreements (whereby pharmacists are permitted to manage the medication on behalf of a prescriber after fulfilling certain training and documentation requirements); or other regulatory changes (Green et al., 2015b) designed to enable more first responders and laypersons to obtain naloxone from community organizations or pharmacies, to carry the medication, and to use it to reverse a witnessed overdose. Additional laws and policies aimed at providing broader access to naloxone at low or no cost to people at risk of opioid overdose are emerging across the country (see Chapter 5 for discussion of these policies). In addition, the trusted, privileged, and critical access to people who use drugs afforded by these programs is particularly important as the opioid epidemic becomes dominated more by illicit than by prescribed opioids.

Naloxone is a known and established medication. Its generic status has meant that the FDA would consider novel delivery devices or alternative routes of administration along the 505(b)(2) regulatory pathway (discussed in Chapter 6). Indeed, the past 2 years has seen entry into the U.S. market of two new, FDA-approved naloxone products. Patients now can choose among prescribed naloxone products, allowing them to factor in their living situation; type of opioid of exposure; comfort level with syringes; and other factors, such as preference for little to no instruction or voice-activated instructions upon administration. Across all products and access points, instructions stress that training a family member, friend, or caregiver to use naloxone is recommended.

The cost of naloxone is a key consideration for most people (Beletsky et al., 2009) and a major impediment for the branded naloxone products.

The community-based and volunteer capacity of many naloxone distribution programs depends on innovations in pricing, donations, billing, and other distribution factors to sustain low- or no-cost naloxone. It is unclear whether the emergence of multiple new naloxone products will benefit patients, family members, and community-based programs. Unless covered by insurance, the out-of-pocket cost of $40 to $150 for naloxone makes it inaccessible for most people, especially if it is being administered in larger quantities or more frequently in the presence of potent opioids such as fentanyl. Prescription formulary coverage of the different prescription naloxone products varies, but with time and increasing demand (Jones et al., 2016), greater coverage is expected. Indeed, public and private insurers increasingly include naloxone in their formularies, thereby creating a sustainable and accessible source of the medication through medical and pharmacy routes. When naloxone is covered by insurance, its uptake improves, and states such as Rhode Island that have instituted both statewide pharmacy access to naloxone and broad insurance coverage of multiple products have seen the emergence of sustainable models of naloxone access as a complement to community-based programs. However, the new products, and increasingly the generic ones as well, are beyond the financial reach of most community-based programs, many of which have had to rely on small grants or donations. In the face of unprecedented numbers of opioid overdoses and the infiltration of fentanyl into the illicit drug supply, the FDA and other federal agencies would be well advised to take steps to ensure that organizations and institutions with privileged access to those with high overdose risk have free (or lowest-cost) naloxone so as to maximize the reach and sustainability of their efforts. Examples of such steps include novel pricing, alternative models, or price controls.

Finally, several FDA public meetings have considered the prospects and requirements for making naloxone an over-the-counter (OTC) product. A first public meeting in 2012 featured presentations from researchers in naloxone and overdose, the FDA, and others on the state of the science and regulatory requirements for an OTC naloxone product. Absent a branded product, few to no current naloxone manufacturers were willing or able to undertake the studies necessary to achieve that status. Three years after this initial public meeting, a new FDA-approved naloxone product was available, joined by another the following year. At this time, no naloxone product has attained OTC status, and in the meantime, as discussed above, states have greatly expanded access to naloxone through pharmacies, emergency departments, community-based organizations, and first responders using various implementation models. Research is needed to understand the impact and reach of these models. Given the variety of settings in which naloxone providers and programs operate and the unique access of many programs to populations at high risk of overdose, it is unclear how an

OTC naloxone product would improve the accessibility and availability of naloxone at the community level.

Summary

Medication to treat a pernicious side effect of opioid exposure and overdose is available, and two new FDA-approved medications join several generic naloxone products. The provision of naloxone to overdose victims by health professionals in the prehospital setting is the standard of care, and in response to rising community overdose rates, community-based programs and first responder agencies have adopted this protocol for treating opioid overdose. Mechanisms for increasing naloxone prescribing and dispensing and equipping of first responders, and possibly enabling direct patient access (e.g., an OTC status), are warranted, but are impeded by high and unpredictable costs for the medication.

SUMMARY AND RECOMMENDATIONS

While it is unrealistic to expect that the diversion and misuse of pain medications can be entirely eradicated, the effects of these drugs on public health need to be acknowledged, tracked, and mitigated. The interrelated nature of the prescription and illicit opioid epidemics means that one cannot be addressed separately from the other. Moreover, there are both iatrogenic and predictable consequences of opioid exposure at the individual patient and societal levels that can be anticipated and actively mitigated. The downstream effects and societal impact of these intertwined epidemics require consideration by the FDA and other agencies with authority to affect the flow of prescription opioid medications and illicit opioids before, during, and after the introduction of new, similar opioid products into the marketplace. Important research gaps exists in such areas as surveillance; ethnographic studies of drug use behaviors; epidemiologic studies of exposure, natural histories describing transitions in routes of administration and use, and risk of new illicitly manufactureed synthetic opioids; evolving OUD treatment trajectories; changes in opioid markets; and measurement of the impact of use of opioids, particularly heroin and illicit fentanyl, on society and the economy.

Recommendation 4-1. Consider potential effects on illicit markets of policies and programs for prescription opioids. In designing and implementing policies and programs pertaining to prescribing of, access to, and use of prescription opioids, the U.S. Food and Drug Administration, other agencies within the U.S. Department of Health and Human Services, state agencies, and other stakeholders should consider the

potential effects of these interventions on illicit markets—including both the diversion of prescription opioids from lawful sources and the effect of increased demand for illegal opioids such as heroin among users of prescription opioids—and take appropriate steps to mitigate those effects.

Recommendation 4-2. Improve reporting of data on pain and opioid use disorder. The Substance Abuse and Mental Health Services Administration, the U.S. Food and Drug Administration, the National Institutes of Health, and the U.S. Centers for Disease Control and Prevention should collaborate to identify best practices and reporting formats that portray the epidemiology of both pain and opioid use disorder accurately, objectively, and in relation to one another.

Recommendation 4-3. Invest in data and research to better characterize the opioid epidemic. The National Institute on Drug Abuse and the U.S. Centers for Disease Control and Prevention should invest in data collection and research relating to population-level opioid use patterns and consequences, especially nonmedical use of prescription opioids and use of illicit opioids, such as heroin and illicitly manufactured fentanyl.

REFERENCES

Aldridge, J., and D. Décary-Hétu. 2016. Hidden wholesale: The drug diffusing capacity of online drug cryptomarkets. *International Journal on Drug Policy* 35:7-15.

Alpert, A., D. Powell, and R.L. Pacula. 2017. *Supply-side drug policy in the presence of substitutes: Evidence from the introduction of abuse-deterrent opioids*. NBER Working Paper 23031. http://www.nber.org/papers/w23031 (accessed February 28, 2017).

Al-Tayyib, A.A., S. Koester, and P. Riggs. 2017. Prescription opioids prior to injection drug use: Comparisons and public health implications. *Addictive Behaviors* 65:224-228.

Angelotta, C., C.J. Weiss, J.W. Angelotta, and R.A. Friedman. 2016. A moral or medical problem? The relationship between legal penalties and treatment practices for opioid use disorders in pregnant women. *Women's Health Issues* 26(6):595-601.

ASAM (American Society of Addiction Medicine). 2017. *Summary of the Comprehensive Addiction and Recovery Act*. http://www.asam.org/advocacy/issues/opioids/summary-of-the-comprehensive-addiction-and-recovery-act (accessed March 1, 2017).

Baldini, A., M. Von Korff, and E.H. Lin. 2012. A review of potential adverse effects of long-term opioid therapy: A practitioner's guide. *Primary Care Companion for CNS Disorders* 14(3).

Banerjee, G., E.J. Edelman, D.T. Barry, W.C. Becker, M. Cerda, S. Crystal, J.R. Gaither, A.J. Gordon, K.S. Gordon, R.D. Kerns, S.S. Martins, D.A. Fiellin, and B.D. Marshall. 2016. Non-medical use of prescription opioids is associated with heroin initiation among U.S. veterans: A prospective cohort study. *Addiction* 111(11):2021-2031.

Bart, G. 2012. Maintenance medication for opiate addiction: The foundation of recovery. *Journal of Addictive Diseases* 31(3):207-225.

Bartels, K., L.M. Mayes, C. Dingmann, K.J. Bullard, C.J. Hopfer, and I.A. Binswanger. 2016. Opioid use and storage patterns by patients after hospital discharge following surgery. *PLoS One* 11(1):e0147972.

Baum, R.M. 1985. New variety of street drugs poses growing problem. *Chemical and Engineering News* 63(36):7-16.

Baumblatt, J.A.G., C. Wiedeman, J.R. Dunn, W. Schaffner, L.J. Paulozzi, and T.F. Jones. 2014. High-risk use by patients prescribed opioids for pain and its role in overdose deaths. *JAMA Internal Medicine* 174(5):796-801.

Beaudoin, F.L., R.C. Merchant, and M.A. Clark. 2016. Prevalence and detection of prescription opioid misuse and prescription opioid use disorder among emergency department patients 50 years of age and older: Performance of the Prescription Drug Use Questionnaire, patient version. *American Journal of Geriatric Psychiatry* 24(8):627-636.

Becker, W.C., J.L. Starrels, M. Heo, X. Li, M.G. Weiner, and B.J. Turner. 2011. Racial differences in primary care opioid risk reduction strategies. *Annals of Family Medicine* 9(3):219-225.

Beletsky, L., S. Burris, and A. Kral. 2009. *Closing death's door: Action steps to facilitate emergency opioid drug overdose reversal in the U.S.* https://papers.ssrn.com/sol3/papers.cfm?abstract-id=1437163 (accessed March 1, 2017).

Bell, J., C.V. Towers, M.D. Hennessy, C. Heitzman, B. Smith, and K. Chattin. 2016. Detoxification from opiates during pregnancy. *American Journal of Obstetrics and Gynecology* 215(3):374.e1-6.

Binswanger, I.A., M.F. Stern, R.A. Deyo, P.J. Heagerty, A. Cheadle, J.G. Elmore, and T.D. Koepsell. 2007. Release from prison—A high risk of death for former inmates. *New England Journal of Medicine* 356(2):157-165.

Binswanger, I.A., P.J. Blatchford, R.G. Lindsay, and M.F. Stern. 2011. Risk factors for all-cause overdose and early deaths after release from prison in Washington state. *Drug and Alcohol Dependence* 117(1):1-6.

Binswanger, I.A., P.J. Blatchford, S.R. Mueller, and M.F. Stern. 2013. Mortality after prison release: Opioid overdose and other causes of death, risk factors, and time trends from 1999 to 2009. *Annals of Internal Medicine* 159(9):592-600.

Bird, S.M., A. McAuley, S. Perry, and C. Hunter. 2016. Effectiveness of Scotland's national naloxone programme for reducing opioid-related deaths: A before (2006-10) versus after (2011-13) comparison. *Addiction* 111(5):883-891.

Blinick, G., R.W. Wallach, and E. Jerez. 1969. Pregnancy in narcotic addicts treated by medical withdrawal. The methadone detoxification program. *American Journal of Obstetrics and Gynecology* 105(7):997-1003.

Bohnert, A.S., M. Valenstein, M.J. Bair, D. Ganoczy, J.F. McCarthy, M.A. Ilgen, and F.C. Blow. 2011. Association between opioid prescribing patterns and opioid overdose-related deaths. *Journal of the American Medical Association* 305(13):1315-1321.

Bohnert, A.S.B., J.E. Logan, D. Gnoczy, and D. Dowell. 2016. A detailed exploration into the association of prescribed opioid dosage and prescription opioid overdose deaths among patients with chronic pain. *Medical Care* 54(5):435-441.

Boutwell, A.E., A. Nijhawan, N. Zaller, and J. Rich. 2006. Arrested on heroin: A national opportunity. *Journal of Opioid Management* 3(6):328-332.

Braden, J.B., J. Russo, M.Y. Fan, M.J. Edlund, B.C. Martin, A. DeVries, and M.D. Sullivan. 2010. Emergency department visits among recipients of chronic opioid therapy. *Archives of Internal Medicine* 170(16):328-332.

Brogly, S.B., K.A. Saia, A.Y. Walley, H.M. Du, and P. Sebastian. 2014. Prenatal buprenorphine versus methadone exposure and neonatal abstinence syndrome: Systematic review and meta-analysis. *American Journal of Epidemiology* 180(7):673-686.

Brooks, J.T. 2017. *CDC outbreak investigations involving OPANA® ER*. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM547237.pdf (accessed April 23, 2017).

Buajordet, I., A.C. Naess, D. Jacobsen, and O. Brors. 2004. Adverse events after naloxone treatment of episodes of suspected acute opioid overdose. *European Journal of Emergency Medicine* 11(1):1923.

Butler, S.F., E.C. McNaughton, and R.A. Black. 2015. Tapentadol abuse potential: A postmarketing evaluation using a sample of individuals evaluated for substance abuse treatment. *Pain Medicine* 16(1):119-130.

Calcaterra, S., J. Glanz, and I.A. Binswanger. 2013. National trends in pharmaceutical opioid related overdose deaths compared to other substance related overdose deaths: 1999–2009. *Drug and Alcohol Dependence* 131(3):263-270.

Caulkins, J.P., and P. Reuter. 2010. *How drug enforcement affects drug prices*. http://faculty.publicpolicy.umd.edu/sites/default/files/reuter/files/Drug%20Enforcement%20and%20Drug%20Price.pdf (accessed February 28, 2017).

Caulkins, J.P., B. Kilmer, P.H. Reuter, and G. Midgette. 2015a. Cocaine's fall and marijuana's rise: Questions and insights based on new estimates of consumption and expenditures in U.S. drug markets. *Addiction* 110(5):728-736.

Caulkins, J.P., J. Sussell, B. Kilmer, and A. Kasunic. 2015b. How much of the cocaine market are we missing? Insights from respondent-driven sampling in a mid-sized American city. *Drug and Alcohol Dependence* 147:190-195.

CDC (U.S. Centers for Disease Control and Prevention). 2013. *Thrombotic Thrombocytopenic Purpura (TTP)–like illness associated with intravenous Opana ER abuse—Tennessee, 2012*. https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6201a1.htm (accessed June 13, 2017).

CDC. 2014. Quickstats: Rates of drug poisoning deaths involving heroin, by selected age and racial/ethnic groups—United States, 2002 and 2011. *Morbidity and Mortality Weekly Report* 63(27):595.

CDC. 2015a. *National Center for Health Statistics. Multiple cause of death 1999-2014 on CDC WONDER online database, released 2015. Data are from the Multiple Cause of Death Files, 1999-2014, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program*. http://wonder.cdc.gov/mcd-icd10.html (accessed May 25, 2017).

CDC. 2015b. *CDC statement on syringe services programs—December 21, 2015*. https://www.cdc.gov/nchhstp/newsroom/2015/syringe_service_statement.html (accessed January 5, 2017).

CDC. 2015c. *Today's Heroin Epidemic Infographics*. https://www.cdc.gov/vitalsigns/heroin/infographic.html#graphic (accessed January 22, 2017).

CDC. 2016a. *Hepatitis C FAQs for the public*. https://www.cdc.gov/hepatitis/hcv/cfaq.htm (accessed April 21, 2017).

CDC. 2016b. *Hepatitis C information. Statistics and surveillance*. https://www.cdc.gov/hepatitis/hcv/statisticshcv.htm (accessed April 21, 2017).

CDC. 2016c. *Prescription opioid overdose data*. https://www.cdc.gov/drugoverdose/data/overdose.html (accessed April 23, 2017).

CDC. 2017a. *HIV and injection drug use*. https://www.cdc.gov/hiv/risk/idu.html (accessed April 21, 2017).

CDC. 2017b. *QuickStats*: Rates of drug overdose deaths involving heroin, by selected age groups—United States, 2006–2015. *Morbidity and Mortality Weekly Report* 65(52):1497.

Cerdá, M., Y. Ransome, K.M. Keyes, K.C. Koenen, M. Tracy, K.J. Tardiff, D. Vlahov, and S. Galea. 2013. Prescription opioid mortality trends in New York City, 1990–2006: Examining the emergence of an epidemic. *Drug and Alcohol Dependence* 132(1):53-62.

Chen, L.H., H. Hedegaard, and M. Warner. 2014. *Drug-poisoning deaths involving opioid analgesics: United States, 1999–2011*. NCHS Data Brief 166. Hyattsville, MD: National Center for Health Statistics.

Chou, R., J.A. Turner, E.B. Devine, R.N. Hansen, S.D. Sullivan, I. Blazina, T. Dana, C. Bougatsos, and R.A. Deyo. 2015. The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Annals of Internal Medicine* 162(4):276-286.

Cicero, T.J., and M.S. Ellis. 2015. Abuse-deterrent formulations and the prescription opioid abuse epidemic in the United States: Lessons learned from OxyContin. 2015. *JAMA Psychiatry* 72(5):424-430.

Cicero, T.J., M.S. Ellis, H.L. Surratt, and S.P. Kurtz. 2014. The changing face of heroin use in the United States: A retrospective analysis of the past 50 years. *JAMA Psychiatry* 71(7):821-826.

Clarke, H., H. Soneji, D.K. Ko, L. Yun, and D.N. Wijeysundera. 2014. Rates and risk factors for prolonged opioid use after major surgery: Population based cohort study. *British Medical Journal* 348:g1251.

Cleary, B.J., J. Donelly, J. Strawbridge, P.J. Gallagher, T. Fahey, M. Clarke, and D.J. Murphy. 2010. Methadone dose and neonatal abstinence syndrome—systematic review and meta-analysis. *Addiction* 105(12):2071-2084.

Coffin, P.O., E. Behar, C. Rowe, G. M. Santos, D. Coffa, M. Bald, and E. Vittinghoff. 2016. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. *Annals of Internal Medicine* 165(4):245-252.

Comer, S.D., M.A. Sullivan, E. Yu, J.L. Rothenberg, H.D. Kleber, K. Kampman, C. Dackis, and C.P. O'Brien. 2006. Injectable, sustained-release naltrexone for the treatment of opioid dependence: A randomized, placebo-controlled trial. *Archives of General Psychiatry* 63(2):210-218.

Comer, S.D., M.A. Sullivan, R.A. Whittington, S.K. Vosburg, and W.J. Kowalczyk. 2008. Relative abuse liability of prescription opioids compared to heroin in morphine-maintained heroin abusers. *Neuropsychopharmacology* 33(5):1179-1191.

Comfort, M.L., and K. Kaltenbach. 1999. Bio-psychosocial characteristics and treatment outcomes of pregnant cocaine dependent women in residential and outpatient substance abuse treatment. *Journal of Psychoactive Drugs* 30(3):279-289.

Compton, W.M., C.M. Jones, and G.T. Baldwin. 2016. Relationship between nonmedical prescription-opioid use and heroin use. *New England Journal of Medicine* 374(2):154-163.

Connock, M., A. Juarez-Garcia, S. Jowett, E. Frew, Z. Liu, R. Taylor, A. Fry-Smith, E. Day, N. Lintzeris, and T. Roberts. 2007. Methadone and buprenorphine for the management of opioid dependence: A systematic review and economic evaluation. *Health Technology Assessment* 11(9):1-171, iii-iv.

Cook, P.J. 2007. *Paying the tab: The costs and benefits of alcohol control*. Princeton, NJ: Princeton University Press.

Coplan, P.M., N.E. Sessler, V. Harikrishnan, R. Singh, and C. Perkel. 2017. Comparison of abuse, suspected suicidal intent, and fatalities related to the 7-day buprenorphine transdermal patch versus other opioid analgesics in the National Poison Data System. *Postgraduate Medicine* 129(1):55-61.

Dart, R.C., H.L. Surratt, T.J. Cicero, M.W. Parrino, S.G. Severtson, B. Bucher-Bartelson, and J.L. Green. 2015. Trends in opioid analgesic abuse and mortality in the United States. *New England Journal of Medicine* 372(3):241-248.

Dart, R.C., H.L. Surrat, M.C. LeLait, Y. Stivers, V.S. Bebarta, C.C. Freifeld, J.S. Brownstein, J.J. Burke, S.P. Kurtz, and N. Dasgupta. 2016. Diversion and illicit sale of extended release Tapentadol in the United States. *Pain Medicine* 17(8):1490-1496.

Dasgupta, N., C. Freifeld, J.S. Brownstein, C.M. Menone, H.L. Surratt, L. Poppish, J.L. Green, E.J. Lavonas, and R.C. Dart. 2013. Crowdsourcing black market prices for prescription opioids. *Journal of Medical Internet Research* 15(8):e178.

Dashe, J.S., G.L. Jackson, D.A. Olscher, E.H. Zane, and G.D. Wendel. 1998. Opioid detoxification in pregnancy. *Obstetrics and Gynecology* 92(5):854-858.

Davis, A.M., and C.E. Inturrisi. 1999. d-Methadone blocks morphine tolerance and *N*-methyl-D-aspartate-induced hyperalgesia. *Journal of Pharmacology and Experimental Therapeutics* 289(2):1048-1053.

Davis, M., H.W. Goforth, and P. Gamier. 2013. Oxycodone combined with opioid receptor antagonists: Efficacy and safety. *Expert Opinion on Drug Safety* 12(3):389-402.

DEA (U.S. Drug Enforcement Administration). 2013. *National drug threat assessment summary, 2013*. https://www.dea.gov/resource-center/DIR-017-13%20NDTA%20Summary%20final.pdf (accessed April 23, 2017).

DEA. 2016a. *Counterfeit prescription pills containing fentanyl: A global threat*. https://content.govdelivery.com/attachments/USDOJDEA/2016/07/22/file_attachments/590360/fentanyl%2Bpills%2Breport.pdf (accessed February 28, 2017).

DEA. 2016b. *2016 national drug threat assessment summary*. https://www.dea.gov/resource-center/2016%20NDTA%20Summary.pdf (accessed April 23, 2017).

DEA. 2016c. *National heroin threat assessment summary—updated*. http://www.emsi.org/webfm_send/220 (accessed February 28, 2017).

DEA. 2016d. *Public safety alert from Drug Enforcement Administration counterfeit hydrocodone tablets containing fentanyl*. https://www.dea.gov/divisions/sf/2016/sf040116.shtml (accessed June 12, 2017).

Debelak, K., W.R. Morrone, K.E. O'Grady, and H.E. Jones. 2013. Buprenorphine + naloxone in the treatment of opioid dependence during pregnancy: Initial patient care and outcome data. *American Journal on Addictions* 22(3):252-254.

Deck, D., W. Wiitala, B. McFarland, K. Campbell, J. Mullooly, A. Krupski, and D. McCarty. 2009. Medicaid coverage, methadone maintenance, and felony arrests: Outcomes of opiate treatment in two states. *Journal of Addictive Diseases* 28(2):89-102.

Degenhardt, L., R. Bruno, R. Ali, N. Lintzeris, M. Farrell, and B. Larance. 2015. The introduction of a potentially abuse deterrent oxycodone formulation: Early findings from the Australian National Opioid Medications Abuse Deterrence (NOMAD) study. *Drug and Alcohol Dependence* 151:56-67.

Dolan, K.A., J. Shearer, M. MacDonald, R.P. Mattick, W. Hall, and A.D. Wodak. 2003. A randomised controlled trial of methadone maintenance treatment versus wait list control in an Australian prison system. *Drug and Alcohol Dependence* 72(1):59-65.

Dole, V.P., and M. Nyswander. 1965. Medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. *Journal of the American Medical Association* 193:646-650.

Dowell, D., T.M. Haegerich, and R. Chou. 2016. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *Morbidity and Mortality Weekly Report* 65(RR-1):1-49.

Duncan, L.G., S. Mendoza, and H. Hansen. 2015. Buprenorphine maintenance for opioid dependence in public sector healthcare: Benefits and barriers. *Journal of Addiction Medicine and Therapeutic Science* 1(2):31-36.

Dunn, K.M., K.W. Saunders, C.M. Rutter, C.J. Banta-Green, J.O. Merrill, M.D. Sullivan, C.M. Weisner, M.J. Silverberg, C.I. Campbell, B.M. Psaty, and M. VonKorff. 2010. Opioid prescriptions for chronic pain and overdose: A cohort study. *Annals of Internal Medicine* 152(2):85-92.

DuPont, R.L. 1971. Profile of a heroin-addiction epidemic. *New England Journal of Medicine* 285(6):320-324.

DuPont, R.L. 1973. Coming to grips with an urban heroin addiction epidemic. *Journal of the American Medical Association* 223(1):46-48.

DuPont, R.L. 1974. The rise and fall of heroin addiction. *Natural History* 83(6):66-71.

DuPont, R.L., and M.H. Greene. 1973. The dynamics of a heroin addiction epidemic. *Science* 181(4101):716-722.

Dysart, K., H. Hsieh, K. Kaltenbach, and J.S. Greenspan. 2007. Sequela of preterm versus term infants born to mothers on a methadone maintenance program: Differential course of neonatal abstinence syndrome. *Journal of Perinatal Medicine* 35(4):344-346.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2015a. *European drug report 2015: Trends and developments*. Lisbon, Portugal: EMCDDA.

EMCDDA. 2015b. *Preventing overdose deaths in Europe*. Lisbon, Portugal: EMCDDA.

EMCDDA. 2016. *Preventing opioid overdose deaths with take-home naloxone*. Lisbon, Portugal: EMCDDA.

Farrell, M., and J. Marsden. 2008. Acute risk of drug-related death among newly released prisoners in England and Wales. *Addiction* 103(2):251-255.

Fatima, M., S. Srivastav, and A.C. Mondal. 2017. Prenatal stress and depression associated neuronal development in neonates. *International Journal of Developmental Science* 60:1-7.

Faul., M., M. Bohm, and C. Alexander. 2017. Methadone prescribing and overdose and the association with Medicaid preferred drug list policies—United States, 2007–2014. *Morbidity and Mortality Weekly Report* 66:320-323.

FDA (U.S. Food and Drug Administration). 2016. *FDA requires strong warnings for opioid analgesics, prescription opioid cough products, and benzodiazepine labeling related to serious risks and death from combined use*. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm518697.htm (accessed March 2, 2017).

FDA. 2017a. *FDA news release: FDA requests removal of Opana ER for risks related to abuse*. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery (accessed June 8, 2017).

FDA. 2017b. *Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting opioid analgesics*. https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm (accessed June 10, 2017).

Ferri, M., M. Davoli, and C.A. Perucci. 2011. Heroin maintenance for chronic heroin-dependent individuals. *Cochrane Database of Systematic Reviews* 12:CD003410.

Ferri, M., S. Minozzi, A. Bo, and L. Amato. 2013. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database of Systematic Reviews* 6:CD009879.

Fiellin, D.A., M.V. Pantalon, M.C. Chawarski, B.A. Moore, L.E. Sullivan, P.G. O'Connor, and R.S. Schottenfeld. 2006. Counseling plus buprenorphine-naloxone maintenance therapy for opioid dependence. *New England Journal of Medicine* 355:365-374.

Finnegan, L.P., and K. Kaltenbach. 1992. Neonatal abstinence syndrome. In *Primary pediatric care*, 2nd ed., edited by R.A. Hoekelman, S.B. Friedman, and N.M. Nelson. St. Louis, MO: Mosby. Pp. 1367-1378.

Gaalema, D.E., T.L. Scott, S.H. Heil, M.G. Coyle, K. Kaltenbach, G.J. Badger, A.M. Arria, S.M. Stine, P.R. Martin, and H.E. Jones. 2012. Differences in the profile of neonatal abstinence syndrome signs in methadone—versus buprenorphine—exposed infants. *Addiction* 107(Suppl. 1):53-62.

Gibson, K.S., S. Stark, D. Kumar, and J. Bailit. 2017. Relationship between gestational age and the severity of neonatal abstinence syndrome. *Addiction* 112(4):711-716.

Gomes, T., M.M. Mamdani, I.A. Dhalla, J.M. Paterson, and D.N. Juurlink. 2011. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Archives of Internal Medicine* 171:686-691.

Gray, E. 2014. *Heroin gains popularity as cheap doses flood the U.S.* http://time.com/4505/heroin-gains-popularity-as-cheap-doses-flood-the-u-s (accessed March 1, 2017).

Green, M.S., and R.A. Chambers. 2015. Pseudoaddiction: Fact or fiction? An investigation of the medical literature. *Current Addiction Reports* 2(4):310-317.

Green, T.C., and M. Gilbert. 2016. Invited commentary: Counterfeit medications and fentanyl. *JAMA Internal Medicine* 176(10):1555-1557.

Green, T.C., C. Griffel, T. Dailey, P. Garg, E. Thorley, C. Kaczmarsky, and S.F. Butler. 2015a. How did you know you got the right pill? Prescription opioid identification and measurement error in the abuse deterrent formulation era. *Addiction Science & Clinical Practice* 10(Suppl. 1):A16.

Green, T.C., E.F. Dauria, J. Bratberg, C.S. Davis, and A.Y. Walley. 2015b. Orienting patients to greater opioid safety: Models of community pharmacy-based naloxone. *Harm Reduction Journal* 12:25.

Hagan, H., E.R. Pouget, and D.C. Des Jarlais. 2011. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. *Journal of Infectious Diseases* 204(1):74-83.

Hall, A.J., J.E. Logan, R.L. Toblin, J.A. Kaplan, J.C. Kraner, D. Bixler, A.E. Crosby, and L.J. Paulozzi. 2008. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *Journal of the American Medical Association* 300(22):2613-2620.

Hansen, H., C. Siegel, J. Wanderling, and D. DiRocco. 2016. Buprenorphine and methadone treatment for opioid dependence by income, ethnicity and race of neighborhoods in New York City. *Drug and Alcohol Dependence* 164:14-21.

Hardman, J.G., L.E. Limberd, and A.G. Gilman, Eds. 2001. *Goodman and Gilman's the pharmacologic basis of therapeutics*. 10th ed. New York: McGraw-Hill.

Hartung, D.M., D. McCarty, R. Fu, K. Wiest, M. Chalk, and D.R. Gastfriend. 2014. Extended-release naltrexone for alcohol and opioid dependence: A meta-analysis of healthcare utilization studies. *Journal of Substance Abuse Treatment* 47(2):113-121.

Häuser, W., F. Petzke, L. Radbruch, and T.R. Tölle. 2016. The opioid epidemic and the long-term opioid therapy for chronic noncancer pain revisited: A transatlantic perspective. *Pain Management* 6(3):249-263.

Havens, J.R., C.G. Leukefeld, A.M. DeVeaugh-Geiss, P. Coplan, and H.D. Chilcoat. 2014. The impact of a reformulation of extended-release oxycodone designed to deter abuse in a sample of prescription opioid abusers. *Drug and Alcohol Dependence* 139:9-17.

Heimer, R., H. Catania, R.G. Newman, J. Zambrano, A. Brunet, and A.M. Ortiz. 2006. Methadone maintenance in prison: Evaluation of a pilot program in Puerto Rico. *Drug and Alcohol Dependence* 83(2):122-129.

Henderson, A.W., K.M. Babu, R.C. Merchant, and F.L. Beaudoin. 2015. Prescription opioid use and misuse among older adult Rhode Island hospital emergency department patients. *Rhode Island Medical Journal* 98(3):28-31.

HHS (U.S. Department of Health and Human Services). 2016. *Opioids Factsheet*. https://www.hhs.gov/sites/default/files/Factsheet-opioids-061516.pdf (accessed January 11, 2017).

Holmes, A.V., E.C. Atwood, B. Whalen, J. Beliveau, J.D. Jarvis, and S.L. Ralston. 2016. Rooming-in to treat neonatal abstinence syndrome: Improved family centered care and lower cost. *Pediatrics* 137(6).

Hubbard, R.L., and M.E. Marsden. 1986. Relapse to use of heroin, cocaine, and other drugs in the first year after treatment. *NIDA Research Monograph* 72:157-166.

Hudak, M.L., and R.C. Tan. 2012. Neonatal drug withdrawal. *Pediatrics* 129(2):e540-e560.

Hughes, A., M.R. Williams, R.N. Lipari, J. Bose, E.A.P. Copello, and L.A. Kroutil. 2016. *Prescription drug use and misuse in the United States: Results from the 2015 National Survey on Drug Use and Health*. https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.htm (accessed August 14, 2017).

Hunt, E., R.H. Peters, and J. Kremling. 2015. Behavioral health treatment history among persons in the justice system: Findings from the Arrestee Drug Abuse Monitoring II Program. *Psychiatric Rehabilitation Journal* 38(1):7-15.

Inciardi, J.A., H.L. Surratt, S.P. Kurtz, and T.J. Cicero. 2007. Mechanisms of prescription drug diversion among drug-involved club- and street-based populations. *Pain Medicine* 8(2):171-183.

Inciardi, J.A., H.L. Surratt, T.J. Cicero, S.P. Kurtz, S.S. Martin, and M.W. Parrino. 2009. The "black box" of prescription drug diversion. *Journal of Addictive Diseases* 28(4):332-347.

IOM (Institute of Medicine). 1995. *Federal regulation of methadone treatment*. Washington, DC: National Academy Press.

IOM. 2011. *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington, DC: National Academy Press.

Isbell, H., A. Wikler, N.E. Eddy, J.L. Wilson, and C.F. Moran. 1947. Tolerance and addiction liability of 6-dimethylanimo-4-4-diphenylheptanone-3 (Methadon). *Journal of the American Medical Association* 135(14):888-894.

Iwanicki, J.L., S.G. Severtson, H. McDaniel, A. Rosenblum, C. Fong, T.J. Cicero, M.S. Ellis, S.P. Kurtz, M.E. Butttram, and R.C. Dart. 2016. Abuse and diversion of immediate release opioid analgesics as compared to extended release formulations in the United States. *PLoS One* 11(12):e0167499.

Jansson, L.M., J.A. Dipietro, A. Elko, and M. Velez. 2007. Maternal vagal tone changes in response to methadone associated with neonatal abstinence syndrome severity in exposed infants. *Journal of Maternal-Fetal and Neonatal Medicine* 20(9):677-685.

Jansson, L.M., J.A. Diepietro, A. Elko, and M. Velez. 2010. Infant autonomic functioning and neonatal abstinence. *Drug and Alcohol Dependence* 109(1-3):198-204.

Jarvis, M.A., and S.H. Schnoll. 1994. Methadone treatment during pregnancy. *Journal of Psychoactive Drugs* 26(2):151-161.

Jonas, A.B., A.M. Young, C.B. Oser, C.G. Leukefeld, and J.R. Havens. 2012. OxyContin® as currency: OxyContin® use and increased social capital among rural Appalachian drug users. *Social Science & Medicine* 74(10):1602-1609.

Jones, C.M. 2013a. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers—United States, 2002–2004 and 2008–2010. *Drug and Alcohol Dependence* 132(1-2):95-100.

Jones, C.M. 2013b. *Trends in the distribution of selected opioids by state, US, 1999–2011*. Presented at National Meeting Safe States Alliance, Baltimore, MD, June 6.

Jones, C.M., and J.K. McAninch. 2015. Emergency department visits and overdose deaths from combined use of opioids and benzodiazepines. *American Journal of Preventive Medicine* 49(4):493-501.

Jones, C.M., J. Logan, R.M. Gladden, and M.K. Bohm. 2015. Vital signs: Demographic and substance use trends among heroin users—United States, 2002–2013. *Morbidity and Mortality Weekly Report* 64(26):719-725.

Jones, C.M., P.G. Lurie, and W.M. Compton. 2016. Increase in naloxone prescriptions dispensed in U.S. retail pharmacies since 2013. *American Journal of Public Health* 106(4):689-690.

Jones, H.E., and A. Fielder. 2015. Neonatal abstinence syndrome: Historical perspective, current focus, future directions. *Prevention Medicine* 80:12-17.

Jones, H.E., M.L. Velez, M.E. McCaul, and D.S. Svikis. 1999. Special treatment issues for women. In *Methadone treatment for opioid dependence*, edited by E.C. Strain and M. Stizer. Baltimore, MD: John Hopkins University Press. Pp. 251-280.

Jones, H.E., K.E. O'Grady, D. Malfi, and M. Tuten. 2008. Methadone maintenance vs. methadone taper during pregnancy: Maternal and neonatal outcomes. *American Journal on Addictions* 17(5):372-386.

Jones, H.E., K. Kaltenbach, S.H. Heil, S.M. Stine, M.G. Coyle, A.M. Arria, K.E. O'Grady, P. Selby, P.R. Martin, and G. Fischer. 2010. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *New England Journal of Medicine* 363(24):2320-2331.

Jones, H.E., L.P. Finnegan, and K. Kaltenbach. 2012. Methadone and buprenorphine for the management of opioid dependence in pregnancy. *Drugs* 72(6):747-757.

Jones, H.E., S.H. Heil, M. Tuten, M.S. Chisolm, J.M. Foster, K.E. O'Grady, and K. Kaltenbach. 2013. Cigarette smoking in opioid dependent pregnant women: Neonatal and maternal outcomes. *Drug and Alcohol Dependence* 131(3):271-277.

Jones, H.E., M. Terplan, and M. Meyer. 2017. Medically assisted withdrawal (detox): Considering the mother–infant dyad. *Journal of Addiction Medicine* 11(2):90-92.

Kaltenbach, K., and L.P. Finnegan. 1986. Neonatal abstinence: Pharmacotherapy and developmental outcome. *Neurobehavioral Toxicology and Teratology* 8(4):353-355.

Kaltenbach, K., and H.E. Jones. 2016. Neonatal abstinence syndrome: Presentation and treatment considerations. *Journal of Addiction Medicine* 10(4):217-233.

Kaltenbach, K., V. Berghella, and L.P. Finnegan. 1998. Opioid dependence during pregnancy: Effects and management. *Obstetrics and Gynecology Clinics of North America* 25(1):139-151.

Kaltenbach, K., A. Holbrook, M. Coyle, S.H. Heil, A.L. Salisbury, S. Stine, P.R. Martin, and H.E. Jones. 2012. Predicting treatment for neonatal abstinence syndrome in infants born to women maintained on opioid agonist medication. *Addiction* 107(Suppl. 1):45-52.

Kaplan, J. 1983. *Heroin: The hardest drug*. Chicago, IL: University of Chicago Press.

Kenan, K., K.A. Mack, and L. Paulozzi. 2012. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000–2010. *Open Medicine* 6(2):41-47.

Kennedy-Hendricks, A., A. Gielen, E. McDonald, E.E. McGinty, W. Shields, and C.L. Barry. 2016. Medication sharing, storage, and disposal practices for opioid medications among U.S. adults. *JAMA Internal Medicine* 176(7):1027-1029.

Kerr, T., N. Fairbairn, M. Tyndall, D. Marsh, K. Li, J. Montaner, and E. Wood. 2007. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. *Drug and Alcohol Dependence* 87(1):39-45.

Khalid, L., J.M. Liebschutz, Z. Xuan, S. Dossabhov, Y. Kim, D. Crooks, C. Shanahan, A. Lange, O. Heymann, and K.E. Lasser. 2015. Adherence to prescription opioid monitoring guidelines among residents and attending physicians in the primary care setting. *Pain Medicine* 16(3):480-487.

Kilmer, B., and J. Caulkins. 2014. Hard drugs demand solid understanding. *USA Today*, March 8. https://www.usatoday.com/story/opinion/2014/03/08/heroin-abuse-hoffman-research-column/6134337 (accessed April 12, 2017).

Kilmer, B., S. Everingham, J. Caulkins, G. Midgette, R. Pacula, P. Reuter, R. Burnes, B. Han, and R. Lundberg. 2014. *What America's users spend on illegal drugs: 2000-2010*. http://atforum.com/documents/wausid_results_report.pdf (accessed February 28, 2017).

Kinlock, T.W., M.S. Gordon, R.P. Schwartz, T.T. Fitzgerald, and K.E. O'Grady. 2009. A randomized clinical trial of methadone maintenance for prisoners: Results at 12 months postrelease. *Journal of Substance Abuse Treatment* 37(3):277-285.

Ko, J.Y., S.W. Patrick, V.T. Tong, R. Patel, J.N. Lind, and W.D. Barfield. 2016. Incidence of neonatal abstinence syndrome-28 states, 1999–2013. *Morbidity and Mortality Weekly Report* 65(31):799-802.

Kolodny, A., D.T. Courtwright, C.S. Hwang, P. Kreiner, J.L. Eadie, T.W. Clark, and G.C. Alexander. 2015. The prescription opioid and heroin crisis: A public health approach to an epidemic of addiction. *Annual Review of Public Health* 36:559-574.

Kraft, W.K., K. Dysart, J.S. Greenspan, E. Gibson, K. Kaltenbach, and M.E. Ehrlich. 2011. Revised dose schema of sublingual buprenorphine in the treatment of neonatal opioid abstinence syndrome. *Addiction* 106(3):574-580.

Kraft, W.K., S.C. Adenivi-Jones, I. Chervoneya, J.S. Greenspan, D. Abatemarco, K. Kaltenbach, and M.E. Ehrlich. 2017. Buprenorphine for the treatment of the neonatal abstinence syndrome. *New England Journal of Medicine* 376:2341-2348.

Kreek, M.J. 1973. Medical safety and side effects of methadone in tolerant individuals. *Journal of the American Medical Association* 223(6):665-668.

Krupitsky, E.M., and E.A. Blokhina. 2010. Long-acting depot formulations of naltrexone for heroin dependence: A review. *Current Opinion in Psychiatry* 23(3):210-214.

Krupitsky, E., E. Avartau, E. Blokhina, E. Verbitskaya, V. Wahlgren, M. Tsoy-Podosenin, N. Bushara, A. Burakov, D. Masalov, T. Romanova, A. Tyurina, V. Palatkin, T. Slavina, A. Pecoraro, and G.E. Woody. 2012. Randomized trial of long-acting sustained-release naltrexone implant vs. oral naltrexone or placebo for preventing relapse to opioid dependence. *Archives of General Psychiatry* 69(9):973-981.

Lankenau, S.E., S.M. Schrager, K. Silva, A. Kocejevic, J.J. Bloom, C. Wong, and E. Iverson. 2012. Misuse of prescription and illicit drugs among high-risk young adults in Los Angeles and New York. *Journal of Public Health Research* 1(1):22-30.

Larance, B., R. Mattick, R. Ali, N. Lintzeris, R. Jenkinson, N. White, I. Kihas, R. Cassidy, and L. Degenhardt. 2015. Diversion and injection of buprenorphine-naloxone films two years post-introduction in Australia. *Drug and Alcohol Review* 35:83-91.

Lee, J.D., R. McDonald, E. Grossman, J. McNeely, E. Laska, J. Rotrosen, and M.N. Gourevitch. 2015. Opioid treatment at release from jail using extended-release naltrexone: A pilot proof-of-concept randomized effectiveness trial. *Addiction* 110(6):1008-1014.

Liang, Y., and B.J. Turner. 2015. Assessing risk for drug overdose in a national cohort: Role for both daily and total opioid dose? *The Journal of Pain* 16(4):313-325.

Logan, K., and S. Deutsch. 2015. Room for improvement in the New York State pharmacy-based syringe access program. *Columbia Medical Review* 1(1):40-50.

Lund, I.O., H. Fitzimons, M. Tuten, M.S. Chisolm, and H.E. Jones. 2012. Comparing methadone and buprenorphine maintenance with medication assisted withdrawal for the treatment of opioid dependence in pregnancy. *Substance Abuse Rehabilitation* 3(Suppl. 1):17-25.

Lund, I.O., G. Fischer, G.K. Welle-Strand, K.E. O'Grady, K. Debelak, W.R. Morrone, and H.E. Jones. 2013. A comparison of buprenorphine + naloxone to buprenorphine and methadone in the treatment of opioid dependence during pregnancy: Maternal and neonatal outcomes. *Substance Abuse Research and Treatment* 7:61-74.

Ly, K.N., E.M. Hughes, R.B. Jiles, and S.D. Holmberg. 2016. Rising mortality associated with hepatitis C virus in the United States, 2003–2013. *Clinical Infectious Diseases* 62(10):1287-1288.

MacArthur, G.J., S. Minozzi, N. Martin, P. Vickerman, S. Deren, J. Bruneau, L. Degenhardt, and M. Hickman. 2012. Opiate substitution treatment and HIV transmission in people who inject drugs: Systematic review and meta-analysis. *British Medical Journal* 345:e5945.

Massachusetts Department of Public Health. 2016. *An assessment of opioid-related deaths in Massachusetts (2013–2014)*. Boston, MA: Massachusetts Department of Public Health.

Mateu-Gelabert, P., H. Guarino, L. Jessell, and A. Teper. 2015. Injection and sexual HIV/HCV risk behaviors associated with nonmedical use of prescription opioids among young adults in New York City. *Journal of Substance Abuse Treatment* 48:13-20.

Mattick, R.P., C. Breen, J. Kimber, and M. Davoli. 2009. Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews* 3:CD002209.

McKenzie, M., N. Zaller, S.L. Dickman, T.C. Green, A. Parihk, P.D. Friedmann, and J.D. Rich. 2012. A randomized trial of methadone initiation prior to release from incarceration. *Substance Abuse* 33(1):19-29.

McLellan, A.T., I.O. Arndt, D.S. Metzger, G.E. Woody, and C.P. O'Brien. 1993. The effects of psychosocial services in substance abuse treatment. *Journal of the American Medical Association* 269:1953-1959.

McNaughton, E.C., R.A. Black, S.E. Weber, and S.F. Butler. 2015. Assessing abuse potential of new analgesic medications following market release: An evaluation of Internet discussion of tapentadol abuse. *Pain Medicine* 16(1):131-140.

McQueen, K., and J. Murphy-Oikonen. 2016. Neonatal abstinence syndrome. *New England Journal of Medicine* 375:2468-2479.

Merrall, E.L., A. Kariminia, I.A. Binswanger, M.S. Hobbs, M. Farrell, J. Marsden, S.J. Hutchinson, and S.M. Bird. 2010. Meta-analysis of drug-related deaths soon after release from prison. *Addiction* 105(9):1545-1554.

Miller, M., C.W. Barber, S. Leatherman, J. Fonda, J.A. Hermos, K. Cho, and D.R. Gagnon. 2015. Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Internal Medicine* 175(4):608-615.

Miller, T., and D. Hendrie. 2008. *Substance abuse prevention dollars and cents: A cost-benefit analysis*. DHHS Publication (SMA) 07-4298. Rockville, MD: Center for Substance Abuse Prevention, Substance Abuse and Mental Health Services Administration.

Muhuri, P., J. Gfroerer, and M.C. Davies. 2013. *Associations of nonmedical pain reliever use and initiation of heroin use in the United States*. CBHSQ Data Review 2013 (August). https://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm (accessed May 25, 2017).

NICE (National Institute for Health and Care Excellence). 2007. *Methadone and buprenorphine for the management of opioid dependence*. https://www.nice.org.uk/guidance/ta114/resources/methadone-and-buprenorphine-for-the-management-of-opioid-dependence-pdf-82598072878789 (accessed May 1, 2017).

NIDA (National Institute on Drug Abuse). 2014. *America's addiction to opioids: Heroin and prescription drug abuse*. https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2016/americas-addiction-to-opioids-heroin-prescription-drug-abuse (accessed February 11, 2017).

NIDA. 2015. *Community Epidemiology Work Group (CEWG)*. https://www.drugabuse.gov/about-nida/organization/workgroups-interest-groups-consortia/community-epidemiology-work-group-cewg (accessed April 12, 2017).

NIDA. 2016. *What is fentanyl?* https://www.drugabuse.gov/publications/drugfacts/fentanyl (accessed June 13, 2017).

Nielsen, S., B. Larance, and N. Lintzeris. 2017. Opioid agonist treatment for patients with dependence on prescription opioids. *Journal of the American Medical Association* 317(9): 967-968.

NIJ (National Institute of Justice). 2014. *NIJ's drugs and crime research: Arrestee drug abuse monitoring programs*. https://www.nij.gov/topics/drugs/markets/adam/pages/welcome.aspx (accessed April 12, 2017).

Olshansky, S.J., T. Antonucci, L. Berkman, R.H. Binstock, A. Boersch-Supan, J.T. Cacioppo, B.A. Carnes, L.L. Carstensen, L.P. Fried, D.P. Goldman, J. Jackson, M. Kohli, J. Rother, Y. Zheng, and J. Rowe. 2012. Differences in life expectancy due to race and educational differences are widening, and many may not catch up. *Health Affairs* 31(8):1803-1813.

Osterwalder, J.J. 1996. Naloxone—for intoxications with intravenous heroin and heroin mixtures—harmless or hazardous? A prospective clinical study. *Journal of Toxicology: Clinical Toxicology* 34(4):409-416.

Oviedo-Joekes, E., D. Guh, S. Brissette, K. Merchand, S. MacDonald, K. Lock, S. Harrison, A. Jonmohamed, A.H. Anis, M. Krausz, D.C. Marsh, and M.T. Schechter. 2016. Hydromorphone compared with diacetylmorphine for long-term opioid dependence: A randomized clinical trial. *JAMA Psychiatry* 73(5):447-455.

Park, T.W., R. Saitz, D. Ganoczy, M.A. Ilgen, and A.S.B. Bohnert. 2015. Benzodiazepine prescribing patterns and deaths from drug overdose among U.S. veterans receiving opioid analgesics: Case-cohort study. *British Medical Journal* 350:h2698.

Patrick, S.W., R.E. Schumacher, B.D. Benneyworth, E.E. Krans, J.M. McAllister, and M.M. Davis. 2012. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *Journal of the American Medical Association* 307(18): 1934-1940.

Patrick, S.W., M.M. Davis, C.U. Lehman, and W.O. Cooper. 2015. Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States, 2009-2012. *Journal of Perinatology* 35:650-655.

Paulozzi, L.J. 2012. Prescription drug overdoses: A review. *Journal of Safety Research* 43(4):283-289.

Paulozzi, L.J., J.E. Logan, A.J. Hall, E. McKinstry, J.A. Kaplan, and A.E. Crosby. 2009. A comparison of drug overdose deaths involving methadone and other opioid analgesics in West Virginia. *Addiction* 104(9):1541-1548.

Peavy, K.M., C.J. Banta-Green, S. Kingston, M. Hanrahan, J.O. Merrill, and P.O. Coffin. 2012. "Hooked on" prescription-type opiates prior to using heroin: Results from a survey of syringe exchange clients. *Journal of Psychoactive Drugs* 44(3):259-265.

Pollini, R.A., C.J. Banta-Green, J. Cuevas-Mota, M. Metzner, E. Teshale, and R.S. Garfein. 2011. Problematic use of prescription-type opioids prior to heroin use among young heroin injectors. *Substance Abuse and Rehabilitation* 2(1):173-180.

President's Commission on Law Enforcement and Administration of Justice. 1967. *The challenge of crime in a free society*. Washington, DC: U.S. Government Printing Office.

Pritham, U.A., J.A. Paul, and M.J. Hayes. 2012. Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. *Journal of Obstetric, Gynecologic and Neonatal Nursing* 41(20):180-190.

Quintana, P., M. Ventura, M. Grifell, A. Palma, L. Galindo, I. Fornis, C. Gil, X. Carbon, F. Caudevilla, M. Farre, and M. Torrens. 2017. The hidden web and the fentanyl problem: Detection of ocfentanil as an adulterant in heroin. *International Journal on Drug Policy* 40:78-83.

Raffa, R.B., R. Taylor, and J.V. Pergolizzi. 2014. Sequestered naltrexone in sustained release morphine or oxycodone: A way to inhibit illicit use? *Expert Opinion on Drug Safety* 13(2):181-190.

Ray, W.A., C.P. Chung, K.T. Murray, W.O. Cooper, K. Hall, and C.M. Stein. 2015. Out-of-hospital mortality among patients receiving methadone for noncancer pain. Out-of-hospital mortality among patients receiving methadone for noncancer pain. *JAMA Internal Medicine* 175(3):420-427.

Reuter, P., and M. Kleiman. 1986. Risks and prices: An economic analysis of drug enforcement. In *Crime and justice: A review of research*, Vol. 7, edited by M. Tonry and N. Morris. Chicago, IL: University of Chicago Press. Pp. 289-340.

Rich, B.A., and L.R. Webster. 2011. A review of forensic implications of opioid prescribing with examples from malpractice cases involving opioid-related overdose. *Pain Medicine* 12(Suppl. 2):S59-S65.

Rich, J.D., M. McKenzie, S. Larney, J.B. Wong, L. Tran, J. Clarke, A. Noska, M. Reddy, and N. Zaller. 2015. Methadone continuation versus forced withdrawal on incarceration in a combined U.S. prison and jail: A randomised, open-label trial. *Lancet* 386(9991):350-359.

Rockett, I.R., G. Hobbs, D. De Leo, S. Stack, J.L. Frost, A.M. Ducatman, N.D. Kapusta, and R.L. Walker. 2010. Suicide and unintentional poisoning mortality trends in the United States, 1987–2006: Two unrelated phenomena? *BMC Public Health* 10:705.

Rowe, C., E. Vittinghoff, G.M. Santos, E. Behar, C. Turner, and C.O. Coffin. 2016. Performance measures of diagnostic codes for detecting opioid overdose in the emergency department. *Academic Emergency Medicine* 24(4):475-483.

Rudd, R.A., N. Aleshire, J.E. Zibbell, and R.M. Gladden. 2016a. Increases in drug and opioid overdose deaths—United States, 2000–2014. *Morbidity and Mortality Weekly Report* 64(50-51):1378-1382.

Rudd, R.A., P. Seth, F. David, and L. Scholl. 2016b. Increases in drug and opioid-involved overdose deaths—United States, 2010–2015. *Morbidity and Mortality Weekly Report* 65:1445-1452.

Ruwanpathirana, R., M.E. Abedel-Latif, L. Burns, J. Chen, F. Craig, K. Lui, and J.L. Oei. 2015. Prematurity reduces the severity and need for treatment of neonatal abstinence syndrome. *Acta Paediatrica* 104(5):e188-e194.

Sachs, H.C. 2013. The transfer of drugs and therapeutics into human breast milk. *Pediatrics* 132(3):e796-e809.

SAMHSA (Substance Abuse and Mental Health Services Administration). 2007. *Methadone mortality: A reassessment—report of the meeting and follow-up activities, July 2007*. Rockville, MD: U.S. Department of Health and Human Services.

SAMHSA. 2009. *Substance abuse treatment addressing the specific needs of women. A treatment improvement protocol. TIP 51*. http://store.samhsa.gov/shin/content/SMA13-4426/SMA13-4426.pdf (accessed March 7, 2017).

SAMHSA. 2010. *Treatment Episode Data Set: 2007. Discharges from substance abuse treatment services*. HHS Publication SMA 10-4479. Rockville, MD: SAMHSA.

SAMHSA. 2012. *Results from the 2011 National Survey on Drug Use and Health: Summary of national findings*. HHS Publication SMA 12-4713, NSDUH Series H-44. Rockville, MD: SAMHSA.

SAMHSA. 2013a. *Results from the 2012 National Survey on Drug Use and Health: Summary of national findings*. HHS Publication SMA 13-4795, NSDUH Series H-46. Rockville, MD: SAMHSA.

SAMHSA. 2013b. *Treatment Episode Data Set (TEDS): 2001–2011. State admissions to substance abuse treatment services*. Rockville, MD: SAMHSA. https://www.samhsa.gov/data/sites/default/files/TEDS2011St_Web/TEDS2011St_Web/TEDS2011St_Web.pdf (accessed May 25, 2017).

SAMHSA. 2014. *National Survey on Drug Use and Health*. NSDUH-2014. http://datafiles.samhsa.gov/study/national-survey-drug-use-and-health-nsduh-2014-nid13618 (accessed January 10, 2017).

SAMHSA. 2016a. *2015 National Survey on Drug Use and Health: Detailed tables*. Rockville, MD: SAMHSA. https://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015/NSDUH-DetTabs-2015.pdf (accessed April 7, 2017).

SAMHSA. 2016b. *About emergency department data*. https://www.samhsa.gov/data/emergency-department-data-dawn/about (accessed January 18, 2017).

SAMHSA. 2016c. *Collaborative approach to the treatment of pregnant women with opioid use disorders*. https://ncsacw.samhsa.gov/files/Collaborative_Approach_508.pdf (accessed March 1, 2017).

SAMHSA. 2017a. *Apply to increase patient limits*. https://www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management/increase-patient-limits (accessed June 12, 2017).

SAMHSA. 2017b. *Buprenorphine waiver management*. https://www.samhsa.gov/medication-assisted-treatment/buprenorphine-waiver-management (accessed March 1, 2017).

Sarpatwari, A., M.S.S. Sinha, and A.S. Kesselheim. 2017. The opioid epidemic: Fixing a broken pharmaceutical market. *Harvard Law and Policy Review* 11:463-484.

Schwartz, R.P., S.M. Kelly, K.E. O'Grady, D. Gandhi, and J.H. Jaffe. 2012. Randomized trial of standard methadone treatment compared to initiating methadone without counseling: 12-month findings. *Addiction* 107:943-952.

Seal, K.H., R. Thawley, L. Gee, J. Bamberger, A.H. Kral, D. Ciccarone, M. Downing, and B.R. Edlin. 2005. Naloxone distribution and cardiopulmonary resuscitation training for injection drug users to prevent heroin overdose death: A pilot intervention study. *Journal of Urban Health* 82(2):303-311.

Seligman, N.S., N. Salva, E.J. Hayes, K.C. Dysart, E.C. Pequinot, and J.K. Baxter. 2008. Predicting length of treatment for neonatal abstinence syndrome in methadone exposed infants. *American Journal of Obstetrics and Gynecology* 199(4):396.e1-e7.

Sells, S., R. Demaree, and C. Hornick. 1979. *Comparative effectiveness of drug abuse treatment modalities*. Washington, DC: U.S. Department of Health, Education, and Welfare, Public Health Service.

Shah, A., C.J. Hayes, and B.C. Martin. 2017. Characteristics of initial prescription episodes and likelihood of long-term opioid use—United States, 2006–2015. *Morbidity and Mortality Weekly Report* 66(10):265-269.

Siegal, H.A., R.G. Carlson, D.R. Kenne, and M.G. Swora. 2003. Probable relationship between opioid abuse and heroin use. *American Family Physician* 67(5):942-945.

Sigmon, S.C. 2015. Interim treatment: Bridging delays to opioid treatment access. *Prevention Medicine* 80:32-36.

Sigmon, S.C., T.A. Ochalek, A.C. Meyer, B. Hruska, S.H. Bell, G.J. Badger, G. Rose, J.R. Brooklyn, R.P. Schwartz, B.A. Moore, and S.T. Higgins. 2016. Interim buprenorphine vs. waiting list for opioid dependence. *New England Journal of Medicine* 375(25):2504-2505.

Smith, G. 2016. *Maine's new opioid prescribing law & the opioid crisis: Implications for providers*. https://www.mainemed.com/sites/default/files/content/2016_Opioid_Law_c488%20_PowerPoint_9-7-2016.pdf (accessed August 14, 2017).

Smith, M.E., N. Robinowitz, P. Chaulk, and K.E. Johnson. 2014. Self-care and risk reduction habits in older injection drug users with chronic wounds: A cross-sectional study. *Harm Reduction Journal* 11:28.

Sporer, K.A. 1999. Acute heroin overdose. *Annals of Internal Medicine* 130(7):584-590.

Sporer, K.A. 2003. Strategies for preventing heroin overdose. *British Medical Journal* 326(7386):442-444.

Starrels, J.L., W.C. Becker, M.G. Weiner, X. Li, M. Heo, and B.J. Turner. 2011. Low use of opioid risk reduction strategies in primary care even for high risk patients with chronic pain. *Journal of General Internal Medicine* 26(9):958-964.

Stein, B.D., A.J. Gordon, A.W. Dick, R.M. Burns, R.L. Pacula, C.M. Farmer, D.L. Leslie, and M. Sobrero. 2015. Supply of buprenorphine waivered physicians: The influence of state policies. *Journal of Substance Abuse Treatment* 48(1):104-111.

Stein, B.D., M. Sorbero, A.W. Dick, R.L. Pacula, R.M. Burns, and A.J. Gordon. 2016. Physician capacity to treat opioid use disorder with buprenorphine-assisted treatment. *Journal of the American Medical Association* 316(11):1211-1212.

Stewart, R.D., D.B. Nelson, E.H. Adhikari, D.D. McIntire, S.W. Roberts, J.S. Dashe, and J.S. Sheffield. 2013. The obstetrical and neonatal impact of maternal opioid detoxification in pregnancy. *American Journal of Obstetrics and Gynecology* 209(3):267.e1-e5.

Strang, J., and G. Tober. 2003. *Methadone matters: Evolving community methadone treatment of opiate addiction*. Boca Raton, FL: CRC Press.

Strang, J., J. McCambridge, D. Best, T. Beswick, J. Bearn, S. Rees, and M. Gossop. 2003. Loss of tolerance and overdose mortality after inpatient opiate detoxification: Follow up study. *British Medical Journal* 326(7396):959-960.

Strang, J., W. Hall, M. Hickman, and S.M. Bird. 2010. Impact of supervision of methadone consumption on deaths related to methadone overdose (1993–2008): Analyses using OD4 index in England and Scotland. *British Medical Journal* 341:c4851.

Strang, J., T. Groshkova, A. Uchtenhagen, W. van den Brink, C. Haasen, M.T. Schechter, N. Lintzeris, J. Bell, A. Pirona, E. Oviedo-Joekes, R. Simon, and N. Metrebian. 2015. Heroin on trial: Systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction. *British Journal of Psychiatry* 207(1):5-14.

Strathdee, S.A., and C. Beyrer. 2015. Threading the needle—How to stop the HIV outbreak in rural Indiana. *New England Journal of Medicine* 373:397-399.

Stumbo, S.P., B.J. Yarborough, D. McCarty, C. Weisner, and C.A. Green. 2017. Patient-reported pathways to opioid use disorders and pain-related barriers to treatment engagement. *Journal of Substance Abuse Treatment* 73:45-54.

Su, Q., H. Zhang, Y. Zhang, H. Zhang, D. Ding, J. Zeng, Z. Zhu, and H. Li. 2015. Maternal stress in gestation: Birth outcomes and stress-related hormone response of the neonates. *Pediatrics & Neonatology* 56(6):376-381.

Sun, E.C., A. Dexit, K. Humphreys, B.D. Darnall, L.C. Baker, and S. Mackey. 2017. Association between concurrent use of prescription opioids and benzodiazepines and overdose: Retrospective analysis. *British Medical Journal* 356:j760.

Suryaprasad, A.G., J.Z. White, F. Xu, B.A. Eichler, J. Hamilton, A. Patel, S.B. Hamdounia, D.R. Church, K. Barton, C. Fisher, K. Macomber, M. Stanley, S.M. Guilfoyle, K. Sweet, S. Liu, K. Igbal, R. Tohme, U. Sharapov, B.A. Kupronis, J.W. Ward, and S.D. Holmberg. 2014. Emerging epidemic of hepatitis C virus infections among young nonurban persons who inject drugs in the United States, 2006–2012. *Clinical Infectious Diseases* 59(10):1411-1419.

Terman, G. 2012. *Naloxone: Effects and side effects*. Paper presented at Role of Naloxone in Opioid Overdose Fatality Prevention; Request for Comments; Public Workshop, Silver Spring, MD.

Terplan, M., A. Kennedy-Hendricks, and M. Chisolm. 2015. Prenatal substance use: Exploring assumptions of maternal unfitness. *Substance Abuse* 9(Suppl. 2):1-4.

Thomas, C.P., C.A. Fullerton, M. Kim, L. Montejano, D.R. Lyman, R.H. Dougherty, A.S. Daniels, S.S. Ghose, and M.E. Delphin-Rittmon. 2014. Medication-assisted treatment with buprenorphine: Assessing the evidence. *Psychiatric Services* 65(2):158-170.

Traynor, K. 2016. Maine enacts statewide limits on opioid prescribing. *American Journal of Health System Pharmacy* 73(12):854-856.

Uchtenhagen, A. 2010. Heroin-assisted treatment in Switzerland: A case study in policy change. *Addiction* 105(1):29-37.

Unick, G.J., D. Rosenblum, S. Mars, and D. Ciccarone. 2013. Intertwined epidemics: National demographic trends in hospitalizations for heroin- and opioid-related overdoses, 1993–2009. *PLoS One* 8(2):e54496.

Vadivelu, N., A.M. Kai, V. Kodumudi, R. Zhu, and R. Hines. 2017. Pain management of patients with substance abuse in the ambulatory setting. *Current Pain and Headache Reports* 21(2):9.

Vestal, C. 2016. *At Rikers Island, a legacy of medication-assisted opioid treatment. Stateline: The Pew Charitable Trusts*. http://www.pewtrusts.org/en/research-and-analysis/blogs/stateline/2016/05/23/at-rikers-island-a-legacy-of-medication-assisted-opioid-treatment (accessed February 27, 2017).

Villapiano, N.L.G., T.N.A. Winkelman, K.B. Kozhimannil, M.M. Davis, and S.W. Patrick. 2017. Rural and urban differences in neonatal abstinence syndrome and maternal opioid use, 2004–2013. *JAMA Pediatrics* 171(2):194-196.

Volkow, N.D., and A.T. McLellan. 2016. Opioid abuse in chronic pain—Misconceptions and mitigation strategies. *New England Journal of Medicine* 374:1253-1263.

Volkow, N.D., T.R. Frieden, P.S. Hyde, and S.S. Cha. 2014. Medication-assisted therapies—tackling the opioid-overdose epidemic. *New England Journal of Medicine* 370(22): 2063-2066.

Wachman, E.M., P.K. Newby, J. Vreeland, J. Byun, A. Bonganzi, and H. Baucher. 2011. The relationship between maternal opioid agonists and psychiatric medications on length of hospitalization for neonatal abstinence. *Journal of Addiction Medicine* 5(4):293-299.

Wachman, E.M., M.J. Hayes, M.S. Brown, J. Paul, W.K. Harvey, N. Terrin, G.S. Huggins, J.V. Aranda, and J.M. Davis. 2013. Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of neonatal abstinence syndrome. *Journal of the American Medical Association* 309(17):1821-1827.

Wachman, E.M., M.J. Hayes, B.M. Lester, N. Terin, M.S. Brown, D.A. Neilson, and J.M. Davis. 2014. Epigenetic variation in the mu-opioid receptor gene in infants with neonatal abstinence syndrome. *Journal of Pediatrics* 165(3):472-478.

Wachman, E.M., M.J. Hayes, R. Sherva, M.S. Brown, J.M. Davis, L.A. Farrer, and D.A. Nielsen. 2015. Variations in opioid receptor genes in neonatal abstinence syndrome. *Drug and Alcohol Dependence* 155:253-259.

Walley, A.Y., Z. Xuan, H.H. Hackman, E. Quinn, M. Doe-Simkins, A. Sorensen-Alawad, S. Ruiz, and A. Ozonoff. 2013. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: Interrupted time series analysis. *British Medical Journal* 346:f174.

Walsh, S.L., P.A. Nuzzo, S. Babalonis, V. Casselton, and M.R. Lofwall. 2016. Intranasal buprenorphine along and in combination with naloxone: Abuse liability and reinforcing efficacy in physically dependent opioid abusers. *Drug and Alcohol Dependence* 162:190-198.

Webster, L.R., and R.M. Webster. 2005. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the Opioid Risk Tool. *Pain Medicine* 6(6):432-442.

Weiss, R.D., J.S. Potter, D.A. Fiellin, M. Byrne, H.S. Connery, and W. Dickenson. 2011. Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: A 2-phase randomized controlled trial. *Archives of General Psychiatry* 68:1238-1246.

West, N.A., S.G. Severtson, J.L. Green, and R.C. Dart. 2015. Trends in abuse and misuse of prescription opioids among older adults. *Drug and Alcohol Dependence* 149:117-121.

Wheeler, E., T. Jones, M. Gilbert, and P. Davidson. 2015. Opioid overdose prevention programs providing naloxone to laypersons—United States, 2014. *Morbidity and Mortality Weekly Report* 64(23):631-635.

WHO (World Health Organization). 2003. *Introduction to drug utilization research*. http://apps.who.int/medicinedocs/pdf/s4876e/s4876e.pdf (accessed March 1, 2017).

WHO. 2009. *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence*. http://www.who.int/substance_abuse/publications/opioid_dependence_guidelines.pdf (accessed February 27, 2017).

WHO. 2015. *WHO model list of essential medicines*. 19th list (April 2015) (amended November 2015). http://www.who.int/medicines/publications/essentialmedicines/en (accessed March 1, 2017).

Wiegand, S.L., E.M. Stringer, A.M. Stuebe, H.E. Jones, C. Seashore, and J. Thorp. 2015. Buprenorphine and naloxone comparison with methadone treatment in pregnancy. *Obstetrics and Gynecology* 125(2):363-368.

Wilson, M.E., R.P. Schwartz, K.E. O'Grady, and J.H. Jaffe. 2010. Impact of interim methadone maintenance on HIV risk behaviors. *Journal of Urban Health* 87(4):586-591.

Wolfe, D., M.P. Carrieri, N. Dasgupta, A. Wodak, R. Newman, and R.D. Bruce. 2011. Concerns about injectable naltrexone for opioid dependence. *Lancet* 377(9776):1468-1470.

Woody, G.E., S.A. Poole, G. Subramaniam, K. Dugosh, M. Bogenschutz, P. Abbott, A. Patkar, M. Publicker, K. McCain, J.S. Potter, R. Forman, V. Vetter, L. McNicholas, J. Blaine, K.G. Lynch, and P. Fudala. 2008. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: A randomized trial. *Journal of the American Medical Association* 300(17):2003-2011.

WSIN (Western States Information Network). 2016. *Drug price and purity guide, 2016*. Sacramento, CA: WSIN.

Yang, Z., B. Wilsey, M. Bohm, M. Weyrich, K. Roy, D. Ritley, C. Jones, and J. Melnikow. 2015. Defining risk of prescription opioid overdose: Pharmacy shopping and overlapping prescriptions among long-term opioid users in Medicaid. *The Journal of Pain* 16(5):445-453.

Yealy, D.M., P.M. Paris, R.M. Kaplan, M.B. Heller, and S.E. Marini. 1990. The safety of prehospital naloxone administration by paramedics. *Annals of Emergency Medicine* 19(8):902-905.

Zaller, N., M. McKenzie, P.D. Friedmann, T.C. Green, S. McGowan, and J.D. Rich. 2013. Initiation of buprenorphine during incarceration and retention in treatment upon release. *Journal of Substance Abuse Treatment* 45(2):222-226.

Zedler, B., L. Xie, L. Wang, A. Joyce, C. Vick, F. Kariburyo, P. Rajan, O. Baser, and L. Murrelle. 2014. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. *Pain Medicine* 15(11):1911-1929.

Zibbell, J.E., K. Iqbal, R.C. Patel, A. Suryaprasad, K.J. Sanders, L. Moore-Moravian, J. Serrecchia, S. Blankenship, J.W. Ward, and D. Hotzman. 2015. Increases in Hepatitis C virus infection related to injection drug use among persons aged ≤30 Years—Kentucky, Tennessee, Virginia, and West Virginia, 2006–2012. *Morbidity and Mortality Weekly Report* 64(17):453-458.

5

Evidence on Strategies for Addressing the Opioid Epidemic

Years of sustained, coordinated, and vigilant effort will be required to contain the present opioid epidemic and ameliorate its harmful effects on society. At least 2 million people have an opioid use disorder (OUD) involving prescription opioids, and almost 600,000 have an OUD associated with heroin (HHS, 2016). These numbers are likely to increase in the coming years, regardless of what policies are put in place. Follow-up studies of individuals receiving treatment for OUD involving heroin (e.g., Hser et al., 2001) find very high rates of premature mortality (in the neighborhood of one-third) due to overdose or other complications of the disorder. Thus, even if the nation ramps up treatment availability substantially and immediately, death rates will climb and quality of life will be dramatically reduced for many people for years to come. Likewise, the continued progression of still more people from prescription opioid use to OUD will demand sustained and coordinated effort to establish and implement the scientifically grounded policies and clinical practices necessary to reshape prescribing practices and reduce the occurrence of new cases of prescription opioid-induced OUD.[1]

What should be done to contain the opioid epidemic and to prevent new cases of iatrogenic addiction and associated overdose, death, and other harms? The purpose of this chapter is to review available evidence on strategies that have been used to address the problems of opioid misuse, OUD,

[1]Vigilance will also be needed to reduce the risk of similar problems in the future with other classes of medications for which there exists demand for clinical uses other than the indicated conditions and/or active black markets for their resale.

and related deaths. The chapter begins with prefatory sections addressing (1) the nature of the evidence on policies implemented at the jurisdictional level (typically a state or a nation), as opposed to clinical interventions operating at the level of an individual patient; and (2) the need for a systems approach, including the importance of recognizing the potential effects that interventions focused on misuse of prescription opioids have on misuse of opioids more generally. Next the chapter reviews the evidence on the effectiveness of strategies for addressing the opioid epidemic in four categories: (1) restricting supply, such as by regulating the types of products approved for use (e.g., abuse-deterrent opioids) and regulating/restricting conditions of lawful access to approved drugs; (2) influencing prescribing practices, such as through provider education and the issuance of prescribing guidelines; (3) reducing demand, such as by educating patients about opioids and increasing access to treatment for OUD; and (4) reducing harm, such as through provision of naloxone to prevent opioid overdose and needle exchange programs for people who use injection drugs.

NATURE OF THE EVIDENCE

Theoretically, the comparative effectiveness of different opioid-related policies could be quantified through use of randomized controlled trials (RCTs). For example, consider a clinical strategy that eschews prescribing opioids to treat chronic noncancer pain if the patient scores high on a scale used to measure risk of developing opioid addiction. The effectiveness of this strategy for preventing OUD could be evaluated in an RCT in which patients were assigned to either that policy intervention or an alternative one with fewer restrictions on opioid prescription. An RCT is the preferred source of evidence for causal inference because the random assignment is expected to result in comparable groups of individuals assigned to each strategy. In a large RCT of different approaches to opioid prescribing for preventing OUD, for example, one would expect patients in each group to have, on average, the same risk factors for developing OUD. That is, any future differences between the groups in the frequency of OUD could be ascribed to the different treatment strategies to which they were assigned rather than to differences in the characteristics of the individuals receiving each strategy. As a result, the outcome distribution in each group could be interpreted as the counterfactual outcome distribution that would have been observed in that population under the corresponding strategy.[2]

[2]Of course, even RCTs are not perfect. For example, they may overlook indirect effects on people other than those participating in the study. Parmar and colleagues (2017) describe an RCT of the distribution of naloxone to heroin injectors being released from prison in which only one-third of the naloxone administrations in the treatment group were to the ex-prisoners

RCTs, however, are rare for policies that require implementation at the level of an entire jurisdiction, nor are they ethically permissible in many policy contexts. In the absence of RCTs, other sources of evidence are needed to estimate the counterfactual outcome distribution under different strategies. One such source of evidence is the collection of data on individuals who happen to receive the strategies of interest as part of their routine care, often from electronic health records. The so-called observational analyses based on such data are attempts to emulate the RCT that cannot be conducted (the target trial). In these observational analyses, however, the comparability of the groups receiving each strategy is not guaranteed. In the real world, for example, the restricted opioid prescription policy might more likely be applied to individuals visiting providers in urban health care settings who also received other interventions to reduce the risk of addiction. As a result, a direct comparison of the outcome distribution between those who received each strategy would be confounded by the concomitant interventions.

Observational analyses attempt to eliminate bias due to confounding by adjusting for all measured prognostic factors that are distributed differentially between the groups. For example, the comparison might be conducted separately among individuals in urban and rural health care settings. If all confounding factors are appropriately measured and adjusted for, the observational analysis will adequately emulate the target trial and correctly estimate the counterfactual scenarios under each strategy. But even if confounding is eliminated in an observational analysis, this source of evidence is inherently limited with respect to the counterfactual scenarios it can recreate. Analyses of observational data may be helpful for estimating the comparative effects of different treatment strategies applied to a clinical population, but may not capture population-level effects under different policies. For example, an observational analysis of patients of certain health care providers will not quantify effects due to scaling up a treatment strategy as a policy applied to the entire health system.

In fact, this chapter typically investigates the effects of strategies that operate at the level of a jurisdiction, such as a locality or state, or that of the country as a whole. Because random assignment is exceedingly rare in such circumstances (no one, for example, is authorized to randomly assign New Hampshire and 24 other states to receive one policy or to freeze policy in the other 25 states so they can serve well as controls), and observational analyses of clinical populations cannot capture system-wide effects (even if they could successfully adjust for confounding), other approaches are

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in the study themselves; the majority of the administrations were to others who were outside the scope of data collection. The trial was closed prematurely as a result of this and related problems.

needed. All of these approaches will lack physical randomization of the strategies being examined and therefore will be subject to confounding, but they nonetheless are essential sources of evidence for estimating the effectiveness of various strategies.

Before–After Comparisons

A common nonrandomized source of evidence is before–after comparisons, or the comparison of population outcomes before and after a strategy has been implemented in a single population. Because of underlying trends, however, this comparison may provide a biased estimation of the counterfactual scenarios. For example, the strategy might have been implemented in a population precisely because conditions in that population had been deteriorating. If the underlying factors that gave rise to this trend persisted, conditions might continue to worsen after the strategy was implemented even if the strategy was helpful because it diminished but did not reverse the rate of deterioration. Or the implementation process might move so slowly that the strategy did not take effect until the underlying problem had already exhausted its momentum, and a sort of regression to the mean thus created the illusion that the policy was more effective than it truly was. Therefore, a before–after comparison may not correctly identify the counterfactual of how the world would have looked in the absence of the strategy's implementation.

Ecological Comparisons

Another nonrandomized source of evidence is ecological comparisons, or comparison of outcomes between two different populations, only one of which has received the strategy. Again, however, this comparison may provide a biased estimation of the counterfactual scenarios because the policy may have been implemented in one of the populations precisely because conditions had been deteriorating, or other important between-population differences in prognostic factors may have affected the outcome.

An additional challenge for nonrandomized sources of evidence is that many strategies may exert effects that extend across jurisdictional boundaries or manifest only with a considerable lag. For example, even a successful intervention might noticeably reduce the incidence of overdose only many years after being implemented. Indeed, some interventions that successfully reduced diversion of prescription opioids might, at least in theory, initially *increase* rather than decrease the number of overdose deaths, even if they reduced deaths in the long run, as the result of an initial surge in deaths among people already addicted to prescription opioids who turned to black market substitutes, whose potency is more variable. Furthermore,

some interventions may have different effects depending on the metric employed; thus, for example, distributing naloxone might reduce the number of fatal overdoses but—particularly if there were some risk compensation or other behavioral adaptation—increase the total number of overdose events. Strang and colleagues (1999), for instance, found that 6 percent of individuals in treatment for opioid addiction who were interviewed (9 of 142) reported that access to naloxone might lead them to increase their heroin dosage.

Another problem is that of nonlinear response in systems that have their own internal dynamics. For example, resale or other diversion of prescription opioids by people who had already "traded down" to cheaper black market opioids might cause others to initiate misuse of prescription opioids, others who themselves might later trade down, divert, and supply still others. This problem is illustrated by the difficulty of talking about the number of cases of an infectious disease that are prevented per vaccination as if it were a universal constant, whereas that number in fact depends on the number of other vaccinations being given and the current prevalence of the disease.

THE NEED FOR A SYSTEMS APPROACH

A complementary approach to evaluating intervention strategies implemented at the jurisdictional level in systems with lags and nonlinearities is to use some model of the system in question to project what might be expected with and without the intervention of interest. This approach has been used in a variety of contexts, including air traffic control (Bertsimas and Patterson, 1998; Long et al., 1999; Terrab and Odoni, 1993), fisheries management (Bjørndal et al., 2004; Clark, 1990; Megrey, 1988), vaccination (Goldstein et al., 2005; Kaplan et al., 2002; Medlock and Galvani, 2009), and tobacco control (IOM, 2007, 2015; Levy et al., 2005), among many other important policy domains.

The dynamics of prescription opioid misuse are complicated, particularly when one takes into account the markets for diverted and purely illegal opioids, but a simple sketch helps clarify the value of a systems approach. A typical clinical trajectory that policy changes would like to prevent starts with medically appropriate use of prescription opioids, escalates to misuse and then to OUD, and then evolves to trading down to cheaper black market opioids before manifesting in overdose. Thus, a leaky prescription drug system increases the flow of people into the state of having OUD. People tend to remain in that state for a very long time, an average of 10 to 20

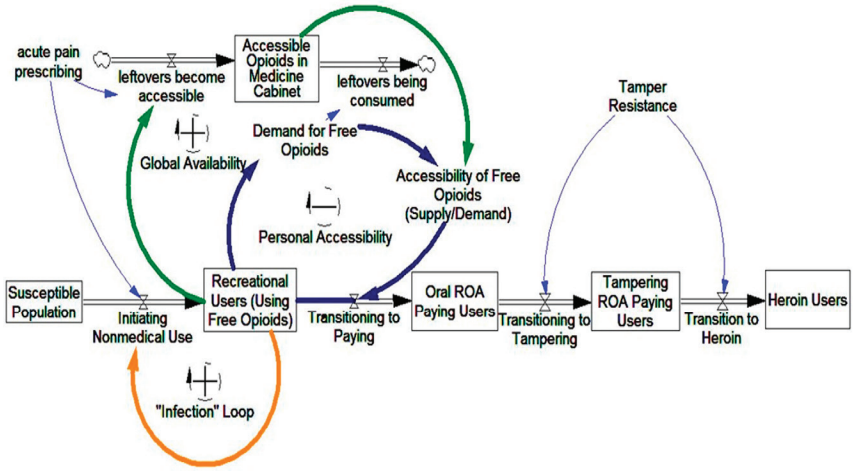

FIGURE 5-1 A systems model of the opioid misuse problem.
SOURCE: Reprinted from Wakeland et al., 2015.

years, with modest flows out of that state through overdose death, death from other causes, or permanent cessation of use.[3]

The number of overdoses per year might be roughly proportional to the number of people who currently had an active OUD, but this number would *not* be proportional to the current inflow of new people developing OUD, which is what many interventions aimed at controlling the misuse of prescription opioids would affect most directly. Those interventions would not instantly change the prevalence of OUD and hence would generally not have an immediate effect on overdose. By contrast, interventions that reduced the likelihood that an overdose would occur, or that it would be fatal, might reduce fatalities right away. A fair comparison of the effectiveness of interventions designed to reduce diversion with those designed to reduce the frequency or lethality of overdoses requires a true systems model, not just simple statistics. Wakeland and colleagues (2015) provide an example of such a systems model, reproduced in Figure 5-1.

Constructing such models is a major research endeavor in its own right, and the committee is unaware of any existing model that incorporates all of the strategies discussed in this chapter; therefore, the relative effectiveness of these strategies cannot be compared. Creating such models would

[3]More sophisticated models will have a second pool consisting of people who have temporarily ceased use but are vulnerable to relapse.

have important advantages: it would guide and strengthen surveillance and research, foster a common policy vocabulary among all agencies with decision-making authority over opioid regulation and enforcement (federal, state, and local), and facilitate the exchange of information among them. Investing in research and possible development of such a model is worthy of consideration by the U.S. Food and Drug Administration (FDA) and other agencies. In any event, since no formal systems model now exists, the committee provides an overview of the key conceptual features and implications of a systems approach (without a formal model) to identify some of the considerations that need to be taken into account in reviewing the possible impact of alternative strategies. However, empirical analysis of the various strategies reviewed in this chapter relies on the traditional statistical methods outlined in the previous section.

A Systems Approach to Opioid Misuse

The boundaries delineating governmental agencies' respective responsibilities do not always align with the real boundaries of markets or behaviors concerning OUD and resulting overdose. While the FDA's regulatory authority may give it a particular interest in reducing addiction and mortality caused by prescription opioids, the nation's overall public health interest lies in reducing addiction and mortality caused by opioids of all sorts. A person with prescription opioid–related OUD may escalate his or her opioid misuse, and an overdose leaves a grieving family wondering whether or not the person's last dose was obtained through a prescription.

Prescription and nonprescription opioids intertwine on both the demand and supply sides of the market because all opioids belong to one family of chemicals that operate on similar molecular pathways; the molecules bind to a neuroreceptor regardless of whether they are associated with a prescription. In addition, as shown in Chapter 4, the prescription opioid epidemic is interwoven with the illegal drug market. Therefore, this chapter considers policy options for reducing OUD, mortality due to opioid overdose, and other opioid-related harms among people who have ever used prescription opioids, rather than focusing exclusively on options for reducing misuse of or overdoses from prescription opioids alone.

In the economic sense of the term, all opioids are substitutes (as opposed to complements) in the same sense that oil, gas, coal, nuclear, solar, and hydro are substitute sources of energy for producing electric power. Substitutes are not identical and interchangeable; a molecule of morphine is different from a molecule of fentanyl, just as a barrel of oil differs from a ton of coal. There are distinguishable groupings within broad families of substitutes. Energy policy distinguishes fossil fuels from sources with lower carbon footprints; in this context, one can distinguish partial from com-

plete opioid agonists. But just as one cannot develop a sensible response to global warming by changing only policies toward oil, one cannot develop a sensible response to the nation's opioid problem by adjusting only policies concerning prescription opioids.

The central economic idea about substitutes is that people will tend to use more of item A and less of item B when the price of A falls relative to the price of B, where price is construed broadly to mean the total cost of obtaining and using the item. For opioids, that total cost includes not only the dollar price, but also the time and inconvenience of obtaining the drug and all relevant risks in terms of health and possible criminal justice sanctioning (Moore, 2013; Reuter and Kleiman, 1986; Rocheleau and Boyum, 1994). A related concept is substitution driven by changes in income; as people become poorer, they may substitute hamburger in place of steak and heroin in place of prescription opioids (Petry and Bickel, 1998).

As noted earlier and discussed in greater depth in Chapter 4, in the case of the opioid epidemic, one common pathway to death over the past 20 years has been becoming addicted to prescription opioids, no longer being able to sustain that habit financially, and so trading down to cheaper black market opioids before dying of an overdose or suicide. Trading down can also involve beginning to inject drugs, since that is a more efficient mode of ingesting psychoactive substances. Therefore, additional opioid-relevant public health outcomes include morbidity and mortality stemming from bloodborne infection (e.g., hepatitis C virus [HCV], HIV), both for the individuals injecting and for others (e.g., sexual partners). These outcomes remain relevant even if, for example, no prescription opioids were taken during the month preceding death due to AIDS.

Conversely, finding large amounts of a prescription opioid in the decedent's body does not imply that the person had a prescription. It is common for people who have traded down to black market drugs to retain their prescriptions for purposes of reselling those drugs on the black market. In 2016, typical street prices were $10–$30 for a 30 mg tablet of oxycodone, $5–$20 for a methadone tablet, $3–$8 for Vicodin, and $1 per mcg per hour for fentanyl patches (WSIN, 2016). Thus, diverting to the black market a prescription for two 30 mg tablets per day can produce revenues of $7,300–$21,900 over the course of 1 year. That income is tax-free and mostly pure profit because the copays for those prescriptions are typically small, as is the case for those filled through Medicaid, for example.

Thinking beyond prescription-related misuse becomes all the more important when one recognizes that the same chemicals that appear in prescription drugs are increasingly reaching users not only through diversion but also via distribution chains that are illegal from top to bottom. So even when an autopsy shows that the decedent's body contained a drug

that is available by prescription, this does not mean that the fatal dose was obtained through a prescription by the decedent or anyone else.

In particular, drug trafficking organizations increasingly use fentanyl to adulterate black market heroin and counterfeit pills that have been stamped to look like prescription drugs. This black market fentanyl is produced in the same countries—perhaps even in the same laboratories—that sell fentanyl to pharmaceutical companies that supply prescription fentanyl in lozenges and transdermal patches. Likewise, the pill presses and dyes that these firms sell to the drug trafficking organizations that press the powdered fentanyl into counterfeit tablets of opioid painkillers (e.g., oxycodone) and benzodiazepines in North America are the same as those used by other firms to make the tablets sold to the pharmaceutical companies (DEA, 2016a, p. 7). Thus, not only is black market fentanyl the same chemical compound as pharmaceutical fentanyl, but it may even have the same provenance. That in turn means there is no practical way to count precisely how many overdose deaths are due to prescription opioids even in the narrow sense that the proximate cause of death was a dose that had been prescribed.

It is worth noting that black market fentanyl is a relatively recent phenomenon. Until 2014, the number of fentanyl exhibits reported by the National Forensic Laboratory Information System (NFLIS) remained below 1,000, except for a spike to 1,594 in 2006, when a single clandestine lab in Toluca, Mexico, fueled the fentanyl outbreak. The number of exhibits soared in 2014, accompanied by sharp increases in deaths despite no comparable increase in prescribing (Gladden et al., 2016), and reached 13,002 in 2015 (DEA, 2016a).

Price data suggest this trend may continue to intensify. The U.S. Drug Enforcement Administration (DEA) reports that traffickers can buy powdered fentanyl from suppliers for a few thousand dollars per kilogram when buying in bulk (e.g., 20 or 40 kg lots) (DEA, 2016a). Since a counterfeit tablet contains only about 0.9–6.9 mg of fentanyl, the active ingredient can cost high-level traffickers just a penny or two for a pill that wholesales for $6.50 and retails on the street for $10–$20. By comparison, over the past decade, black market retail prices were roughly $500 for a gram of powder 30 percent heroin by weight. So while black market heroin has been much less expensive than (real) diverted prescription opioids, fentanyl is now much less expensive per morphine-equivalent dose than has been the case for black market heroin.

Drug markets are often characterized by substantial price increases as one moves down the distribution chain, but in the case of opioids these increases can be comparatively extreme (in some locations) (Caulkins et al., 2016), which suggests that the current price structure is unstable (Caulkins et al., 2016; Reuter and Kleiman, 1986). The situation is unprecedented, so it is difficult to know how it will develop, but it would not be entirely

surprising if the market for counterfeit prescription pills were to undermine the market for real prescription pills. Should this occur, it might reduce the prescription drug overdose problem in its narrowest form, but it would not decrease the total number of opioid-related deaths.

The desire to root opioid policy making in an integrated systems perspective has three corollaries that bear discussion: (1) an ongoing research program is needed to continuously improve understanding of how the various opioids in all their combinations are used and misused in fact, as opposed to just as intended; (2) investment is warranted in an underlying data infrastructure, as opposed to piecemeal efforts local to particular considerations; and (3) the capability to monitor, understand, and model that behavior can be shared among all agencies that have decision-making authority over opioid policy (federal, state, and local), as not all agencies can or should invest in model building within their own silos.

Need for a Formal Quantitative Model

Ideally, an integrated framework for regulatory decision making, discussed further in Chapter 6, would rely on an explicit model of the opioid ecosystem. This is because, as discussed above, decisions made about complex systems with endogenous feedback can be myopic in the absence of a formal model. It would be sensible for the FDA, in collaboration with the U.S. Centers for Disease Control and Prevention (CDC), to commission a panel of experts to develop a quantitative model of prescribed and illicit opioid use and distribution and establish the data infrastructure needed to support and apply that model. With such a model, the FDA and other government agencies could predict the effects of changes in policy or other changes in the opioid ecosystem.

If a model capturing the relevant outcomes in the opioid ecosystem were to be developed, that effort would not be accomplished overnight. The process would take time, and important decisions regarding opioids would have to be made in the interim. For now, then, agencies will need to integrate and weigh data from multiple sources and consider the multiple complex feedback processes without the benefit of a formal model. In Chapter 6, the committee outlines some key attributes of any sound framework for decision making involving opioid regulation. At the very least, these attributes will help in making judgments transparent, highlighting areas of uncertainty and the nature of the qualitative judgments that were made.

In sum, when evaluating past policies and estimating the effects of future interventions, it is necessary to use a comprehensive approach that takes full account of the interactions between prescription and black market opioids. Ideally, this approach could take the form of a quantitative model,

although developing such a model would itself be an ambitious research undertaking.

Categorizing Strategies for Addressing the Opioid Epidemic

In traditional policy discourse relating to use of addictive drugs, analysts typically categorize available strategies (including specific policies and interventions) as aiming either to (1) reduce supply or the availability of the addictive drug, (2) reduce demand for the addictive drug, or (3) reduce the likelihood that use of the drug will have *harmful consequences* (see Box 5-1 for a list of strategies discussed in this chapter). Like all typologies, this one presents challenges of classification, but it will serve well enough in the present context by enabling the committee to summarize the evidence on the effectiveness of the wide range of policies and interventions now being deployed to address the opioid epidemic.

Several preliminary observations are necessary to avoid misunderstanding. First, each strategy has its own costs and entails trade-offs. Obviously, one of the key trade-offs at the heart of this report is the tension between reducing the supply of opioids to reduce harms associated with their misuse and making opioids available to provide pain relief for individuals who have no satisfactory alternative. Second, strategies cannot be fully evaluated in isolation from one another. Sometimes they are seen, mistakenly, to be in tension with one another, as in the example that making naloxone available to prevent a fatal overdose (harm reduction) can counteract policies aiming to discourage opioid misuse. In other cases, different strategies may have additive effects or even potentiate one another, such that each is stronger and more effective than it otherwise would have been; for example, some observers have pointed out that one way in which some tobacco control interventions are effective is through synergy of multiple intervention components (Green and Kreuter, 2010). In still other cases, successful implementation of some strategies (and the effectiveness of a jurisdiction's overall approach) may require that strategies be implemented in tandem with one another. A good example is that a strictly enforced supply reduction strategy may cause substantial harms to individuals with OUD (and to society) unless treatment opportunities are aggressively increased.

Finally, it is important to note that very little research has addressed the relationship among strategies. Thus, strategies A, B, and C may each have a small effect, but what would happen if they were all implemented simultaneously and vigorously is unknown. This limitation is critically important in the context of this report. The data reviewed in this chapter suggest that many strategies might each have a small effect in reducing opioid misuse and related harms, but simultaneous and vigorous implementation of all of

BOX 5-1
Strategies for Addressing the Opioid Epidemic

Restricting Supply and Reducing Demand

Regulating the approved product (e.g., abuse-deterrent formulations)

Restricting lawful access
- Scheduling
- Preventing and penalizing diversion
- Drug take-back programs
- Other state and local policies restricting access

Influencing prescribing practices
- Provider education
- Prescribing guidelines
- Electronic medical records and decision support
- Insurer policies
- Prescription drug monitoring programs

Patient and public education

Increasing access to and utilization of medical treatment for opioid use disorder

Reducing Harmful Consequences

Use of naloxone to reverse overdose

Reducing disease transmission
- Syringe exchange
- Supervised injection facilities
- Drug checking
- Behavioral interventions

these strategies would still leave a huge reservoir of people misusing and addicted to opioids for years if not decades to come.

Another important point to make at the outset is that the strategies reviewed in this chapter have been adopted and implemented by a wide variety of public and private entities at the national, state, and local levels. The literature reviewed in this chapter demonstrates that there is currently no national strategy. Nor is there a lead agency responsible for crafting and implementing such a strategy or integrating efforts across levels of government (local, state, or national). While formulating a national strategy and

suggesting which agencies should implement it are beyond this committee's charge, this approach is worthy of consideration.

STRATEGIES FOR RESTRICTING SUPPLY

As discussed previously, the responsible clinical use of prescription opioids can be a powerful tool for pain management under some circumstances. The primary area of continuing concern relates to long-term use of opioids to alleviate chronic noncancer pain. A constellation of policies related to lawful access and judicious clinical decision making can help ensure that opioid-related harms are minimized while providing access to these drugs for patients with appropriate clinical indications. This section reviews such supply-side strategies, including regulation of legal access to opioids for legally approved uses. The next section addresses legal regulations and professional policies aimed at reducing lawful access by discouraging unnecessary opioid prescribing or promoting safe prescribing practices. Although both types of strategies aim to control access to opioids, the former focuses on legal restrictions on distribution, while the latter focuses on efforts to influence the decisions of health care providers as the gatekeepers to lawful access by patients.

Regulating the Approved Product: Abuse-Deterrent Opioids as a Case Study

The FDA's decision to approve a new drug follows a rigorous review of product- and indication-specific benefits and risks. In the case of opioids, a drug is reviewed for its ability to provide analgesia, weighed against the potential risk of adverse effects (e.g., dependence, addiction, nausea and other side effects to the patient). Often, the benefit calculus includes product-specific features, such as high-dose extended-release (ER) formulations for pain that is long-lasting and especially severe. The drug is then ultimately approved for use in a specific population for a specific clinical indication, based on the totality of evidence considered by the FDA for that particular population and indication (see Chapter 6 for a suggested approach for FDA decision making on and post-market monitoring of opioids).

However, one consequence of early ER opioid formulations was unexpectedly high misuse. In response, a new product feature—designated abuse-deterrent formulations (ADFs)—has been a focus of FDA policy for addressing the opioid epidemic. ADFs are opioid medications that have been reformulated to reduce the possibility or the likelihood that the medication will be "abused." While users may misuse opioid medications by swallowing pills whole, the misuse often involves manipulation of the pills.

For example, a user may crush the pill and then swallow, snort, or smoke it, or dissolve and inject it. Many ADFs are designed to discourage manipulation either by making the pill difficult to manipulate or by rendering it ineffective or unpleasant once manipulated. Abuse-deterrent technologies include the following (FDA, 2015a):

- Physical designs that are crush/extraction-resistant—For example, OxyContin, a form of ER oxycodone, incorporates a hard polymer matrix that makes crushing or chewing the pill difficult and that transforms into a viscous gel when dissolved in water (which prevents extraction). Formulations that integrate such physical barriers often are referred to as "tamper-resistant opioids."
- Chemical barriers that prevent extraction of the opioid with solvents.
- Agonist/antagonist combinations that interfere with the euphoria associated with use of opioids—These ADFs include coformulations of opioids with sequestered naltrexone or naloxone. Inadequate pain relief and even acute opioid withdrawal are concerns with the use of these formulations.
- Aversion formulations that include a substance that produces an unpleasant effect if the medication is misused.
- Delivery systems that are resistant to "abuse," such as subcutaneous implants.
- New molecular entities and prodrugs that have novel effects, such as becoming active only when the pill reaches the gastrointestinal (GI) tract.
- Combinations of these technologies.

The development of ADFs is an evolving area of research, and introduction and regulatory consideration of additional methods are expected.

An industry-sponsored review by Michna and colleagues (2014) found that, relative to placebo, ADFs and non-ADFs were comparably effective and safe for individual patients with noncancer pain. However, it is important to understand that none of the available formulations is designed to prevent all types of misuse—for example, excessive oral ingestion is not prevented by an ADF designed to limit intravenous misuse. Interestingly, currently marketed ADF products do not claim on their labels that they are abuse-deterrent; rather, information on the label describes the studies that suggest abuse deterrence to inform prescribers. The reason is that there is no long-term evidence on the products' real-world impact on reducing misuse, which the FDA would require for such a claim. Indeed, an FDA advisory committee recently voted to remove a particular formulation of oxycodone hydrochloride from the market, citing unexpectedly high poten-

tial for intravenous misuse (and associated public health harms) despite attempts to render the drug resistant to insufflation (FDA, 2017a). Thus, while ADFs represent a potentially promising area of opioid drug development, it remains aspirational.

For this reason, the FDA requires that manufacturers of all currently approved ADF products gather data demonstrating the magnitude of the products' effect on real-world misuse relative to existing comparator products and the broader opioid ecosystem (FDA, 2015a). Multiple factors will determine the impact of any given ADF on public health through reduced prescription opioid misuse, addiction, and subsequent misuse of black market opioids. These include prescribing uptake and resulting market share, whether substitutions are made for other comparably harmful prescribed or illicit opioids, and whether ADFs are delivered to those patients with the highest risks of misuse. ADFs may do little to prevent misuse by determined individuals (or actions by a minority of dishonest prescribers), but may play an important role in preventing escalation to misuse. If evidence showed that abuse-deterrent opioids presented truly effective barriers to misuse and that patients with high risk of misuse or diversion were identifiable, one can envision clinical guidelines recommending the prescription of these formulations for such high-risk patients. It remains to be seen whether the FDA's post-market research requirements for opioid manufacturers (see Annex 6-1 in Chapter 6), along with the ADF-specific data gathering mentioned previously, will eventually serve this purpose and reduce the misuse liability of individuals being prescribed opioids.

Another important question is whether the existence of relatively cheap heroin or fentanyl should be taken into account in deciding whether to phase out non-abuse-deterrent opioids, as has been strongly advocated by many analysts. While Severtson and colleagues (2013) report reductions in OxyContin-associated misuse and diversion following introduction of an ADF reformulation, Cicero and colleagues (2012) observe that indicators of fentanyl, hydromorphone, and heroin use went up during roughly the same period. Coplan and colleagues (2013) raise similar concerns based on National Poison System data, as do Cassidy and colleagues (2014) using data on 232,874 individuals assessed for substance use disorder treatment in 2008–2011. Coplan and colleagues (2016) examined the harms associated with reformulated OxyContin compared with other comparator prescription opioids, reporting a noticeable relative decrease for OxyContin, although this study did not specifically examine collateral outcomes such as potential transition to heroin and related harms. A recent state-by-state analysis suggests that the introduction of ADF OxyContin in 2010 resulted in reduced OxyContin misuse, but with a trade-off of increased heroin-related deaths and evidence of an overall trend of increased opioid overdose deaths (Alpert et al., 2017).

Black market exchange could play an additional role for individuals misusing prescription opioids whose access to non-abuse-deterrent formulations was replaced with ADFs. Even if such a person did not know how to defeat the abuse-deterrent technology, he or she could still sell the ADF drugs for cash and use the cash to buy heroin or other black market opioids. ADFs such as the new formulations of OxyContin sell for a moderate discount compared with the non-abuse-deterrent formulations,[4] but markets for them nonetheless still exist.

There is also at least the theoretical possibility of "boomerang" effects. Andrew Kolodny, chief medical officer at Phoenix House, has echoed concerns in the field that the abuse-deterrent information on the label might lull some doctors into thinking that these formulations are not misusable and/or are not addictive and so be less cautious in their prescribing (Arlotta, 2016). Also, some attempts to defeat abuse-deterrent properties could create uncertainty as to the actual dose ingested, which might in certain circumstances increase the risk of overdose. Such perverse effects do not necessarily have the potential to outweigh the beneficial effects of ADFs, but that they are readily imagined does underscore the point that no clinical trial finding an ADF to be safe and effective when the unit of analysis is the individual patient necessarily indicates that the ADF will have a net positive effect on public health. In summary, although ADFs of opioids would be expected to reduce some opioid-related harms, it is necessary to consider whether these benefits are offset by their potential effect on movement to illicit markets (either for diverted non-ADF prescription opioids or for illegal drugs such as heroin) among people who misuse opioids or have OUD.

Given the complexity discussed above (and also in Chapter 4), the committee views the evidence surrounding ADFs as not compelling enough to warrant a recommendation at this time. The potential for benefit remains counterbalanced by recent examples of unexpected harm, and ongoing studies will help to clarify the optimal role for ADFs as a strategy for reducing misuse of prescription opioids. The FDA's current cautious approach appears to be well advised. Further discussion of ADFs in the context of the FDA's regulatory oversight of prescription opioids can be found in Chapter 6.

Regulating/Restricting Conditions of Lawful Access to Approved Drugs

Once the FDA has approved an opioid formulation (or other controlled substance) for therapeutic use, federal and state agencies have the authority to control the amount, storage, and distribution of the drug at every stage

[4]Severston and colleagues (2013) describe prices that are 22 percent lower. RADARS System Technical Report, 2014-Q2 describes declines closer to 33 percent.

in the course of commerce. One key purpose of these restrictions is to limit access to and use of the drug to the amounts and indications for which it was lawfully prescribed and to curtail its distribution outside of lawful channels of commerce. This section reviews evidence regarding the effects of the federal and state controlled substances acts and their enforcement on access to approved drugs (i.e., in deterring diversion) and, ultimately, on use (either legal or illegal) of these drugs and associated harms.[5] It should be noted that curtailing illegal production and distribution of unapproved/illegal drugs (i.e., heroin and other Schedule I drugs and illegally manufactured versions of legally available drugs) lies outside the scope of this study (see the committee's statement of task in Box 1-1 in Chapter 1). The discussion here also encompasses so-called take-back programs that facilitate the return or destruction of lawfully obtained but unneeded medication, as well as additional state and local restrictions on amounts that can be dispensed or prescribed within specific periods. Related tools include licensing and limiting the class of persons or entities authorized to manufacture, ship, distribute, dispense, and prescribe the approved drugs. The DEA license confers a considerable benefit and provides a source of leverage for regulation and enforcement. Restricting the pool of physicians and other practitioners who are licensed/authorized to prescribe opioids under state or federal law is discussed in the next section. It should be emphasized that all of these efforts to control legitimate access will involve complex policy choices because they may trade off reduced relief from pain and be accompanied by illegal access/use.

"Scheduling" Drugs Under the Controlled Substances Act

In the United States, "controlling" a drug with a "potential for abuse" means placing it within one of the five schedules defined by the Controlled Substances Act (CSA) or shifting it between schedules. (Schedule I is for substances with no "accepted medical use,"[6] while Schedules II–V apply to substances with recognized medical value,

[5]Enforcement and punishment strategies for curtailing illegal production and distribution of unapproved/illegal drugs (i.e., heroin and other Schedule I drugs and illegally manufactured versions of legally available drugs) lies outside the scope of this study. However, see the National Research Council report *Informing America's Policy on Illegal Drugs: What We Don't Know Keeps Hurting Us* (NRC, 2001).

[6]This section addresses restrictions on drugs that have been approved by appropriate authorities for medical use, i.e., that are not allowed for nonmedical use. Different policy challenges arise in the design and implementation of regulatory schemes that control access to and use of a drug for nonmedical purposes. Prominent examples are alcohol and marijuana. It is possible to have separate legal regimes for medical and nonmedical uses. All of these issues are beyond the scope of this report.

depending on their potential for abuse. See Chapter 6 for a more specific discussion of the CSA as it relates to opioid regulation.) A moderately large empirical literature exists on the effects of "scheduling" or "rescheduling" a substance under the CSA. This section also refers to studies regarding analogous actions by regulatory authorities in other countries, but the names and particular definitions of the categories differ. Most of these studies are simple "before and after" or interrupted time series comparisons, sometimes with one or multiple outcome indicators (e.g., calls to poison centers).

Scheduling of hydrocodone Perhaps the single most relevant example of opioid rescheduling is the DEA's moving hydrocodone products from Schedule III to Schedule II on October 6, 2014,[7] but evidence concerning this event is still emerging. Early studies document clear reductions in prescribing of hydrocodone and increases in prescribing of other opioids, but none examined effects on health outcomes such as death or OUD on the one hand or deficits in pain control on the other.

Oehler and colleagues (2016), for example, document that among emergency department patients in one academic tertiary hospital who received a pain-related prescription, the proportion receiving a prescription for hydrocodone-containing products fell from 58.1 to 13.2 percent following the rescheduling. Seago and colleagues (2016) examined the effects on dispensing by 14 pharmacies in central Texas. They found pronounced reductions in prescriptions for hydrocodone/acetaminophen combinations offset by sharp increases in prescriptions for alternative analgesics, including tramadol and codeine/acetaminophen, leaving total morphine equivalents dispensed after rescheduling only slightly below what they were before rescheduling. The authors conclude that "this study demonstrates several shortcomings of the federal rescheduling of hydrocodone products" (p. 270). However, the ultimate goal of scheduling drugs under the CSA is to reduce misuse and diversion and the addiction, deaths, and other adverse effects associated with misuse. Seago and colleagues do not assess effects on any of those outcomes. Similarly, Haynes and colleagues (2016) report reductions in hydrocodone exposures reported to Texas poison control centers, but increases in mentions of codeine, oxycodone, and tramadol that may reflect substitution. However, this study used no control group, and opioid poisonings may have been increasing for other reasons as well.

Scheduling of other substances in the United States There are other reports of sharp declines in single drug–related indicators after a drug's classification as a controlled substance. Loeffler and Craig (2013) note an 89 percent

[7] 21 C.F.R. Part 1308.

decline in calls concerning bath salts in the United States after the DEA's October 11, 2011, decision to "control" the substance under the CSA. Likewise, Stogner and colleagues (2012) report that self-reported current and past-year use of salvia fell after Florida classified it as a Schedule I drug on July 1, 2008. Spiller and colleagues' (2010) study of the effects of the scheduling of tramadol by Kentucky and Arkansas is particularly relevant, since it involves an opioid and takes advantage of comparison with two control states (Ohio and West Virginia) that did not schedule the drug. Poison control center cases mentioning tramadol increased in all four states before the scheduling policy intervention, and thereafter continued to increase in the control states but fell in Kentucky and Arkansas.

An older example concerns paregoric. Lerner (1966) documents a geometric rise in the number of paregoric-related arrests in Detroit from 0 in 1955 to 713 in 1963. Michigan ended nonprescription sales of the drug in April 1964, whereupon arrests collapsed, falling to 10 by 1965.

Restrictions on precursor and essential chemicals A related literature explores the effect of adding legal restrictions on precursor and essential chemicals used in the production of controlled substances. McKetin and colleagues (2011) review 10 studies of 13 regulations (plus two enforcement operations) directed at precursors for methamphetamine production in the North American market. Most of these studies found reductions in methamphetamine-related outcomes (of 12 to 77 percent), with no evidence of shifts to other types of drug use; the exceptions were instances in which substitutes for the restricted chemicals were readily available. However, the authors of one of the studies (Dobkin and Nicosia, 2009), while acknowledging short-term effects of that size, stress the impermanence of the reductions as other methods of production were developed over the longer term.

Cunningham and Liu, the lead authors of the majority of the papers reviewed by McKetin and colleagues (2011), also studied regulation of chemicals essential to the production of cocaine. They again report evidence of reductions in various indicators of production and consumption (Cunningham et al., 2015, 2016). In particular, they attribute the dramatic reduction in U.S. cocaine consumption between 2006 and 2010 to regulation of sodium permanganate implemented on December 18, 2006. That decline is significant because it is among the largest in an illegal drug market in recorded history (Caulkins et al., 2014). Thus, key regulatory tools of controlled substance legislation—especially tightening controls (in particular through Schedule II of the CSA) and banning precursor substances to prevent illicit manufacture—can be effective in accomplishing their purposes.

Preventing and Penalizing Diversion of Controlled Drugs

A key element of a regulatory system for controlling dangerous drugs is preventing and penalizing diversion of the drugs from the channels of distribution that have been authorized for medical use. Prescription drugs are diverted to nonmedical use in myriad ways, but it is useful to distinguish three categories: (1) diversion *before* a prescription has been filled (e.g., theft from production facilities or retail pharmacies), (2) diversion *via* the filling of a prescription, and (3) diversion *after* a prescription has been filled.

While the first category undoubtedly occurs, it appears to be of quite modest scale. As noted in Chapter 4, the DEA (2016b, p. 34) reports that in recent years, 12–17 billion dosage units of opioid narcotics were dispensed at the retail level. By contrast, the DEA (2016b, p. 35) reports that in the entire country in 2015, only 9.1 million dosage units were lost to robbery of pharmacies or otherwise "lost in transit." Those are very small numbers relative to the 12–17 billion dosage units disbursed at the retail level.

By contrast, the third category, diversion *after* a prescription has been filled, is much more common. One recent survey found that about one in five adults with an opioid prescription self-reported having shared those opioids with another person, most frequently for the purpose of helping to manage pain (Kennedy-Hendricks et al., 2016). However, such individual-level actions generally are not the concern of federal law enforcement, which focuses on misbehavior by DEA registrants and large-scale diversion by industry (Sapienza, 2006).[8]

Some diversion within the second category, diversion *via* the filling of a prescription, also falls outside the priorities of federal law enforcement—notably diversion that is driven by the patient (e.g., doctor shopping), facilitated by at most inattention or carelessness by the prescriber but not with criminal intent. The portion of this diversion category that is more likely to attract the attention of federal law enforcement is that which involves the knowing misbehavior of DEA registrants, such as with so-called pill mills.

Some of these actions are civil, not criminal. For example, the DEA has pursued action against CVS in multiple states for filling forged prescriptions or knowingly dispensing to individuals without a legitimate medical need (DOJ, 2016; Wang, 2016). Such action has led to agreements to pay fines in Massachusetts ($3.5 million) and Maryland ($8 million), among other states. The sanction in many DEA cases against practitioners is simply revocation of prescribing privileges, although some of those revocations stem from personal circumstances and errors, such as a practitioner who develops an OUD and is prescribing to him- or herself, not the more egre-

[8]The actions of organized criminal groups also apply here, but they generally are not involved in prescribing.

gious cases. The largest criminal case involving prescription drug diversion, Operation Piluted, led to 280 arrests, including 22 doctors and pharmacists, for illegally prescribing and distributing controlled substances, including oxycodone and hydrocodone (DEA, 2015a). One of the doctors charged is accused of selling prescriptions for $500 each, which subsequently yielded profit from sale of the pills on the black market (e.g., selling 100 pills from a prescription at $30 each would gross $3,000).

In a series of investigative journalism stories, *The New York Times* reporter Katie Thomas (2014a,b, 2015, 2016a,b) documented the criminal activity of InSys Therapeutics. Employees were indicted for offering bribes and kickbacks to doctors and nurses in exchange for their prescribing more of the company's fentanyl product, Subsys, and several of the company's former executives have been charged under the Racketeer Influenced and Corrupt Organizations (RICO) Act. Two doctors who were paid more than $100,000 in "speaking fees" in 2014 were each responsible for prescriptions that generated more than $1 million in Medicare reimbursements.

Drug Take-Back Programs

The DEA, among other agencies and organizations, also tries to reduce the supply of prescription opioids by facilitating the return of unused medications through drug take-back programs. Typically, these are ad hoc or occasional events that allow individuals with unused medications to bring them in to be disposed of properly. Perhaps the best-known is an annual program sponsored by the DEA since 2010 (Stewart et al., 2015).

These programs are popular, and the literature on them is generally favorable, although all but devoid of high-quality evidence concerning effects on final outcomes, such as overdose (Haegerich et al., 2014). Rather, the literature finds that the programs raise awareness (e.g., Yanovitzky, 2016) and that substantial quantities of drugs are brought in for collection (DEA, 2015b; Stewart et al., 2015)—for example, 69.6 million unit doses of medication (of all kinds) brought back in to Operation Medicine Drop in North Carolina (Fleming et al., 2016) over 4 years. However, while the quantities may be substantial in absolute terms, they represent a very small proportion of the total dispensed. Egan and colleagues (2017), for instance, found that over 4 weeks in one community, 21 million units of controlled medication were dispensed, but only 21 thousand were collected.

Furthermore, evaluations of such programs generally cannot assess directly effects on such outcomes as OUD and mortality. Moreover, the reduction in harm may be even smaller than the reduction in volume of medications in circulation if the doses that are voluntarily surrendered are not the ones that would have caused OUD and death had they not been

collected. One might speculate that people struggling with OUD or selling pills on the black market would be among those least likely to surrender pills voluntarily.

On the other hand, it is important to note that asking whether take-back programs are an effective way to ameliorate problems with prescription opioids is a very narrow framing. Opioids are one of many categories of medications, and the literature is concerned as much with environmental harms from improper disposal as with harms from nonmedical use.[9]

Despite the effort invested in occasional take-back programs, proper disposal of unused medications is relatively rare in the United States (Glassmeyer et al., 2009; Law et al., 2015; Maeng et al., 2016), and surveys find that many prescribed drugs are not used (e.g., Kennedy-Hendricks et al., 2016). Maughan and colleagues (2016) found that this was the case for a majority of opioid pills dispensed to patients who had undergone surgical tooth extraction. Likewise, Harris and colleagues (2013) found that one-third of patients prescribed opioids after dermatology surgery did not fill their prescriptions, and 86 percent of those who did had leftover pills. And Welham and colleagues (2015) found that among opioid prescriptions returned for disposal, the majority of the dispensed amount was unused. A large proportion of respondents report keeping medications around, even when they are not needed, and then disposing of them improperly, whether in the trash or down the drain.

Reducing misuse may not be sufficient motivation for members of the public at large to go much out of their way to return drugs; in one study, far fewer participants were motivated by concern about accidental poisoning (14 percent) than by environmental considerations (45 percent) or a simple desire to clean house (68 percent) (Gray and Hagemeier, 2012). The literatures on other environmental problems conclude that getting the public to do what is right (e.g., to recycle) depends on making it very convenient. The United States has largely failed in this regard with respect to disposing of unused medications. Once-per-year take-back programs do not meet that test, and the patchwork of state, local, and pharmacy-specific programs may confuse and deter the public.

By contrast, many peer nations have simple systems whereby most people can return any drug to any pharmacy on any day of the year. Austra-

[9]There can be some tension between these objectives. While both interests agree that the first-best outcome is for unused medications to be returned to pharmacies or other institutions that can dispose of them properly, that is the exception, not the norm, and there can be disagreement about what is the best fallback. Some who are concerned about misuse urge that leftover drugs be flushed down the toilet, but that is arguably the worst option from an environmental perspective because sewage treatment plants seldom remove medications from water, and those concerned about environmental consequences may prefer that leftover drugs be disposed of in the trash (Daughton, 2007).

lia's Return Unwanted Medicines program gets high marks in this regard, as do the programs in several of Canada's provinces, including British Columbia's Medications Return Program (Daughton, 2003). Glassmeyer and colleagues (2009) report that many countries in Europe offer a similar service. Sometimes these programs are funded by taxpayers, sometimes by the pharmaceutical industry, and sometimes by a mix of the two. Regardless of who pays, the basic idea of disposing of unwanted materials by operating the standard distribution system backward has many advantages and is a cornerstone of reverse logistics. Box 5-2 provides further detail on one example of a national-level take-back program. It is also important to note that many unused medications are in institutions, such as nursing homes, so ensuring that take-back programs are available to them, not just individual consumers, is important.

Ironically, both environmental and drug control laws make implementing convenient drug take-back programs challenging in the United States (Glassmeyer, 2009). The Resource Conservation and Recovery Act exempts household hazardous wastes from many regulations, but when they are

BOX 5-2
An Example of a National Drug Take-Back Program: France's Cyclamed

Cyclamed is a nonprofit organization in France tasked with collecting and disposing of unused drugs. It began operating in 1993, originally focusing on the collection of waste packaging materials and expanding in 2007 following passage of a law requiring pharmacists to collect unused drugs. Cyclamed is funded entirely by the pharmaceutical industry through a tax on boxes of medication distributed (€0.0022 per box). A network of more than 22,000 pharmacies helps recover drugs from French households, supported by a robust communication campaign aimed at both providers and the general public with the tagline, "Medicinal drugs are useful, let's not make them harmful."

Research on public awareness of the program has found that three-quarters of French people return some amount of unused medication, with 70 percent of that number claiming to "always" do so. As a result, in 2014 more than 15,000 metric tons of waste (including both packaging and medication) was processed and, when necessary, incinerated, resulting in the recovery of energy sufficient to power 7,000 homes for 1 year according to Cyclamed's estimates. Through its partnership with industry, the program aims to refine its efficiency and improve uptake, and thereby maximize the return on investment to the benefit of all stakeholders and the public.

SOURCE: Cyclamed, 2014.

collected, they are regulated. So it is perfectly legal for 1,000 individual consumers to dispose of their unused drugs in the worst possible manner, but if an organization collects those unused drugs and disposes of them in a much better but not ideal way, the organization performing that service may run afoul of the law.

Historically, an even greater problem was a requirement of the CSA that scheduled drugs be under the control of law enforcement. Thus, a pharmacy could run afoul of the CSA if it allowed consumers to bring back opioids at any time unless law enforcement personnel were present (Glassmeyer et al., 2009). On September 9, 2014, the DEA published new guidelines allowing certain DEA registrants to become authorized collectors of returned controlled medications (DEA, 2014), although it is unclear whether full advantage is being taken of that new flexibility.

Certainly some organizations find ways to overcome the obstacles and create permanent drop-box options (e.g., Gray et al., 2015), and the committee is not expert in either the legal challenges or logistical practicalities of such programs. However, the advantages of allowing consumers to return medications on any day of the year to any of many locations they visit regularly (e.g., all pharmacies) are clear. As one example of early success, a U.S. pharmacy chain reports that the first year of a program establishing secure dropboxes for unwanted medication (in 600 of its pharmacies across 44 states) has resulted in the collection of 72 tons of medication (Walgreens, 2017).

Education for patients as to why safe disposal is important also is needed. Kennedy-Hendricks and colleagues (2016) report that almost half of survey respondents who were prescribed opioids said they did not recall receiving any instructions regarding safe storage or disposal.

The available evidence suggests that drug take-back programs in the United States can increase awareness about the safe disposal or return of many unused drugs, but effects of these programs on such downstream outcomes as diversion and overdose are unknown. As noted, moreover, many drug take-back programs in the United States are once-per-year events, and the patchwork of state, local, and pharmacy-specific programs may confuse the public. Nevertheless, international examples and the recent success of a year-round disposal program at one pharmacy chain support policies expanding such programs to reduce the amount of unused opioids in the community. **The committee recommends that states convene a public–private partnership to implement drug take-back programs allowing individuals to return drugs to any pharmacy on any day of the year, rather than relying on occasional take-back events (Recommendation 5-1).**

State and Local Policies Restricting Access

States vary widely in rates of prescribing opioids (e.g., Zerzan et al., 2006), and not surprisingly, evidence indicates that such policy interventions as mandating coverage and reimbursement can affect prescribing of pharmaceuticals generally (Green et al., 2010). There is, after all, a long history of published concern that misinformed and exaggerated fears about liability related to misuse of and addiction to opioids lead regulators to stifle the prescribing of these medications for patients who need them for pain relief (e.g., Hill, 1996). What is less clear is whether one can infer from the variation among states or other evidence whether particular state policies are effective at reducing diversion and misuse of opioids without adversely impacting their availability for pain control. Meara and colleagues (2016), for example, find no association over a 7-year period between opioid-related outcomes in Medicare administrative data and states' adoption of controlled substance laws of the sort described further below.

Haegerich and colleagues (2014) provide a useful review of English-language MEDLINE articles in this literature. Unfortunately, they conclude that the available empirical studies are generally of low quality, and that the outcomes studied are often intermediate, such as prescribing practices, and not final, such as overdose. The largest number of studies uncovered pertained to prescription drug monitoring programs (PDMPs), naloxone, and clinical guidelines, all of which are addressed separately in this chapter; the others are briefly discussed here.

Haegerich and colleagues describe the literature evaluating state policy actions pertaining to regulation of pain clinics (which when they are sources of large numbers of prescriptions may be referred to as "pill mills") and doctor shopping as "extremely limited" (Haegerich et al., 2014). The pain clinic laws coincide with reductions in the number of clinics and the supply of drugs, but the nature of the evidence is weak. Florida is a special case, discussed further below. Studies of doctor shopping interventions are no better in terms of enabling causal inference concerning health outcomes.

One might say the literature documents that these policies exist and have been implemented, and in a dog-not-barking sense, infer that they can be implemented without resulting in obvious catastrophic failures. Furthermore, there are clear logic models for why one might expect these policies to have some beneficial effect. However, these studies are unconvincing if one adheres to the standards of scientific skepticism and disbelieves that interventions have any bottom-line effect unless clear evidence from high-quality empirical studies demonstrates this to be the case. A Maine law that went into effect January 1, 2017, for example, limits prescriptions for opioids or opioid-containing medications to 100 morphine milligram equivalents (MME) per day. In addition, the law limits the number of

opioid pills that can be prescribed to patients (except in cases of inpatient, cancer-related, palliative, and end-of-life care, as well as treatment for substance use disorder) to no more than a 7- and 30-day supply for acute and chronic pain, respectively (Traynor, 2016). In Massachusetts, a new law places a 7-day supply limit on first-time opioid prescriptions for adults and a 7-day limit at any time for minors.[10] Yet it remains to be seen what impact these types of restrictions will have on curbing opioid-related harms, particularly for individuals that do not have OUD.

One particular case study merits discussion: Florida's experience circa 2010–2012. Multiple policy interventions were being implemented simultaneously at that time, so it is impossible to use this case study as evidence concerning any one of them. Nonetheless, the changes in adverse outcomes were so abrupt both in absolute terms and relative to other states that it appears highly plausible that some combination of those interventions was responsible for the changes, and hence for averting thousands of premature deaths (Chang et al., 2016; Gau and Brooke, 2016; Johnson et al., 2014; Meinhofer, 2016; Rutkow et al., 2015; Surratt et al., 2014). The interventions were predominantly on the supply side, including closing approximately 600 pain clinics, revoking medical licenses and/or DEA certificates of registration, and placing restrictions on physicians dispensing (as opposed to prescribing) Schedule II–IV controlled substances.[11] A PDMP was implemented about 1 year later. The law enforcement component ("Operation Pill Nation") was led by the DEA but heavily involved state and local law enforcement as well, and targeted not only providers, pain clinics, and pharmacies but also four wholesale distributors.

Meinhofer (2016) shows that these supply reduction measures more than tripled street prices for oxycodone and sharply reduced oxycodone-related mortality and hospitalization with apparently minimal spillover effects on other states, suppliers, or drugs—the only exception being some substitution of heroin, which was small relative to the reductions in oxycodone use. She observes that in the years preceding the operation, 2007–2010, Florida's oxycodone supply per capita had risen from close to the national average to quadruple the national average. After the intervention, it fell back to the national average. Consumption of various substitutes never departed appreciably from national averages, and no other state experienced a spike in oxycodone supply even close to the same magnitude as that experienced in Florida. The effects were dramatic, with the time trajectory of oxycodone deaths mirroring that of oxycodone supply.

[10]Massachusetts Public Law H.4056.

[11]The ADF of OxyContin ER also emerged around this time, but this was a national not a state-specific intervention and so cannot account for the peculiar trajectory of outcomes in Florida.

On the one hand, this circumstantial evidence suggests that supply-side interventions against prescription opioids can have dramatic effects. On the other hand, Florida may have been experiencing a uniquely bad baseline situation in 2010 that may never again be replicated. Examining Texas's pill mill law, for example, Lyapustina and colleagues (2016) found reductions in the number of opioid prescriptions, number of pills dispensed, opioid volume, and average morphine-equivalent dose per transaction, but the reductions were 8–24 percent, not the enormous reductions seen in Florida. Overall, although further research is warranted, limited evidence suggests that state and local interventions aimed at reducing the supply of prescription opioids in the community may be effective. It should be emphasized, however, that none of these studies investigated the impact of reduced access on the well-being of individuals suffering from pain whose access to opioids was curtailed.

STRATEGIES FOR INFLUENCING PRESCRIBING PRACTICES

Reducing prescribing of opioids is at once a tool both for reducing lawful supply (by limiting the indications for prescribing them or otherwise reducing the number of patients holding prescriptions) and for reducing demand, or aggregate desire for using or misusing the drugs. Reduced prescribing can affect demand in two ways: first, by reducing patients' reliance on opioids to manage pain by satisfying their needs through other forms of pain management; and second, by reducing the number of patients or others who develop OUD and increasing the incentive for treatment among patients with OUD. This section describes a range of formal and informal policies, interventions, and tools designed to shape, guide, and regulate the prescribing practices of physicians and other health care professionals (the gatekeepers) authorized to prescribe these drugs.

Provider Education

The relief of pain represents one of the primary responsibilities of the practice of medicine (Federation of State Medical Boards, 2013). As detailed in this section, the breadth and depth of educational efforts to train physicians, nurses, pharmacists, occupational/physical therapists, and other health professionals have often fallen short of their goals for developing appropriate clinical competencies in pain management. Compared with the progressive advancement of medical education surrounding such fields as cardiology and oncology, advances in pain management education are entirely absent or minimally developed—often limited to a few hours of didactic lectures over multiple years of training.

Although detailed protocols have been developed through rigorous

clinical trials for specific conditions (e.g., in the treatment of chest pain as a result of ischemic heart disease), the management of chronic noncancer pain has no equivalent foundation. Moreover, no single entity or organization has overall jurisdiction for the development of pain management guidelines, clinical pain competencies, or opioid prescribing practices. What exists appears to be a group of loosely aligned efforts sponsored by federal, state, and local agencies surrounded by professional organizations and private industry influences. These efforts are summarized below for their respective agencies and organizations.

U.S. Food and Drug Administration

Known by its modern name since 1930, the FDA is the oldest consumer protection agency in the U.S. federal government (FDA, 2015b). Building on its key milestone, the 1906 legislation that outlawed adulterated and misbranded food and drugs, the FDA has grown in scope and size to ensure the health and safety of a broad range of therapeutics, including opioid and nonopioid analgesics. As detailed in Chapter 6, the FDA reviews and approves new and reformulated drugs for use for defined medical indications. Importantly, it can also serve as a hub for advanced training (FDA, 2016a), including the opioid-specific Risk Evaluation and Mitigation Strategy (REMS), as part of an effort to reduce "risks of serious adverse outcomes including addiction, unintentional overdose, and death" (p. 2) from prescription opioid analgesics (FDA, 2017b). Notably, provider participation in the educational component of the opioid REMS is currently voluntary, with unclear evidence of reduction in opioid-related harms or impacts on opioid prescribing (FDA, 2016b). See Chapter 6 for further discussion of the role the FDA's REMS can serve in ensuring that the benefits of prescription opioids continue to outweigh their risks.

U.S. Centers for Disease Control and Prevention

The publication of the CDC Guideline for Prescribing Opioids for Chronic Pain (Dowell et al., 2016) may well represent a watershed moment in the education of health care providers in the management of chronic pain, and specifically with respect to the prescribing practices for opioid analgesics. As discussed later in this chapter, this guideline, in whole or in part, is being integrated into a wide range of educational resources (e.g., guidance from state-level medical boards). It is too early to understand its impact on changes in the quality of pain management or on opioid analgesic prescribing practices. Directed research could track such outcomes, especially as components of the guideline are incorporated into various educational materials at the undergraduate and postgraduate levels, as well as

for the public at large. Concerns exist surrounding the proper interpretation of certain aspects of the guideline, especially with respect to the potential restriction of opioids for acute and/or chronic painful conditions. As discussed later in this chapter, patient-centered management, aided by patient educational materials explaining the risks and benefits of long-term opioid use, could be useful in optimal clinical use of the guideline.

National Institutes of Health (NIH)

As discussed in Chapter 3, NIH support for research and educational aspects of pain management is disproportionately small relative to, for example, HIV research. However, in the face of this disparity in resources to support the development of advanced pain care and address the opioid epidemic, small but determined efforts exist within NIH in support of pain research and education.

As a result of a 1996 congressional mandate, for example, the NIH Pain Consortium, including representatives from 24 NIH institutes and centers, was established to coordinate pain research and disseminate its findings. Subsequently, the consortium held a workshop in 2010 on the state of pain education in the United States to help establish a way forward for the future of education for health care providers (medical, dental, nursing, and pharmacy). The findings of this meeting were as alarming then as they are now: the consortium concluded that the nation is failing to properly educate and train the next generation(s) of health care providers entrusted with relieving pain. Then as now, medical students were receiving on average only 8 hours of training in how to measure, diagnose, and treat pain. A consequence of this failure in education is that pain often goes poorly treated, with some patients receiving the wrong treatment and/or medications. Some may receive too little, while others receive more than is warranted, for unspecified durations, and without the benefit of long-term follow-up to abate the risks of addiction or ensure that the plan is safe and effective. Sometimes, unfortunately, the result is OUD and its sequelae.

In response to this systematic failure, an NIH initiative, the Centers of Excellence in Pain Education (CoEPEs) (NIH, 2017), led by the National Institute on Drug Abuse (NIDA), was launched to increase pain education in medical, nursing, pharmacy, and dental schools across the nation. The plan for these centers was intended to support "pain education champions" and their teams in health care schools who have previously demonstrated a commitment to increasing pain education in their institutions. One of the key elements of this initiative is the production of interactive teaching tools, which other institutions can freely download and use to teach their students about pain and its treatment. An example of these modules can be

found on the Pain Consortium website.[12] While these efforts are ongoing and were initially met with great enthusiasm, budgetary restrictions and inconsistent funding sources have progressively undermined the initiative's strength and productivity. Strengthening and expanding this critical effort represents a key opportunity for NIH to support education surrounding opioid analgesia.

The challenge of supporting a national strategy for pain education is surprising in the face of the current opioid epidemic, as well as the recommendations of the Institute of Medicine (IOM) report *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research* (IOM, 2011). Resulting from a study conducted shortly after the passage of the Patient Protection and Affordable Care Act (ACA), that report offers specific recommendations to (1) improve curriculum and education in pain management for health care professionals, and (2) increase the number of health professionals with advanced expertise in pain care. Collaborative actions with other government agencies—for example, the Substance Abuse and Mental Health Services Administration (SAMHSA)—which has developed treatment improvement protocols such as Treatment Improvement Protocol 54 (TIP 54), Managing Chronic Pain in Adults with or in Recovery from Substance Use Disorders—could provide synergy for such educational efforts (SAMHSA, 2012).

Public and Private Universities/Professional Schools

Medical school education has been undergoing a transformation nationwide, requiring a complete redesign of curriculum to incorporate the early integration of clinical encounters, development of an interdisciplinary team approach to care models, and development of clinical competencies prior to graduation (Satterfield et al., 2004). Despite this redesign, however, the tradition of pain management education in undergraduate curriculum has often been more robust in other disciplines, such as pharmacy, dentistry, nursing, and veterinary schools, relative to medicine. In fact, according to one study, topics related to pain pathophysiology and management appear to be more developed in the training of physician assistants than in that of physicians (Doorenbos et al., 2013).

In the past, the limited hours dedicated to pain management education in medical schools have been restricted to a series of didactic lectures given in the first year. This approach has been evolving in recent years so that students are increasingly challenged with clinically relevant reenactments. An example is the "Danovic" case at the University of California,

[12]See http://painmeded.com/wp-content/uploads/adobe_captivate_uploads/EdnaUpdate081616/multiscreen.html (accessed August 16, 2017).

San Francisco, which is presented early in the first-year curriculum (UCSF, 2017). In this case, Mr. Danovic has a history of chronic low back pain that provides multiple opportunities to develop longitudinal interdisciplinary links for his pain management throughout the subsequent 4 years of training and to integrate aspects of other pain management learning. Additional curriculum advances include the Bridges program, based on "inquiry" (i.e., posing questions or scenarios to students as opposed to presenting facts), which emphasizes a systems approach to care. Numerous similar innovations, such as the learning models developed by the Academy of Medical Educators (AoME, 2017), are occurring across the country. These integrated programs represent a broad opportunity for the expansion of pain curriculum at the nation's medical schools. They may also partially offset the influence of industry representatives that often inadvertently fill gaps in undergraduate medical education around prescribing practices (Relman, 2001).

Taken together, undergraduate medical education that integrates longitudinal, inquiry-based curriculum and that stresses interactive sessions over large lecture formats has the potential to greatly improve clinical care delivery for pain through improved communication and clinical competencies. Additionally, the development of integrated topic pathways may improve the teaching of and competency in pain management by replacing traditional topic silos during the third-year core clerkships (Poncelet et al., 2011). Such approaches are intended to break down traditional communication barriers and empower health care providers to embrace an interprofessional model of care that includes pain management—a model that increases the likelihood that all members of a treatment team will advise clinicians to use both pharmacologic and nonpharmacologic alternatives, including multimodal adjuvant therapies (e.g., physical therapy, acupuncture, manipulation or massage, ice, and music therapy). In addition to efforts sponsored by individual professional schools, it may be hoped that modules developed through the NIH CoEPEs (discussed above) will allow additional pain education resources to be made available and introduced throughout any professional health care program.

Professional Societies

Despite the prominence and availability of Web-based patient care guidelines for the management of pain, whether issued by national or international professional societies (e.g., American Academy of Pain Medicine, American Pain Society, International Association for the Study of Pain), the under- and overtreatment of pain remains a widespread challenge. Although such societies may provide a wealth of information through online modules, annual meetings, and seminars, they are often targeting health care provid-

ers who are already engaged in pain management and/or the treatment of OUD. Primary care physicians, often represented by such organizations as the American Academy of Family Physicians, care for the vast majority of patients with acute and chronic pain, but may not be directly connected to or engaged in these pain society resources and thus must develop and provide their own educational resources for pain management (see, for example, AAFP, 2017).

Depending on their participation in such educational initiatives, the majority of physicians likely have practice and knowledge gaps that include inadequate understanding of pain assessment and diagnosis, especially in the context of chronic pain; inappropriate use of analgesic medications; failure to assess and reassess pain systematically and in the context of opioid use; and the inability to distinguish among opioid tolerance, physical dependence, and OUD (Murnion et al., 2010). Just as interprofessional approaches to undergraduate education have emerged, pain and addiction societies could work more closely with organizations supporting primary care providers, as well as seek to find the correct balance of industry sponsorship that does not unduly bias their educational content (Relman, 2001).

State Medical Boards (SMBs)

SMBs are the primary regulatory authority governing physician prescribers of opioids, through the provision/renewal of medical licensure and related functions (e.g., disciplinary actions related to inappropriate prescribing). To varying degrees, SMBs also serve as an educational resource for clinicians in their state through the publication of relevant legal information (e.g., the statutory obligations for prescribers of controlled substances) or the dissemination of best practice guidelines (discussed later in this chapter). In the context of pain management and opioid prescribing practices, this constellation of state-level oversight represents both a powerful tool to assist physicians in providing safe and effective care and a potential source of variability in the broader guidance to physicians across the country.

Summary

Current efforts to improve prescriber pain education and knowledge about prescription opioid misuse, such as the NIH CoEPEs, are inadequate and at risk of collapsing. Providers managing pain are often left to pick and choose from weakly supported alternatives. Addressing this lack of alternatives is a topic discussed in Chapter 3. However, any meaningful effort to improve pain management will require a fundamental paradigm shift in the nation's approach to mandating pain-related medical education; completion of a brief online module will not be sufficient (Holliday et al.,

2017). **The committee recommends that state medical schools and other health professional schools coordinate with their state licensing boards for health professionals (e.g., physicians, nurses, dentists, pharmacists), the National Institutes of Health's Pain Consortium, the U.S. Food and Drug Administration, the U.S. Centers for Disease Control and Prevention, and the U.S. Drug Enforcement Administration to develop an evidence-based national approach to pain education encompassing pharmacologic and nonpharmacologic treatments and educational materials on opioid prescribing (Recommendation 5-2).**

Prescribing Guidelines

As summarized in a Chapter 2, there are many medical situations in which opioids might be considered an appropriate treatment option. The most common indications include (1) acute pain management, such as after injury; (2) management of pain in the context of cancer or the end of life when accompanied by pain; and (3) management of chronic pain not due to a malignancy. Federal, state, and professional organizations have issued clinical guidelines for the use of opioids (e.g., initiation, dosing, monitoring, discontinuation) in each of these situations. The issuance of these guidelines often is accompanied by such efforts as educational outreach, including continuing medical education (CME), to foster implementation (Haegerich, 2016).

Opioids and Acute Pain Management

Acute pain is experienced commonly after surgical or dental procedures, traumatic injuries, and some normally transient medical conditions (e.g., acute low back pain) when its resolution is expected over a time course of hours to several weeks. Depending on the specific situation, opioids, nonopioid medications, nerve blocks, topical medications, and other measures might be used individually or combined in a multimodal approach (see Chapter 2). As discussed in previous chapters, understanding and controlling opioid use in these situations is important as these routes of exposure may lead to long-term use, particularly in certain populations (Sun et al., 2016; Webster et al., 2007). Additionally, as detailed earlier, unused medications provided by hospitals, emergency rooms, and clinics may leak into the community and be used for nonmedical purposes (Inciardi et al., 2007).

The subject of guidelines for acute pain management currently revolves primarily around use rather than dosage or duration. Dosage guidelines are widely available and fairly widely accepted. However, opioids prescribed for acute pain syndromes have too often been provided at doses and dosing intervals and for durations unlikely to yield optimal effects (Humphries

et al., 1997). One attempt at providing general guidelines for the use of opioids for acute pain was made by the Utah Department of Health,[13] and portions of these guidelines have been incorporated into the guidelines used by other states. The process of developing the guidelines involved broad representation of stakeholders on advisory and working groups. These guidelines call for opioids to be used only when nonopioid alternatives are deemed inappropriate, and for the drugs to be issued in carefully limited amounts (in dosage and duration) and after education of the patient concerning appropriate use and storage.

Various groups have independently developed guidelines for the prescribing of opioids for management of acute pain in emergency rooms (del Portal et al., 2016) and for the management of pain in acutely injured workers (Mai et al., 2015). In one study, del Portal and colleagues (2016) found that opioid prescribing decreased significantly in an acute care setting (from 52.7 percent before the guideline was issued to 29.8 percent immediately after its introduction, and to 33.8 percent 12 to 18 months later) based on retrospective chart review for more than 13,000 patient visits. There do not appear to be any widely accepted guidelines for postoperative opioid prescribing, although one study found that the amount of opioid provided often was much larger than the amount required (Hill et al., 2017). The suggestion recently was made that postoperative opioid prescribing be based on the specific surgical procedure, type of anesthesia used, patient age, and other variables (Kim et al., 2016).

Guidelines for the management of back pain issued in 2017 by the American College of Physicians suggest using nonpharmacologic approaches for treatment of acute and subacute back pain, given that this type of pain often resolves on its own over time. When pharmacologic treatment for acute and subacute back pain is desired, the guidelines suggest the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or skeletal muscle relaxants (Qaseem et al., 2017).

Opioids and Pain Management in the Context of Cancer and End of Life

The use of opioids for the treatment of pain in the context of cancer and end of life is broadly supported by outcome studies. While not adequately effective as sole analgesic agents in every patient, opioids, including morphine, oxycodone, fentanyl, and others, can reduce pain due to malignancies, including so-called breakthrough pain, a sometimes severe form of cancer pain of very rapid onset (Zeppetella and Davies, 2013). The use of opioids for cancer pain is codified in the World Health Organization's (WHO's) analgesic ladder, one of the oldest and most widely accepted sets

[13]See http://www.health.utah.gov/prescription/guidelines.html (accessed April 17, 2017).

of opioid treatment guidelines (WHO, 1986). Regrettably, 10–20 percent of cancer patients experience pain that is refractory to standard opioid management. For these patients, a number of opioid- and nonopioid-based options have been described, but evidence is not yet sufficient to develop guidelines for their use (Afsharimani et al., 2015).

A number of studies have estimated compliance with cancer pain management guidelines. The results suggest that, despite the existence of various guidelines, pain assessment and reassessment and some other provisions of the guidelines are not always adhered to, and that pain control can be improved when guidelines are followed (Du Pen et al., 1999; Mearis et al., 2014; Miaskowski et al., 2001). On the other hand, many more people are surviving cancer treatment than was the case during the development of the WHO guidelines. It is unclear what role opioids should play in the management of persistent pain after successful cancer treatment that might be due to surgery, chemotherapy, radiation, or other related causes.

Opioids and Pain Management in the Context of Chronic Pain

The controversial nature of the practice of using opioids to treat chronic pain, as well as growing recognition of its adverse consequences for both individual patients and society, has prompted the development of numerous prescribing guidelines. These guidelines have been sponsored and promulgated by professional societies; SMBs (such as the Federation of State Medical Boards); and federal agencies, such as the CDC.

Of the sets of opioid prescribing guidelines currently available, that developed by the CDC is the most recent, comprehensive, and influential (Dowell et al., 2016). The CDC's inclusive process for developing the guideline emphasized the use of the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to rate the quality of the evidence used in constructing the guideline, as well as the strength of the resulting recommendations. This process further involved the engagement of federal partners that included representatives from SAMHSA, NIDA, the FDA, the U.S. Department of Veterans Affairs (VA), the U.S. Department of Defense (DoD), and others. The development process further involved constituents, including clinicians and patients. Peer review of the guideline was solicited, as were public comments. The 12 key provisions of the resulting guideline (see Box 5-3) emphasize consideration of nonopioid options prior to or in addition to opioids, careful pre-prescribing risk stratification, conservative dosing, careful follow-up, and appropriate discontinuation/tapering.

Because the CDC guideline was issued only recently, its impact on prescribing practices remains unknown. Some have questioned the strength of the data behind some of the recommendations, such as the overall emphasis

BOX 5-3
The U.S. Centers for Disease Control and Prevention's Recommendations for Prescribing Opioids for Chronic Pain Outside of Active Cancer, Palliative, and End-of-Life Care

Determining When to Initiate or Continue Opioids for Chronic Pain

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

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

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

on improvement in function, as well as in pain control, in the consideration of whether benefits of using the drugs are expected to outweigh risks to the patient (Pergolizzi et al., 2016).

With respect to other guidelines for chronic pain management that have been in the field longer than the CDC guideline, researchers have found modest improvement in practice behaviors, such as use of urine

enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed.

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

Assessing Risk and Addressing Harms of Opioid Use

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

SOURCE: Excerpted from Dowell et al., 2016, p. 1638.

drug screens and referral for specialty evaluation, and modest impacts on overall opioid prescribing rates, as well as overdose rates (e.g., Barber et al., 2017; Beaudoin et al., 2016; Chen et al., 2016). Moreover, strong state-level guidelines were associated with a reduction in the number of patients receiving high doses of opioids (Garg et al., 2013; Sullivan et al., 2016). Notably, multipronged efforts that include guidelines as well as other edu-

cational information for providers on how to prescribe opioids safely have been found to be associated with decreases in emergency department visits and deaths from opioid overdose (Cochella and Bateman, 2011; Paone et al., 2015). These findings suggest that guidelines may be able to moderate the most aggressive opioid prescribing but are unlikely to be sufficient on their own to ensure the application of optimal medical practices in all cases, and that multipronged educational interventions and changes in reimbursement for pain management are required.

State Medical Board Guidelines

In an attempt to provide educational resources on the topic of pain management and opioid prescribing practices, many SMBs have either developed their own best practices preceding the release of the CDC guideline in 2016 or subsequently responded by incorporating foundational components of that guideline addressing key decisions encountered during clinical pain management. Although the CDC guideline was intended to serve as a broad resource for primary care physicians, it is being adapted and largely interpreted at the state level for all practicing physicians across the nation. A brief review of three key CDC topic areas across the Web-based resources of five SMBs (California, Florida, Kentucky, Ohio, and Washington) on pain management and opioid prescribing practice reveals examples of content variability:

- **Determining when to initiate or continue opioid treatment—** California's guidance on initiation of opioid therapy for chronic pain references carefully defined, 90-day opioid trials (MBC, 2014), whereas Ohio's SMB cautions against using opioids to treat chronic pain but advises clinician vigilance should they be deemed necessary (GCOAT, 2013).
- **Opioid selection, dosing, and duration—**Advice generally echoes the CDC's "start low and go slow" approach; however, different morphine-equivalent doses are specifically cited by different SMB documents. California mentions 80 mg/day as a threshold above which caution should be used (MBC, 2014), while a joint publication from the Washington State Agency Medical Directors' Group urges caution at any dose, and additionally recommends referral to specialists for cases necessitating doses above 120 mg/day (WSAMDG, 2015).
- **Follow-up, monitoring, and discontinuation of opioid treatment—** Other areas of variation include whether and how to use treatment agreements and screening tools for OUD risk (discussed in Chapter 2), as well as considerations for monitoring patients on

long-term opioid therapy and conditions necessitating treatment discontinuation. Perhaps most important is the degree to which guidance regarding tapering of opioid treatment is provided. SMBs vary in the depth to which this issue is addressed, from simply recommending referral to addiction or pain specialists (Ohio), to describing the risks, benefits, and management of withdrawal symptoms associated with various weekly reductions in opioid use (California and Washington).

Most of the selected SMBs that provide opioid guidance documents recommend consideration of nonopioid/nonpharmacologic pain management strategies prior to initiation of opioid therapy, and contain appendixes varying in number and length providing supplemental data for prescribers and patients. Many of the documents also recommend that opioids for acute pain be prescribed in limited amounts and doses consistent with the expected clinical course of the case (such as postsurgical pain). Such state-to-state variation is to be expected, and often is due to the goal of the particular guidance document (e.g., Washington's guidance focuses on pain management broadly, whereas Ohio has separate documents for chronic and acute pain, with comparatively little emphasis on patient education or other "wraparound" services). States also may vary in the degree of autonomy that is customary among their physicians.

Unfortunately, in some cases, SMB guidance for opioid pain management can be quite limited, describing only the statutory obligations of physicians prescribing controlled substances for pain, although reference also may be made to the CDC guideline (FBM, 2010; KBML, 2003). In short, there are wide disparities in the availability and comprehensiveness of SMBs' prescribing guidance. In April 2017, the Federation of State Medical Boards (FSMB) released a revised "model policy" for chronic use of opioid analgesics (FSMB, 2017), for use by SMBs seeking to evaluate physician management of patients with pain. This guidance is largely consistent with (if not as broad and comprehensive as) the CDC guideline. Notably, FSMB stresses at the outset that "effective means of achieving the goals of these Guidelines vary widely depending on the type and causes of the patient's pain, the preferences of the clinician and the patient, the resources available at the time of care, and other concurrent issues beyond the scope of these Guidelines" (FSMB, 2017, p. 2).

In summary, prescribing guidelines may be able to improve provider prescribing behavior but may be most effective when accompanied by provider education and other measures designed to facilitate implementation.

Electronic Medical Records and Decision Support

The use of electronic medical record (EMR) systems is expanding rapidly in both inpatient and outpatient medical settings. Use of EMRs was led by the VA, but aggressive federal policies have prodded many offices, clinics, hospitals, and integrated health care systems to employ the technology. Clinic notes, study results, laboratory values, pharmacy information, and other key data may be included. Compared with more traditional paper-based systems, EMRs offer potential improvements to health care delivery, including but not limited to increased efficiency, better adherence to guidelines and regimens, and fewer medical errors and related events (Campanella et al., 2016).

These advantages could contribute to safer and more effective opioid prescribing for several reasons. First, notes documenting treatment and follow-up plans may be more easily located by consulting an EMR than by sorting through paper files, and delays in accessing the records are minimized when providers need patient information quickly. Importantly, EMR systems containing sections for current medications, allergies, and other pharmacy-related information (e.g., last medication refill dates and tablet quantities) may aid greatly in managing higher-risk patients. The electronic format is conducive to the use of treatment templates in which opioid follow-up assessments and ongoing prescribing plans can be included.

At present, a modest amount of information helps inform the utility of EMRs and opioid prescribing in different settings. A pre/postimplementation analysis concluded that the implementation of an EMR system may have contributed to higher rates of signed opioid treatment agreements, use of urine drug screens, and documentation of assessment of functional status (Anderson et al., 2016). Another study demonstrated that the inclusion of electronic alerts for the presence of opioid-use care plans within an EMR system may reduce opioid prescribing by emergency departments for high-frequency emergency department patients (Rathlev et al., 2016). Use of EMRs, however, may not always discourage opioid prescribing. A regression analysis to analyze the prescribing behavior of primary care physicians with and without EMR systems showed that visits to physicians with EMRs were more likely to result in opioids being prescribed relative to visits to physicians using more traditional systems (Harle et al., 2014).

Evidence on the effectiveness of clinical decision support systems (CDSSs) for opioids, incorporated within EMRs, is similarly conflicting. Trafton and colleagues (2010) describe a commendable attempt to iteratively improve and deploy a CDSS for primary care physicians treating chronic pain with opioids. In the end, while the CDSS did overcome some perceived barriers to guideline adherence (e.g., medication selection, dosing calculations), remaining systemic barriers at the health care system level

(e.g., lack of time, competing clinical demands) appear to have blunted the beneficial impact of the CDSS on patient outcomes (Trafton et al., 2010). Thus, the impact of electronic and other types of record-keeping systems on pain management or opioid prescribing, whether positive or negative, is not yet fully understood.

Insurer Policies for Pain Management

Insurer policies have a large and logical impact on health care delivery through their considerable financial leverage with respect to covering and reimbursing for specific clinical services or restricting access to others. In pain management, for example, a policy may or may not require specified indications before reimbursement for prescription opioids is authorized; in contrast, other policies may have more stringent requirements for authorization of nonopioid pain therapies and/or inadequate reimbursement structures. These policies, in turn, may result in marked differences in access to services and in desired outcomes. Insurers, including sources of publicly funded health care coverage and pharmacy benefit managers, therefore can play a critical role in shaping clinical practices related to opioids and nonopioid alternatives for pain management. As a result of increasing recognition of the role such policies can play in improving analgesic care, examples are emerging of both reductions in inappropriate opioid prescribing and enhanced access to more comprehensive models of pain management.

Opioid Prescribing Policies

Haegerich and colleagues (2014) reviewed eight studies examining the effect of patient review and restriction (PRR) (i.e., "lock-in") programs on opioid use. PRRs, used by public and private insurance plans, may require patients suspected of misusing controlled substances to obtain prescriptions from a specified prescriber and/or pharmacy. Overall, the findings of this review are impressive. Four of the studies considered both cost savings and health outcomes. These studies generally found that in the four respective programs studied (in Louisiana, Ohio, Oklahoma, and Washington), PRRs were associated with reductions in opioid use of one-third to one-half and with reductions in the number of patients able to successfully access multiple providers or pharmacies. The Washington study, which followed up patients 1 year later, also found significant reductions in emergency department and physician visits and in hospital costs (Haegerich et al., 2014). PDMP data can be used to determine whether a PRR is needed. In a survey of state Medicaid agencies, however, 48 percent (22 states) reported that their fee-for-service PRR program does not have access to the state PDMP (Pew Charitable Trusts, 2016).

Four studies reviewed by Haegerich and colleagues (2014) examined drug utilization review (DUR) programs that review claims data to identify and notify providers of potentially problematic use patterns. Although none of these four studies evaluated health outcomes, all found reductions in drug utilization, and one RCT found reductions in numbers of prescribers and pharmacies used. In a later study, Qureshi and colleagues (2015), utilizing pharmacy claims data from 980 members enrolled in a commercial health plan who met DUR criteria, found a 28.1 percent reduction in potentially unsafe combination therapy involving opioids and other central nervous system drugs (benzodiazepines or antidepressants). State Medicaid programs have implemented the use of DUR to curb inappropriate opioid prescribing.

Finally, Haegerich and colleagues (2014) also examined studies on prior authorization (PA) and quantity limit (QL) programs. PA requires review of medical justifications before drugs are covered by an insurer, while QL limits the amount of a drug that can be dispensed in a given time frame. Haegerich and colleagues (2014) summarize the finding of Morden and colleagues (2008) that the 21 states that implemented PA in their Medicaid programs saw 34 percent reductions in oxycodone use over the study period, whereas those with more lenient PA policies witnessed a slight (but nonsignificant) increase. Three studies of PA and QL by Oregon State University are described as finding significant reductions in use of long-acting (LA) opioids and carisoprodol, but no significant impact on sedatives/hypnotics (Haegerich et al., 2014).

In summary, insurance-based policies, such as those involving PRR, DUR, PA, and QL, have substantial potential to reduce the use of specific prescription drugs, although their impact on health outcomes remains uncertain.

Coverage and Reimbursement of Nonopioid Pain Management

As discussed in Chapter 2, there are multiple nonopioid pharmacologic (e.g., NSAIDs) and nonpharmacologic (e.g., physical therapy, cognitive-behavioral therapy) options available for patients with chronic pain. Nevertheless, insurer policies affect access to and uptake of these treatment options. The IOM report *Relieving Pain in America* specifically points to misaligned incentives in fee-for-service insurance systems as a primary obstacle to comprehensive and effective pain management, citing lower (or absent) reimbursement of psychosocial or nonprocedural treatments (IOM, 2011).

In part in response to the growing opioid epidemic, some insurers and state Medicaid agencies are working to expand access to nonopioid pain management services for common clinical indications, such as back

pain (Cigna, 2016; McLaughlin, 2015; Oregon Health Plan, 2016). This is occurring despite the relatively lower cost of opioid prescriptions, which carry an average out-of-pocket cost of $10 per prescription (although the cost of ER formulations can be more than double that of immediate-release [IR] formulations) (Craig and Strassels, 2010). While relatively more expensive in the short term, integrated or multidisciplinary pain treatment programs have demonstrated long-term cost-effectiveness and increased functional improvement for patients (Turk and Burwinkle, 2005). Promising clinical research into opioid dose reduction programs, more comprehensive pain management, and the effectiveness of nonopioid treatments for pain is discussed further in Chapter 3.

The judicious deployment of insurer policies related to opioid prescribing, outlined above, would logically benefit from a commensurate increase in coverage of and access to nonopioid pain management. This broader approach to pain management is consistent with the guidelines of the CDC (discussed earlier in this chapter), the American College of Physicians, and FSMB, among others, that recommend careful initiation of opioids in the context of a comprehensive pain management plan (Dowell et al., 2016; FSMB, 2017; Qaseem et al., 2017). Accordingly, **the committee recommends that public and private payers develop reimbursement models that support evidence-based and cost-effective comprehensive pain management encompassing both pharmacologic and nonpharmacologic treatment modalities (Recommendation 5-3).**

Prescription Drug Monitoring Programs

PDMPs, currently authorized in every U.S. state except Missouri,[14] as well as in the District of Columbia and the U.S. territory of Guam (Brandeis PDMP TTAC, 2017), are statewide electronic databases designed to prevent diversion and misuse of controlled substances. They require pharmacies and sometimes dispensing physicians to submit to a central office data on controlled substances prescribed and dispensed (e.g., drug type, dose, amount dispensed) (Haegerich, 2016), as well as insurance/payment and patient information. These data can be monitored for patterns in prescribing and dispensing. This monitoring for patterns includes the identification of possible "doctor shoppers" (individuals who visit multiple prescribers or pharmacies to obtain multiple prescriptions), as well as need for treatment, unsafe drug combinations, and inappropriate provider prescribing practices (Brandeis PMP COE, 2012, 2013, 2014; Jann et al., 2014; Patrick et al., 2016). Because PDMPs include virtually all data on prescriptions dispensed to a patient regardless of payment method, they allow for more complete

[14]Several counties and other localities within Missouri have established their own PDMPs.

monitoring than claims databases, which often are limited to data on payments for prescriptions within a particular network (Brandeis PMP COE, 2013).

States vary somewhat in terms of authorized users and recipients of PDMP data (NAMSDL, 2016). In most states, PDMPs are administered by health departments, boards of pharmacy, or a single state authority. Other states' programs are administered by law enforcement agencies, boards of pharmacy in conjunction with other agencies, professional licensing boards, or departments of consumer protection/affairs. As of May 2016, however, in only a handful of states (New Mexico, New York, Ohio, Oklahoma, Utah, and Vermont) were departments of health or commissioners of public safety authorized users of PDMPs, meaning that they are permitted to request and receive information on behalf of agency activities (Davis et al., 2015; Haegerich, 2016; NAMSDL, 2016). Prescribers and dispensers and physician assistants/medical residents/nurse practitioners are authorized recipients of PDMP data in every state, and law enforcement officials are authorized recipients in all but one state (Nebraska). Table 5-1 shows other types of professionals who are authorized users by state. As is shown, several states do not permit access for mental health and substance use and other types of professionals who could potentially use the data to monitor opioid use and related harms.

Although they have operating PDMPs, some states have laws that do not expressly mandate that prescribers and/or dispensers access PDMP information.[15] Most states are permitted to share PDMP data with other state PDMPs and/or with authorized users in other states (NAMSDL, 2016).

With respect to effects on prescribing practice and patient receipt of drugs from multiple health care providers, PDMPs are currently considered promising strategies based on before–after studies and time series analysis (Haegerich, 2016). A contextual review conducted to support development of the CDC's Guideline for Prescribing Opioids for Chronic Pain concluded that there is indirect evidence for the utility of PDMP data for identifying indicators of risky opioid-taking behaviors and prescribing practices (Dowell et al., 2016). A recent analysis of Medicaid data suggests that mandatory prescriber registration with state PDMPs (as opposed to mandatory use of them) can lead to decreased prescribing of Schedule II opioids, although whether this resulted in safer prescribing or limited access to legitimate pain relief could not be assessed (Wen et al., 2017). In patients for whom a decision is made to initiate or continue opioid therapy, the

[15] As of May 2016, these states included Alabama, Alaska, Georgia, Illinois, Indiana, Iowa, Kansas, Minnesota, North Dakota, Oregon, South Carolina, South Dakota, Wisconsin, and Wyoming (NAMSDL, 2016).

TABLE 5-1 States Authorizing Use of PDMP Data, by Selected Professions (as of May 2016)

State	County Coroners, Medical Examiners, and/or State Toxicologists	Medicare, Medicaid, State Health Insurance Programs, and/or Health Care Payment/Benefit Providers or Insurers	Mental Health/ Substance Use Professionals	Worker's Compensation Specialists
Alabama	X	X		
Alaska	X	X	X	X
Arizona	X	X	X	
Arkansas	X			
California				
Colorado	X		X	
Connecticut	X	X		
Delaware	X	X	X	
District of Columbia	X	X	X	
Florida		X	X	
Georgia		X		
Hawaii	X	X	X	
Idaho	X	X		
Illinois	X			
Indiana	X	X	X	
Iowa				
Kansas	X	X	X	
Kentucky	X	X		
Louisiana		X		
Maine	X	X		
Maryland	X	X	X	
Massachusetts	X	X		
Michigan		X		
Minnesota	X	X	X	
Mississippi	X	X		
Missouri	NA	NA	NA	NA
Montana	X	X		X
Nebraska				
Nevada		X		
New Hampshire	X	X		

continued

TABLE 5-1 Continued

State	County Coroners, Medical Examiners, and/or State Toxicologists	Medicare, Medicaid, State Health Insurance Programs, and/or Health Care Payment/Benefit Providers or Insurers	Mental Health/ Substance Use Professionals	Worker's Compensation Specialists
New Jersey	X	X	X	
New Mexico	X	X		
New York	X	X		
North Carolina	X	X		
North Dakota	X	X	X	X
Ohio		X		X
Oklahoma			X	
Oregon	X			
Pennsylvania	X	X	X	
Rhode Island	X	X		
South Carolina		X		
South Dakota		X	X	
Tennessee	X	X	X	
Texas	X			
Utah	X	X	X	X
Vermont	X	X		
Virginia	X	X	X	
Washington	X	X		X
West Virginia	X	X		
Wisconsin	X		X	
Wyoming				

SOURCE: NAMSDL, 2016.

CDC guideline recommends that clinicians review PDMP data for high-risk drug combinations or dosages (see Box 5-3, presented earlier). Furthermore, the guideline states that PDMP data should be reviewed "when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months" (Dowell et al., 2016, p. 1639).

Research on the effectiveness of specific features of PDMPs is currently limited (Patrick et al., 2016). The Brandeis Prescription Monitoring

Program Center of Excellence identified PDMP best practices based on a systematic review of articles published through November 2011 (Clark et al., 2013). None of the studies met criteria for the highest level of evidence (RCT or meta-analysis). Best practices based on the next level of evidence (observational study with comparison group) included using serialized prescription forms and sending unsolicited reports and alerts to prescribers, pharmacists, investigative agencies, and other relevant parties regarding questionable activity (Clark et al., 2013). Current laws in most states allow for unsolicited reporting but vary somewhat in terms of the parties to whom the reports may be provided (NAMSDL, 2016) (see Figure 5-2). Generally, data support the effectiveness of PDMPs in reducing the supply of prescribed controlled substances in the community, which is one, but not the only, causal factor in the risk of OUD and overdose.

Some states have worked to share PDMP data with other programs to support monitoring of prescribing patterns. Washington State's PDMP, for example, shares data with state Medicaid and workers' compensation programs to provide a more complete picture of controlled substances prescribed to patients. State program administrators reported that this effort

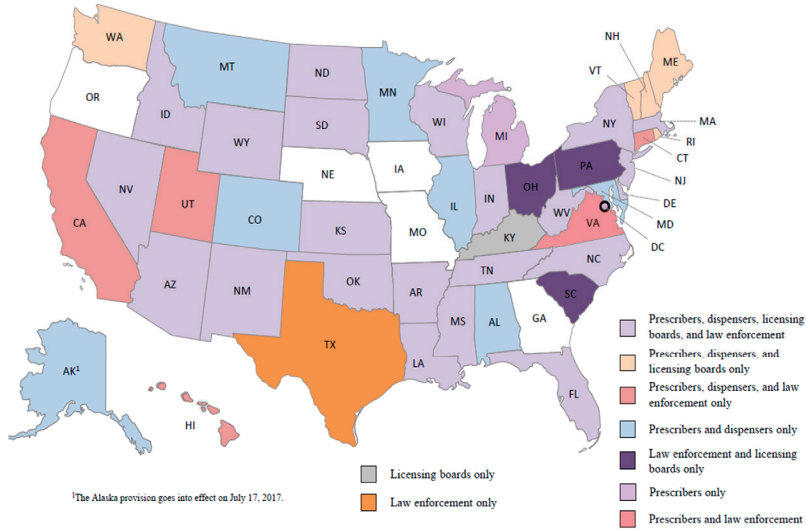

FIGURE 5-2 Unsolicited reporting of prescription drug monitoring program (PDMP) data to prescribers, dispensers, licensing boards, and law enforcement (as of May 2016).
SOURCE: NAMSDL, 2016.

supported improved identification of and early intervention for patients at risk for substance use disorder and overdose, led to reductions in costs associated with unnecessary prescription drug use and diversion and uncoordinated care, and improved education of prescribers about PDMPs, among other positive effects (Brandeis PMP COE, 2013). These findings are not specific to opioids, however. In Ohio and other states, a risk score (the NARxCHECK) that provides an assessment of patients' history of use of controlled substances based on PDMP data is incorporated into EMRs to support intervention efforts.

As noted above, states also utilize PDMP data to address at-risk prescribing through use of such tools as prescriber report cards and reports to licensing boards and law enforcement. Data on how these reports impact prescribing practices are currently limited, however. In Arizona, report cards summarizing prescribing over the past year were sent to outlier prescribers (those for whom PDMP data indicated that the number or total dosage units prescribed were 1 standard deviation above the average in their specialty and county). Preliminary findings for a county 1 year following implementation of the report cards show that the percentage of outlier prescribers fell from 19.2 to 14.2 percent (Brandeis PMP COE, 2014). In such states as Kentucky and Texas, provision to investigators of information regarding problem prescribers is believed to have helped identify and address this problem, both through removal and by providers being encouraged to modify their prescribing practices (Brandeis PMP COE, 2014).

As noted earlier, some states allow substance use and mental health professionals to access PDMP data. In treatment settings, the data may be used to check whether patients are being prescribed controlled substances. Limited evidence suggests that such access by these professionals may play a role in reducing opioid use by individuals in treatment (Brandeis PMP COE, 2015). It is worth noting that federal law itself may pose an additional obstacle related to treatment for substance use disorder: 42 C.F.R. Part 2 prohibits PDMP data from including any information related to substance use disorder services (e.g., receipt of methadone from an opioid treatment program). This provision carves out an additional area of patient privacy, often a contentious issue surrounding PDMPs, but necessarily excludes potentially relevant information from the PDMP.

By reducing the availability of opioids from medical sources in the community, one might reasonably expect that PDMPs would reduce mortality from opioid overdose. Yet relatively few studies have evaluated the impact of PDMPs on opioid-related mortality, and the results of available studies are mixed (Delcher et al., 2015). An analysis of observational data for the period 1999 to 2005 found no significant differences in rates of opioid overdose mortality and rates of opioid drug use between states with and without PDMPs (Paulozzi et al., 2011). However, PDMPs vary so widely

in their legal requirements that little effect would be expected in a "yes or no" comparison. Until recently, for example, PDMPs were used primarily for law enforcement rather than public health purposes in most states, so an effect on drug overdose mortality might not be expected unless their use for this purpose had been articulated (Green et al., 2011). Additionally, utilization of PDMPs by health care providers was not included when the impact of PDMPs on overdose mortality or opioid use was assessed in two studies (Green et al., 2011; Kerlikowske et al., 2011). In another study that evaluated mortality data in states and the District of Columbia with and without PDMPs during 1999–2008, implementation of PDMPs was found not to be associated with reductions in drug overdose mortality in most states (Li et al., 2014).

A time series, quasi-experimental study of Florida's PDMP found that oxycodone-caused mortality declined by 25 percent in the month after implementation of the PDMP in 2011. This finding was significant after controlling for declines in mortality associated with the introduction, before implementation of the PDMP, of tamper-resistant oxycodone hydrochloride (HCL) controlled-release tablets to the market; law enforcement efforts to crack down on pill mills; and stricter rules and regulations related to prescribing of controlled substances (Delcher et al., 2015). However, even the study authors acknowledge the complex interrelationship among variables in the study, and specifically mention their lack of an explanation for the PDMP's mechanism of influencing their reported outcome, calling it an "important [remaining] empirical question" (Delcher et al., 2015, p. 65). This may be because Florida circa 2010, as discussed earlier in this chapter, may have been a unique case study that does not generalize well to other states. Another recent analysis that included all state PDMPs found that implementation of a PDMP was associated with a reduction in opioid-related overdose deaths of 1.12 per 100,000 people in the year after implementation. Greater reductions in opioid-related overdose were observed in states where PDMPs included robust features, such as monitoring of greater numbers of drugs with abuse potential and at least weekly updating of PDMP data (Patrick et al., 2016). As of April 2017, the interval for PDMP data collection was within a week or less in all states except Alaska, which will go to weekly reporting starting in July 2017, and Montana (which reports data every 8 days). Only one state—Oklahoma—had real-time PDMP reporting as of April 2017 (NAMSDL, 2017).

Some researchers have noted that while PDMPs may have an important role to play in preventing opioid overdoses, a multipronged approach that includes PDMPs is needed to foster significant reductions by addressing multiple correlates (Davis et al., 2014). Explicit and public articulation of the application and role of PDMPs in overdose prevention may increase their effectiveness and use for this purpose (Green et al., 2015a).

In summary, evidence suggests that PDMPs can help address the opioid epidemic by allowing prescribers, dispensers, and other stakeholders to track prescribing and dispensing information. State laws differ widely in who has access to PDMP data, with some states denying access to certain stakeholders (e.g., substance use and mental health professionals, health departments) that could use the data to monitor opioid use and related harms. As noted earlier, some states do not require prescribers and/or dispensers to check PDMP information, assuming that a mandate would be overly burdensome and that the PDMP's availability is sufficient to enable responsible prescribing. As a result, PDMP data currently are not being used to their full potential.

The committee recommends that the U.S. Department of Health and Human Services, in concert with state organizations that administer prescription drug monitoring programs, conduct or sponsor research on how data from these programs can best be leveraged for patient safety (e.g., data on drug–drug interactions), for surveillance of policy and other interventions focused on controlled substances (e.g., data on trends in opioid prescribing, effects of prescriber guidelines), for health service planning (e.g., data on discrepancies in dispensing of medications for treatment of opioid use disorder), and for use in clinical care (i.e., in clinical decision making and patient–provider communication) (Recommendation 5-4).

STRATEGIES FOR REDUCING DEMAND

This section reviews strategies aimed at reducing aggregate desire and need for opioids, including both reducing patients' reliance on opioids for pain management and reducing the occurrence and prevalence of untreated OUD. Accordingly, the discussion encompasses two main strategies: education programs focusing on alternatives to opioids for pain management and prudent and limited use of opioids if they are prescribed; and health policies bolstering and improving access to and utilization of evidence-based treatment for OUD.

Patient Education

This section addresses targeted patient education programs as well as mass media campaigns for the general public.

Targeted Patient Education Programs

Patients' understanding of the potential benefits and risks of and alternatives to opioids can be influenced by targeted patient education programs, provider initiatives mediated by professional education, and disclosures by

manufacturers mandated by the FDA. Unfortunately, research on the effectiveness of patient education in reducing the risk of harms from prescription opioids is lacking. In the review of evidence conducted to support development of the CDC Guideline for Prescribing Opioids for Chronic Pain, investigators found no studies evaluating the effectiveness of patient education as a risk mitigation strategy. However, evidence suggests that many patients lack knowledge about opioids, indicating a need for patient education (Dowell et al., 2016). The CDC guideline recommends that before initiating opioid therapy, clinicians and patients weigh the known risks and benefits, available alternatives, and mutual responsibilities for optimal therapy. In connection with its prescribing guideline, the CDC has prepared a number of informational materials for patients on opioids and the risks associated with their use, as well as pharmacologic and nonpharmacologic alternatives for pain management (CDC, 2016b).

Other organizations also have developed informational materials for patients to promote safe opioid use and awareness of alternative therapies, although studies have not been conducted to assess the effectiveness of these materials. In 2016, the FDA issued guidance for patients on what to ask their providers before taking opioids (FDA, 2016c). The guidance recommends that patients ask their providers why they might need the medications (including asking whether there are alternative medications they can take to help with pain relief), how long they should take them, and whether they should have a prescription for naloxone (FDA, 2016c).

The potential value of patient education for reducing opioid-related harms also is supported by a number of health care organizations. The VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain recommends education about opioids and risk mitigation strategies for both patients and family members (VA and DoD, 2017). Pharmacists are trained to educate patients and others on the disposal of prescription medications, and the American Society of Health-System Pharmacists encourages pharmacists to educate patients about the storage, handling, and disposal of prescription medications (ASHP, 2011). A number of states' opioid prescribing guidelines also recommend education for patients on the risks and benefits of opioid therapy, alternative treatment options, and safe storage and disposal.

Part of the committee's charge was to describe education for patients (as well as prescribers) about safe storage and disposal of opioid medications as a means of curbing opioid-related harms. As discussed earlier in this chapter, many patients do not safely store and dispose of their prescription opioid medications, which can lead to misuse (Binswanger and Glanz, 2015; Reddy et al., 2014). Available studies that include a specific focus on the role of education in promoting safe storage and disposal of opioids are preliminary and have small sample sizes.

A pilot study of a brief, Web-based educational intervention found significant improvements in knowledge about safe storage and disposal of prescription opioids postintervention and at 1-month follow-up. The study also found reductions in self-reported misuse (e.g., saving pills, lending medications to others) 1 month postintervention (McCauley et al., 2013). The intervention, which presented safety information in an interactive multimedia format, was administered to 62 adult outpatients who presented for treatment of chronic pain at pain management and dental clinics (McCauley et al., 2013). Likewise, in a prospective study of 300 adult cancer outpatients, those provided with educational material on safe opioid use, storage, and disposal each time they received an opioid prescription were significantly less likely to have unused medication at home (38 versus 47 percent) and significantly more likely to keep their medications in a safe place (hidden, 75 versus 70 percent; locked, 14 versus 10 percent) relative to patients who did not receive such material. The study found further that patients receiving the intervention were significantly more aware of proper opioid disposal methods (76 versus 28 percent) and less likely to share their opioids with others (3 versus 8 percent) (de la Cruz et al., 2017). Finally, a brief behavioral intervention was associated with a 22 percent increase in the proportion of patients who reported disposing of, or intent to dispose of, unused opioids in a pilot RCT involving cancer patients (n = 79), but this finding was nonsignificant (Maughan et al., 2016). The downstream effects of this education, such as effects on opioid misuse and opioid-related morbidity and mortality, are unknown.

In summary, studies evaluating the effectiveness of patient education about prescription opioids are generally lacking. However, evidence does indicate that patients lack information about opioids, suggesting the need for such education. Information about the risks and benefits of opioids and alternative strategies for managing pain is being provided by several organizations, but because these efforts have not been evaluated, their impact is unclear. Preliminary research suggests that patient education on safe storage and disposal of opioids is associated with self-reported improvements in measures of these outcomes.

Mass Media Campaign for General Public

In parallel with the committee's recommended changes to provider education and payer policy is the need to effect a major change in patient expectations in the treatment and management of chronic pain. The committee was struck particularly by the relative lack of attention to the impact of education of the general public (i.e., all potential patients) about the risks and benefits of opioid therapy and the comparative effectiveness of opioid and nonopioid analgesics and nonpharmacologic interventions. There-

fore, **the committee recommends that the nation's public health leadership, including the surgeon general, the U.S. Centers for Disease Control and Prevention, and heads of major foundations and professional organizations, convene a body of experts in communication and in pain and opioid use disorder to evaluate the likely impact (and cost) of an education program designed to raise awareness among patients with pain and the general public about the risks and benefits of prescription opioids and to promote safe and effective pain management (Recommendation 5-5).**[16]

Increasing Access to and Utilization of Medical Treatment for Opioid Use Disorder

As discussed in Chapter 4, medication-assisted treatment (MAT) is the central component of evidence-based treatment for OUD, regardless of whether it is combined with behavioral therapy. The use of medication can help patients cope with withdrawal symptoms, and may relieve drug cravings without producing the "high" of opioids. The medications that are used in MAT are opioid agonists, partial agonists, or antagonists, and include methadone, buprenorphine, naltrexone, and combination buprenorphine-naltrexone (Suboxone®). Research is ongoing into new MAT drug products, including implantable and "vaccine"-type medications.

Delivery Models

Integrating buprenorphine maintenance therapy (BMT) into federally qualified health centers (FQHCs) has been shown to be feasible, to increase access to evidence-based treatment for OUD, to expand the scope of patient-centered medical homes (a model of primary care under the ACA that is patient-centered, comprehensive, accessible, and focused on quality), and to reduce illicit opioid use (Haddad et al., 2013). Integrating BMT into FQHCs also resulted in improved engagement of patients in primary care, preventive screening for other health conditions, and quality health care indicators beyond treatment of OUD. Additional strategies may be needed for women and those retained in treatment for less than 3 months, as they were less likely than their counterparts to receive preventive screening, which resulted in lower-quality health care indicator scores for these populations (Haddad et al., 2015).

[16]A logical complement to all patient and public education efforts is a substantial effort to counteract and possibly restrict direct-to-consumer advertising and other promotional efforts by pharmaceutical manufacturers aimed at increasing the use of opioids. This topic is addressed in Chapter 6.

An RCT comparing three approaches used in emergency department–initiated buprenorphine-naloxone treatment for OUD found that those who received screening, brief intervention, and referral to primary care for 10-week follow-up had superior outcomes relative to two comparison conditions (screening and treatment referral; and screening, brief intervention, and facilitated referral to community-based treatment services). Superior outcomes were noted for engagement in treatment 30 days postrandomization and reduced days of self-reported illicit opioid use per week. The rate of negative urine screens did not differ by study condition (D'Onofrio et al., 2015).

With regard to criminal justice settings, an RCT of prison-initiated buprenorphine treatment for inmates who were heroin-dependent prior to incarceration found significant effects favoring the buprenorphine treatment compared with counseling only (99 versus 80.4 percent) and for entry into treatment in a community setting compared with an opioid treatment center (47.5 versus 33.7 percent). Women were significantly more likely than men to complete treatment (85.7 versus 52.7 percent) (Gordon et al., 2014). A study of the impact of opioid treatment therapy in correctional settings in Australia found high treatment retention during incarceration (82 percent), prescriptions for MAT provided at release (90 percent), and presentation at community clinics for MAT postrelease (94 percent) (Larney et al., 2016).

State and Local Initiatives

Several state and local initiatives have been undertaken to increase access to and utilization of medical treatment for OUD. A buprenorphine initiative in Baltimore, Maryland, reduced opioid treatment waitlists and heroin overdose deaths by using a team of health care workers to support patients while they were in short-term treatment at a substance use disorder treatment facility, help them access Medicaid coverage, and refer them to outpatient providers for continuing care (Schwartz et al., 2013).

The Massachusetts Department of Public Health has implemented a nurse management model that encompasses initial assessment; referral to treatment; adherence monitoring; and communication with prescribing physicians, addiction counselors, and pharmacists. This model allows physicians with buprenorphine waivers to take on more patients (Alford et al., 2011). The expansion of this collaborative model for delivery of opioid agonist therapy with buprenorphine to 14 community health centers in Massachusetts led to a 375 percent increase in the number of waivered physicians (enabling their prescribing of buprenorphine) within 3 years (LaBelle et al., 2016).

Vermont's regional infrastructure for treatment of substance use disorder utilizes both geographic area–specific centers ("hubs") to provide

comprehensive services to individuals with OUD and teams of clinicians ("spokes") to provide treatment, counseling, and other services to individuals who are less clinically complex. A cross-sectional study conducted during 2008 to 2013 evaluated outcomes for Vermont Medicaid beneficiaries with OUD, comparing those receiving MAT with those receiving treatment without medication. Results suggest that MAT is associated with reduced general health care expenditures and utilization, such as inpatient hospital admissions and outpatient emergency department visits. The costs of treatment therefore were offset by these savings (Mohlman et al., 2016).

Treatment Utilization

State Medicaid policies influence enrollees' access to and use of opioid agonists (e.g., methadone and buprenorphine) for treatment of OUD. Most states cover such treatment for Medicaid enrollees, and the number of enrollees covered increased from 2004 to 2013. However, some states do not cover both methadone and buprenorphine. Furthermore, obstacles to utilization of opioid agonists exist, such as prior authorization requirements; copayments; and requirements for concurrent counseling, which if not available can act as a barrier to the treatment (Burns et al., 2015). State policies regarding coverage of the treatment have been associated with an increase in buprenorphine-waivered physicians (Stein et al., 2015) and with use of opioid agonist therapies and buprenorphine in substance use disorder treatment facilities (Bauhoff et al., 2014; Ducharme and Abraham, 2008). Mark and colleagues (2015) found that while 12 percent of Medicaid recipients had substance use disorders, only 13 state Medicaid programs included all medications approved for treatment of alcohol and opioid substance use disorder on their preferred drug lists. The drugs that were most commonly excluded were ER naltrexone, acamprosate, and methadone. Forty-eight Medicaid programs required prior authorization for combined buprenorphine-naloxone treatment, and 11 had 1- to 3-year lifetime treatment limits (Mark et al., 2015).

Availability of Providers and Treatment

Insufficient numbers of providers for treatment of OUD have been noted as a significant barrier to the availability of such treatment. In a state-level analysis of the supply of physicians waivered to prescribe buprenorphine for OUD, Knudsen (2015) found that the average state had 8 waivered physicians per 100,000 residents. In addition, large regional differences were found between states in the Northeast and states in the Midwest, South, and West. The supply of physicians waivered to prescribe buprenorphine was positively associated with the percentage of resi-

dents covered by Medicaid, the population-adjusted availability of opioid treatment programs, and the number of substance use disorder treatment programs. The supply of waivered physicians was positively correlated with states' numbers of overdose deaths, suggesting that physicians may seek waivers in response to the level of the opioid problem in their state (Knudsen, 2015). Recent steps to expand the number of waivered providers include increasing the upper limit of patients that can be treated by waivered physicians, expanding the type of prescribers permitted to be DATA[17] waivered, and integrating the required training into the health care professional educational curriculum (ASAM, 2016). For instance, the state of Rhode Island has taken steps to expand access to OUD treatment by incorporating the required training into existing medical school curriculum (McCance-Katz et al., 2017).

Significant gaps exist between the need for MAT and capacity. Jones and colleagues (2015) report that in 2012, the national rate of opioid misuse or dependence was 891.8 per 100,000 people aged 12 or older, while the treatment capacity was 420.3 for buprenorphine and 119.89 for methadone. Forty-eight states and the District of Columbia had past-year opioid misuse or dependence rates higher than their buprenorphine treatment capacity. While states varied significantly in their treatment need and capacity gap, most states (77.6 percent) reported that at least 75 percent of their treatment programs were operating at 80 percent capacity or greater. Although capacity for MAT increased markedly between 2003 and 2012, driven largely by the increase in the number of waivered physicians, the large gap between treatment need and capacity did not close significantly. The authors call for national and state practice and policy strategies to increase treatment capacity, such as improving training of health care professionals in the diagnosis and treatment of addiction; removing insurance, administrative, and payment-related obstacles; raising the limit on the number of patients physicians can treat with buprenorphine; and expanding the types of providers who can prescribe buprenorphine under the Drug Addiction and Treatment Act (Jones et al., 2015).

Increases in the availability of methadone and buprenorphine treatment have been linked to decreases in overdose deaths (Schwartz et al., 2013). However, MAT has been adopted in fewer than half of private-sector treatment programs, and when offered, only about one-third of patients receive it (Knudsen et al., 2011). Volkow and colleagues (2014) note that contributors to low access to and utilization of treatment with medication include the paucity of trained providers; negative attitudes regarding this form of treatment among providers, patients, and the general public; policy and regulatory barriers, such as utilization management techniques that place

[17]Drug Abuse Treatment Act of 2000.

limits on dosages; treatment length; cumbersome paperwork for authorization and reauthorization; and minimal counseling coverage.

Treatment-Related Disparities

Studies show disparities in access to and utilization of treatment for substance use disorder in general and OUD in particular by race, ethnicity, and income.

Data from the National Epidemiologic Survey on Alcohol and Related Conditions show that both U.S.-born and immigrant Hispanic people who use drugs are less likely than their non-Hispanic white counterparts to have used any type of substance use disorder treatment (Mancini et al., 2015). The relationship between nativity and utilization of substance use disorder services varied among Hispanic groups, with utilization by Puerto Ricans being higher among those born on the island of Puerto Rico relative to those born in the continental United States. The authors point to several documented barriers to substance use disorder treatment among Hispanics, such as family factors, insurance/costs, linguistic and cultural factors, and the fit of service need with existing programs. The lifetime prevalence of use of heroin (as well as other drugs) was greater among U.S.-born relative to immigrant Hispanics after controlling for confounders, a finding that corroborates those of previous studies (Mancini et al., 2015). Data from an urban sample of the Treatment Episode Data Set-Discharges, a national census of annual discharges from substance use disorder treatment facilities, indicate that Hispanics and blacks are less likely to complete outpatient treatment relative to their white counterparts. Among heroin users, Hispanics were only 75 percent as likely as whites to complete a treatment episode (Mennis and Stahler, 2016).

For OUD specifically, a study of geographic and demographic differentials in uptake of buprenorphine compared with methadone treatment in New York City neighborhoods between 2004 and 2013 found that buprenorphine treatment had increased in all social areas over time, but that increases had been significantly higher in areas with the highest income and lowest percentages of Hispanics, blacks, and low-income residents. Overall, methadone treatment had remained stable over time (Hansen et al., 2016). Another study (the RAPiDs study) examined variables affecting enrollment in treatment among Rhode Island young adult users of nonmedical prescription opioids. This study found that nonwhite race and low income, as well as previous incarceration and having experienced drug-related discrimination by medical providers, were associated with significantly lower rates of treatment enrollment (Liebling et al., 2016).

In an analysis of the demographic characteristics and behavioral health of persons aged 12 and older that met criteria for past-year OUD (n = 6,125)

in the 2005–2013 National Surveys on Drug Use and Health, Wu and colleagues (2016) found that greater than 80 percent of those with OUD had another substance use disorder, and 28.7 percent had experienced a major depressive episode. Among persons with OUD, 26.2 percent had used any treatment for alcohol or drug use, and 19.4 percent had used opioid-specific treatment. Opioid-specific treatment was especially underutilized by adolescents, the uninsured, blacks, Native Hawaiians/Pacific Islanders/Asian Americans, persons with prescription OUD only, and persons without major depressive episodes or substance use disorder (Wu et al., 2016).

Individuals involved in the criminal justice system also face barriers to effective treatment. While these individuals have high rates of substance use disorder (60–80 percent), their treatment utilization is low. Examining data from the Arrestee Drug Abuse Monitoring II program, Hunt and colleagues (2015) found that those with a history of heroin use had higher drug use and severity and higher rates of treatment utilization than those reporting use of other drugs. However, a minority (34 percent) of arrestees with drug use histories had received substance use disorder treatment during their lifetime, and only 14 percent had obtained such treatment during the year prior to their arrest. Receipt of mental health treatment services also is extremely low in this population despite a high prevalence of mental health problems.

More than 53 percent of state prison and local jail inmates meet diagnostic criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) for drug abuse or dependence, and 19 percent have a lifetime history of heroin use (Belenko et al., 2013). However, a low proportion of those who could benefit from treatment receive it. When treatment with medication is offered, it is typically limited to detoxification, and often is provided only to pregnant women. Moreover, about half of drug courts have a specific policy against use of treatment with medication. Yet studies have demonstrated the efficacy of treatment with medication (i.e., methadone, buprenorphine, injectable sustained-release naltrexone) in criminal justice populations. Lack of treatment uptake in the criminal justice system may reflect state and local regulations, security concerns, institutional philosophy, and availability and resources. Additional research is needed on strategies for how best to integrate treatment into the criminal justice system at all stages (Belenko et al., 2013).

Summary

MAT for OUD has been found to be effective in a number of delivery models and settings but is greatly underutilized. This underutilization is driven by a combination of factors that include policies related to insurance coverage, payment, and approval and reimbursement limitations; lack of

availability of eligible providers; negative attitudes toward treatment with medication among providers, patients, and the general public; insufficient training in OUD and its treatment among medical providers; and disparities in access and utilization. Aside from its immediate benefits to individuals with OUD, a strategy of increasing access to and utilization of treatment for OUD can be expected to diminish the risk of public health harms in the broader community by lowering the number of individuals engaging in opioid misuse. State and local governments are well positioned to take responsibility for ensuring universal access to treatment of OUD, using whatever financial and technical assistance is available from the federal government. To enhance these benefits, additional research could examine several relevant areas, such as (1) development of new medications; (2) testing of the efficacy of combination drugs (e.g., combining buprenorphine and naloxone to decrease potential for misuse); testing of the efficacy of approaches for increasing utilization in various key treatment settings, reducing negative side effects (including those related to inappropriate opioid/benzodiazepine prescribing), and reducing disparities in utilization; (3) testing of the efficacy of therapies combining medication and behavioral treatment; and (4) testing of alternative pain management methods for reducing the iatrogenic effects of pain management on opioid addiction. See Chapter 3 for the committee's formal research recommendation.

The enormity of the current opioid crisis necessitates an immediate and massive expansion of treatment capacity to provide evidence-based treatment and recovery to millions of individuals. More than 2 million people have a prescription opioid–related OUD, and almost 600,000 have a heroin-related OUD (HHS, 2016). To address the gap between the availability of and demand for treatment, **the committee recommends that states, with assistance from relevant federal agencies, particularly the Substance Abuse and Mental Health Services Administration, provide universal access to evidence-based treatment for opioid use disorder (OUD), including use of medication, in a variety of settings, including hospitals, criminal justice settings, and substance use treatment programs. Efforts to this end should be carried out with particular intensity in communities with a high burden of OUD. State licensing bodies should require training in treatment for OUD for all licensed substance use disorder treatment facilities and providers (Recommendation 5-6).**

The committee recommends that schools for health professional education, professional societies, and state licensing boards require and provide basic training in the treatment of opioid use disorder for health care providers, including but not limited to physicians, nurses, pharmacists, dentists, physician assistants, psychologists, and social workers (Recommendation 5-7).

The committee recommends that the U.S. Department of Health and

Human Services and state health financing agencies remove impediments to full coverage of medications approved by the U.S. Food and Drug Administration for treatment of opioid use disorder (Recommendation 5-8).

STRATEGIES FOR REDUCING HARM

Drug use can have a number of negative consequences, including lowered quality of life, transmission of disease through intravenous needles, and increased morbidity and mortality. Many of the tools of drug policy are aimed at reducing or ending the use of drugs. These tools utilize a variety of methods, including individual rehabilitation and treatment, enforcement of criminal sanctions against drug use or distribution, and public communication campaigns aimed at preventing drug use. The priority of the harm reduction approach, in contrast, is minimizing the negative consequences of drug use instead of focusing solely on reducing drug use itself. Harm reduction encompasses multiple strategies tailored to the needs of particular individuals and communities, and may focus on encouraging safer drug use, managed use, and/or abstinence.

Two of the most significant harms of opioid use are overdose and transmission of bloodborne infections due to injection drug use. As discussed in Chapter 4, opioid-related overdoses have soared in recent years; in 2015, more than 33,000 people died from opioid overdoses, nearly half of which involved a prescription opioid (Rudd et al., 2016). Harm reduction strategies for opioids are aimed primarily at these two harms. Strategies for reducing the harms of opioid use may include dispensing naloxone for use in reversing overdose, providing services that facilitate safer drug use (syringe exchange, supervised injection facilities, and drug checking), and implementing behavioral interventions. Changes in drug laws also can be effective (see Box 5-4 for an international example). Often, harm reduction strategies are implemented together (see Box 5-5 for an example). Thus, naloxone is provided along with training in how to use it, and syringe exchange facilities also facilitate treatment admission or other services, educate users about overdose prevention and abscess and wound care, and provide training in the use of naloxone.

Use of Naloxone to Reverse Overdose

As discussed in Chapter 4, naloxone is an opioid antagonist of the μ opioid receptor. When administered, it blocks the effects of opioids and reverses depression of the respiratory and central nervous systems, preventing death by overdose. Naloxone can be administered via intravenous, intramuscular, subcutaneous, or intranasal routes. In 2014, the FDA approved a naloxone autoinjector system that provides the administrator

BOX 5-4
Outcomes Associated with a Harm Reduction Strategy in Portugal

In Portugal, spearheaded by a multidisciplinary group led by a physician, intentional and aggressive steps were taken to focus on the health of the citizens and effect a shift in attitude from viewing drug use as a crime to viewing it as a health problem to be addressed as a disease. As a result, people who use drugs are considered "physically ill or sick," not "criminal" (Laqueur, 2014). Treatment of the substance use disorder was aggressively emphasized (Bushak, 2016). Possession of a small amount (up to a 10-day supply) of drugs is now dealt with by the local Commission for the Dissuasion of Drug Addiction, composed of an attorney, physician, and social worker.

Approximately 90 percent of antidrug resources in Portugal is now spent on prevention and treatment, with the rest going to incarceration and other punishment. The increased health care costs are thought to be offset by cost reductions in the penal system. Portugal did not keep statistics on drug use or misuse until after 2001, but drug use has not increased since then as was predicted at the time of the change in the law, and has remained relatively unchanged. What did decrease was the negative effects of drug use, such as the number of cases of infection-related morbidity associated with drug misuse, the rate of substance use disorder, and drug-related mortality. The burden on the Portuguese criminal justice system also has significantly decreased. What is unique about the Portugal experience is the combination of decriminalization and an aggressive focus on health care (Bushak, 2016; EMCDDA, 2015; Hughes and Stevens, 2010; Laquer, 2014).

with voice and visual guidance, and in late 2015, the FDA approved a naloxone nasal spray, which is easy to administer and eliminates the risk of a contaminated needle stick. Naloxone is not a controlled substance and has no abuse potential, but when administered to people who are dependent on opioids, it may cause acute withdrawal symptoms, including vomiting.

Overdoses can occur among all groups of opioid users—those who use illicit opioids, those who misuse prescription opioids, and those who use opioids to manage pain as prescribed by a doctor. Naloxone training and distribution programs have historically been targeted at users of illicit opioids, particularly people who use drugs intravenously, because they are at high risk and are also most likely to report using the medication to reverse an overdose (Rowe et al., 2015). However, there is growing interest in translating these programs into clinical settings for patients who take prescription opioids (Mueller et al., 2015). Because anyone who uses opioids is at risk of overdose, various strategies are used to make naloxone avail-

BOX 5-5
Harm Reduction Strategies in Huntington, West Virginia

West Virginia has been hit hard by the opioid epidemic. The state had the highest rate of opioid overdose deaths in the nation in 2015, with 41.5 deaths per 100,000 people (Rudd et al., 2016). Between 2010 and 2016, drug wholesalers shipped millions of opioid pills to West Virginia—433 pills for every man, woman, and child in the state (Eyre, 2016).

In August 2016, paramedics and police officers in the town of Huntington responded to 26 heroin overdoses in one afternoon alone. However, the paramedics and police officers were equipped with naloxone and were experienced in dealing with overdoses, and all 26 people survived. Huntington has responded to its opioid problem by "throwing everything we know at the problem," including harm reduction strategies such as providing naloxone, medication-assisted treatment, and syringe exchange. The town began equipping its police officers with naloxone in spring 2016, and changes to state laws have enabled naloxone distribution to the public and protection of those who report overdoses. The town has eight medically assisted detox beds, which are always full, and a long-term recovery facility with peer mentors. West Virginia's first syringe exchange program opened in Huntington in 2015, and in less than 1 year distributed 150,000 clean syringes to more than 1,700 people. The program also offers medical assessments and referrals to recovery options.

Huntington's groundbreaking programs "have been models for the rest of the state," but unfortunately, the money needed to conduct these programs is running out. Dr. Michael Kilkenney of the Cabell-Huntington Health Department says that the town has "programs ready to launch, and we have no resources to launch them with. We're launching them without resources, because our people are dying, and we can't tolerate that" (Joseph, 2016).

able in a variety of settings. These strategies can be divided roughly into community-based, systems-based, pharmacy-based, and prescriber-based.

There are a number of barriers to the use of naloxone to prevent overdose. First is a simple logistical barrier: the person who is overdosing cannot self-administer naloxone, so there must be someone nearby who can recognize the symptoms of overdose, can quickly access naloxone, and knows how to administer it. There also are legal and regulatory barriers. For example, naloxone requires a prescription in some states, a nonmedical person who administers naloxone can face potential liability, and people who use drugs who summon aid for an overdose can face potential legal ramifications. Most states have passed laws to address these various barriers. New Mexico, for example, passed the first law protecting lay administrators of naloxone in 2001 and the first "Good Samaritan" law to protect

users who summon help in 2007 (Network for Public Health Law, 2016). Dozens of states have followed suit. Rhode Island has made particular progress in eliminating the legal barriers to the use of naloxone (see Box 5-6). The adoption of these laws has been shown to be associated with a decrease in opioid-related deaths. Rees and colleagues (2017) examined the effect of naloxone access laws and Good Samaritan laws. They found that the adoption of a naloxone access law is associated with a 9–11 percent reduction in opioid-related deaths, while the adoption of a Good Samaritan law appears to be associated with a similar reduction, although this association is not statistically significant. The authors note that the naloxone access laws most strongly associated with a decrease in deaths are those that remove criminal liability for possession of naloxone (Rees et al., 2017).

Making changes to the legal landscape requires, of course, some level of public support for the changes, and the public does not always support

BOX 5-6
Improved Access to Naloxone in Rhode Island

Rhode Island is among the top five states in per capita opioid overdose deaths (Rudd et al., 2016); drug overdoses kill more people in the state than motor vehicle crashes (Green et al., 2015b). In the past decade, Rhode Island has been a leader in innovative programs aimed at reducing overdose deaths, including by improving access to naloxone through a variety of avenues. In 2006, Miriam Hospital began a pilot program called Preventing Overdose and Naloxone Intervention (PONI), which provides naloxone kits and training to individuals. PONI also collaborates with the department of corrections to train incarcerated individuals on overdose prevention and distribute naloxone prior to release. In 2012, Rhode Island passed a Good Samaritan law to shield bystanders who administer naloxone and overdose victims from prosecution or civil liability. The same law provides limited drug-related immunity to victims and responders of an overdose. Also in 2012, Walgreens Pharmacy entered into a collaborative practice agreement that permitted it to distribute naloxone without a prescription.

Pharmacy-distributed naloxone evolved into a statewide endeavor with the help of a 2014 emergency regulation that expanded access further by allowing all pharmacists to dispense naloxone to patients without their having to see a prescriber for a prescription. In addition, the law permitted all licensed prescribers to dispense naloxone to organizations and to anyone at risk of overdose, as well as to a friend or family member of such an individual (i.e., a "third party"). In 2017, new legislation furthered access to naloxone by mandating insurance coverage of generic naloxone products for both insured individuals and third parties. Today, naloxone distribution in the state has reached optimal community uptake shown to reduce mortality (Bird et al., 2015).

BOX 5-7
State Laws on Naloxone

In a 2016 report, the Network for Public Health Law tracks multiple questions regarding state laws on naloxone aimed at increasing access among nonprofessional responders, including the following:

- Does the jurisdiction have a naloxone access law?
- Do prescribers have immunity from criminal prosecution for prescribing, dispensing, or distributing naloxone to a layperson?
- Do prescribers have immunity from civil liability for prescribing, dispensing, or distributing naloxone to a layperson?
- Is a layperson immune from criminal liability when administering naloxone?
- Is a layperson immune from civil liability when administering naloxone?
- Are prescriptions of naloxone authorized to third parties?
- Is prescription by a standing order authorized?
- Does the law remove criminal liability for possession of naloxone?

The report states that as of June 2016, 48 states and the District of Columbia had passed naloxone access legislation (Kansas, Montana, and Wyoming were the exceptions, and all three subsequently passed naloxone laws, in April and May 2017). Specific legal provisions in those 48 jurisdictions vary: the laws allow for layperson possession of naloxone without a prescription in 17 jurisdictions; prescribers have immunity from criminal prosecution in 37 jurisdictions and from civil liability in 33; laypersons who administer naloxone are immune from civil liability in 42 jurisdictions and from criminal liability in 36; prescriptions to third parties are authorized in 44 jurisdictions; and prescriptions by standing order are authorized in 39 jurisdictions. Prescribing to third parties is permitted in 44 jurisdictions.

The report also summarizes "Good Samaritan" laws, which provide varying levels of immunity from prosecution for those summoning emergency responders in the event of an overdose, including

- immunity from prosecution for possession of controlled substances, and
- immunity from prosecution for possession of drug paraphernalia.

Some form of "Good Samaritan" law had been passed in 37 jurisdictions, with all 37 providing immunity from prosecution for possession of controlled substances, and 25 additionally providing immunity from prosecution for possession of drug paraphernalia.

SOURCE: Network for Public Health Law, 2016.

the provision of naloxone, despite its obvious and immediate benefits (see Box 5-7 for a review of state laws regarding naloxone). Critics of naloxone programs argue that the availability of naloxone will encourage increased drug use because users will rely on it to save them from overdose, or that using naloxone is futile because people who overdose and are saved will only overdose again in the future. This latter example is supported by modeled evidence: overdose predicts subsequent overdose (Coffin and Sullivan, 2013). However, a similar argument could be made against the use of cardiac catheterization in people who have experienced myocardial infarction (MI) as a strategy to prevent future MI, the difference in this case being that the underlying obesity or other predictors of MI may be less stigmatized than opioid misuse or OUD. This is an important point, because the public's low level of knowledge about or familiarity with naloxone and lack of sympathy for people who use drugs impact the level of support for naloxone distribution (Bachhuber et al., 2015). However, one study showed that these perceptions could be changed through exposure to messaging, particularly that which included factual information along with a sympathetic narrative about an individual who could have been saved with naloxone (Bachhuber et al., 2015). The final barrier is cost. Demand for naloxone has risen dramatically as the opioid epidemic has worsened and as states have facilitated and promoted the lay use of naloxone. Companies recently have raised the price of naloxone; in one case, Kaleo Pharma raised the price for its specific pack of two single-dose injectors from $750 to $3,750 (Silverman, 2016). Lack of widespread insurance coverage further exacerbates the cost issues of naloxone, particularly for third-party prescriptions (currently legal in 44 jurisdictions; see Box 5-7).

Community-Based Programs

Overdose education and naloxone distribution programs are designed to train people in the community who are most likely to witness an overdose—people who use drugs and their friends and family. Training programs that provide information about recognizing and responding to an overdose have existed since the mid-1990s, but in recent years have increasingly focused on providing naloxone to trainees (CDC, 2012). The trainings are often offered in conjunction with other services aimed at people who use drugs, such as syringe exchange programs; as a result, the trainees tend to be largely users of illicit opioids (e.g., heroin), despite the fact that nearly half of opioid overdoses involve a prescription drug (Clark et al., 2014).

A 2014 systematic review of community-based overdose education and naloxone distribution programs found that they are effective at increasing bystander knowledge about recognizing and responding to an overdose, and that this increased knowledge results in the successful use of naloxone

and a high survival rate among those treated (Clark et al., 2014). Among the studies that measured knowledge before and after the training, many found a statistically significant increase in knowledge, although retention of this knowledge was variable. The primary components of the training included information about recognizing and preventing overdose; risk factors for overdose; and appropriate response to overdose, including naloxone administration.

According to an analysis of 19 Massachusetts communities adopting overdose education and naloxone distribution programs, rescue with naloxone was attempted 327 times between September 2006 and December 2009. The reported survival rate of overdose victims was high—98 percent overall—and the authors suggest that these trainings were associated with reduced mortality from opioid overdose at the population level (Walley et al., 2013). In addition to information about naloxone, trainees in these programs often receive information about other appropriate responses to overdose, including placing the person in the "recovery position," using cardiopulmonary resuscitation (CPR), and contacting emergency medical services (EMS). Yet while some studies report that training improved the use of appropriate responses, many trainees continued to use inappropriate responses (e.g., throwing water on the victim), and most did not contact EMS. The failure to contact EMS often was due to a fear of negative consequences, although those who did contact EMS generally reported positive experiences (Clark et al., 2014).

While many users of naloxone obtain the drug through a formal training program, one retrospective cohort study in Massachusetts suggests that people who obtain naloxone through other means (e.g., their social networks) can and do use it successfully to reverse overdoses. Nor do their responses to overdose differ significantly from those of people who have been trained in the provision of naloxone (Doe-Simkins et al., 2014).

Systems-Based Programs

Naloxone distribution and training can also be conducted through health systems such as the Veterans Health Administration (VHA). Veterans are at particular risk of opioid-related harms, as many suffer from chronic pain and take opioids to treat it. About 68,000 veterans—roughly 13 percent of the total population of veterans who take opioids—have OUD, and veterans are twice as likely as nonveterans to die from accidental opioid overdoses (Childress, 2016). To address these issues, the VHA launched its Opioid Safety Initiative in October 2013. This initiative has reduced the use of opioids among veterans while seeking to manage their pain in other ways, and monitors the VHA's opioid dispensing practices systemwide. The VHA also launched the Opioid Overdose Education and Naloxone

Distribution program in May 2014 to reduce opioid-related morbidity and mortality. This program encourages VA providers to consider providing education and naloxone to veterans who are at risk of opioid overdose, and gives providers tools for identifying such veterans using such information as opioid dosage, history of overdose, and other substance use disorder (VA, 2016).

Pharmacy-Based Programs

Research has shown that pharmacists are in an excellent position to train patients and their families on the use of naloxone kits (Bachyrycz et al., 2016; Bailey and Wermeling, 2014; Green et al., 2015b), although availability of the kits is not universal, and attitudes toward their use currently vary (Nielsen et al., 2016). Many states allow pharmacists to distribute naloxone over the counter without a prescription from a doctor. As of December 2016, this was the case in 33 states and the District of Columbia, with plans to expand to 7 more states in 2017 (see Walgreens, 2016). Pharmacists' knowledge, training, and position of trust put them in an ideal position to provide naloxone and counsel patients in when and how to use it. In the course of their work, most pharmacists "likely [are] serving some people who are misusing" prescription or illicit opioids (see APhA, 2015), and "can serve as invaluable instruments in identifying high-risk patients" (Bailey and Wermeling, 2014). Pharmacists interact daily with patients who are filling prescriptions for opioid analgesics, and in states that permit over-the-counter sales of syringes, with people who inject drugs. Because pharmacies are spread throughout neighborhoods and visited frequently by community members, the provision of naloxone through pharmacists greatly expands its accessibility, potentially enabling it to reach communities that are not served by other naloxone distribution programs (Green et al., 2015b).

Provider-Based Programs

Health care providers have an important role to play in reducing the harms of opioid use, both for users of illicit opioids and for patients who use opioid analgesics. Health care professionals can identify patients who are at risk of OUD or overdose, and can prescribe naloxone for patients who are taking opioids. Coprescription of opioids and naloxone is a fairly new practice, but some research suggests that it is well received by patients and can actually result in safer opioid use behaviors. Phillip Coffin, who oversees a project in which California clinics prescribe naloxone to any chronic pain patient who has used opioids for more than 3 months, says he is "looking for a change in the way that people interact with their opioid. The naloxone is there and will

hopefully never be used, but I hope it helps people recognize the real risk of prescription opioids" (Alcorn, 2014). A nonrandomized study of such clinics compared those patients who were and were not prescribed naloxone along with their opioid prescription. Patients who had previously had an opioid-related emergency department visit or who were prescribed higher doses of opioids were more likely to be offered naloxone. Compared with patients who did not receive a naloxone prescription, those who did had 63 percent fewer opioid-related emergency department visits after 1 year. Among those who were prescribed naloxone, 82 percent filled the prescription successfully, and 37 percent reported safer opioid use behaviors after receiving the prescription. Patients generally had a favorable opinion of naloxone: 97 percent said they believed that patients who are prescribed opioids for pain should also be offered naloxone, and 79 percent had either a positive or neutral response to being offered naloxone (Behar et al., 2016; Coffin et al., 2016). While this study was observational and may not be generalizable to other settings, it suggests that coprescription of naloxone is acceptable and may have additional benefits.

Coe and Walsh (2015) argue that while providing naloxone to all prescription opioid users is "probably unnecessary and perhaps not practicable," providers should consider making it available to patients who are at high risk, including those who

- have a diagnosis of alcohol or drug use disorder;
- maintain on a high dose of opioids;
- are initiating or receiving methadone;
- use other prescription medications, particularly benzodiazepines;
- have comorbid psychiatric disorders and are at greater risk for suicide by overdose; and
- have cognitive impairments that could lead to accidental overingestion.

The CDC guideline for prescribing opioids recommends naloxone coprescription in similar cases, with an additional recommendation for those patients who are at risk of returning to high doses and who are no longer tolerant (e.g., patients recently released from prison) (Dowell et al., 2016).

Despite the benefits of coprescription of naloxone, however there are significant barriers to this strategy. Providers may lack knowledge about naloxone and its use to prevent overdose, may be unaware that their patients are at risk for overdose, or may be hesitant to prescribe naloxone for fear that patients will be offended or will treat naloxone as a safety net and take more risks with opioids (Binswanger et al., 2015). One qualitative study of primary care staff who prescribed opioids to patients revealed that many staff had significant gaps in their knowledge about naloxone and were uncertain as to which patients were at risk of overdose. The staff in

the survey suggested that naloxone prescribing could be facilitated through standardized guidelines for prescribing, efforts to reduce the stigma of naloxone, and improved communication from emergency departments about overdoses and guidance for follow-up (Binswanger et al., 2015).

Patients who are at risk for overdose due to illicit drugs face an even greater barrier to obtaining naloxone or other harm reduction medications from their physicians. One study showed that 54 percent of physicians "would never consider prescribing naloxone to a patient who injected drugs" because of discomfort, lack of knowledge, or a belief that providing naloxone may condone risky drug use (Mueller et al., 2015). Health care professionals are in a prime position to identify and assist patients who are at risk for overdose, but stigma reduction efforts, education, and training are needed to capitalize on this opportunity.

Summary

Naloxone is a safe and effective method for reversing overdoses, and can easily be administered by bystanders. However, a number of barriers prevent it from being as widely used as it could be. These barriers include laws that do not allow community members to access naloxone or pharmacists to distribute it, its rising cost, and a lack of knowledge about it among health care providers. **The committee recommends that state medical and pharmacy boards educate and train their members in recognizing and counseling patients who are at risk for opioid use disorder and/or overdose, and encourage providers and pharmacists to offer naloxone when an opioid is prescribed to these patients or when a patient seeks treatment for overdose or other opioid-related issues (Recommendation 5-9).**

Reducing Disease Transmission

Syringe Exchange

Sharing syringes and drug injection equipment puts people who inject drugs at high risk of being infected with HIV and HCV, as well as hepatitis B virus. Unsafe drug use is responsible for about 8 percent of new HIV infections in the United States and has contributed to a recent 150 percent increase in HCV infections (CDC, 2015). Because such infections as HIV and HCV also can be spread through sexual activity or from mother to baby, reducing infections among people who inject drugs can help protect the whole community (CDC, 2015). Syringe exchange programs, whether in a community setting or through pharmacies, have proven an effective method for reducing the risk of infection. In addition to providing clean injection equipment, these programs can facilitate a number of other ser-

vices that are useful for people who use drugs, including helping them find treatment options, HIV testing and counseling, access to naloxone, and education about safer injection practices and safer drug use. Because syringe exchange programs often are just one of a broader set of harm reduction interventions, it is difficult to determine the extent to which they reduce the risk of infection for people who inject drugs. Research does suggest, however, that syringe exchange programs are an effective strategy for reducing HCV seroconversion (Hagan et al., 2011) and are effective at encouraging and facilitating entry into drug treatment (SAMHSA, 2011). In late 2016, the CDC called on state and local health departments to improve access to syringe exchange, citing a CDC report noting that only one in four people who use injection drugs always use sterile injection equipment (Abbasi, 2017). Additionally, a CDC brief cites multiple studies demonstrating the cost savings resulting from legalized syringe exchange programs, primarily through reducing the prevalence of HIV, HCV, and related health care costs (CDC, 2016a).

In some communities, safe injection equipment is available directly from pharmacies. The sale of syringes through pharmacies is regulated by a patchwork of laws and regulations, including state laws that require a prescription for syringes and state drug paraphernalia laws that forbid the sale of items intended to be used to consume illegal drugs (see Box 5-8 for a summary of state laws regulating the possession or distribution of injection equipment).[18] However, some states have taken steps to improve access to clean syringes by exempting syringes from such laws. The American Pharmacists Association is supportive of these efforts; it "encourages state legislatures and boards of pharmacy to revise laws and regulations to permit the unrestricted sale or distribution of sterile syringes and needles by or with the knowledge of a pharmacist in an effort to decrease the transmission of blood-borne diseases" (APhA, 1999).

Making syringes available from pharmacies has great potential to expand the geographic reach of access to clean syringes (Logan and Deutsch, 2015). Pharmacists also can counsel users and facilitate other services; in fact, a 2015 California law mandates that pharmacies selling nonprescription syringes provide written or verbal counseling at the time of sale about accessing drug treatment, accessing HIV and HCV testing and treatment, and safely disposing of used injection equipment.[19]

[18]See http://www.temple.edu/lawschool/phrhcs/otc.htm (accessed April 17, 2017).

[19]See http://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201320140AB1743&search_keywords= (accessed April 17, 2017).

BOX 5-8
Laws Concerning Injection Equipment

State laws affect the ability of a person who uses drugs to access clean syringe equipment. Laws that make it difficult to access equipment make it more likely that a user will share or reuse equipment, leading to infectious disease or infection. The Policy Surveillance Program tracks three primary questions regarding syringe access:

- Does state law prohibit the sale or distribution of drug paraphernalia?
- Does state law regulate the retail sale of syringes?
- Is syringe exchange explicitly authorized by state law?

Every state except Alaska criminalizes the sale or distribution of drug paraphernalia, but many jurisdictions have some exemptions for drug injection equipment: 7 jurisdictions explicitly exclude injection equipment from these laws, while 17 jurisdictions define syringes as illegal drug paraphernalia but have exceptions to allow for distribution of syringes to prevent bloodborne diseases. Twenty-four states have no such exceptions to their drug paraphernalia laws.

Twenty-five states have state laws that regulate the retail sale of syringes. Regulations include limits on the number of syringes that may be sold, the requirement that the buyer have a prescription for syringes, or requirements for the seller to collect specific information from the buyer. Eighteen jurisdictions explicitly authorize syringe exchange.

For much of the past 30 years, a ban on the use of federal funds for syringe exchange programs has been in place, but this ban was partially lifted in January 2016. Federal funds may not be used directly for syringes or needles, but may be used for program and staff expenses.

SOURCE: Policy Surveillance Program, 2012.

Supervised Injection Facilities

Supervised injection facilities (SIFs) provide users a safe space to inject drugs (that are obtained elsewhere) under clinical supervision. The facilities often offer clean injection equipment; information about safer drug use; referrals for medical care, testing, and treatment; and other services (We are the Drug Policy Alliance, 2017). Research has shown that SIFs are associated with safer injection practices and higher uptake of treatment services (Beletsky et al., 2008). In addition to the benefits for people who use drugs, SIFs reduce drug-related public nuisances, such as public drug use and discarded syringes (Beletsky et al., 2008). There are more than 100 SIFs operating in 11 countries worldwide, but none in the United States (*ScienceDaily*,

2016). Efforts are under way to implement SIF pilot projects in the United States; a 2016 study estimated that a single SIF in San Francisco could generate $3.5 million in health savings per year (*ScienceDaily*, 2016). The city of Ithaca, New York, has developed a comprehensive drug plan that calls for the exploration of a SIF. The plan explains that a SIF could "prevent fatal and non-fatal overdose, infectious disease, and bacterial infections; reduce public drug use and discarded needles; and provide primary care and referrals to basic services, housing, and substance use services and treatment" (City of Ithaca, 2016, p. 7). In light of these initiatives, it appears likely that severely affected localities will seek to establish SIFs. If they do so, however, legal questions may arise about whether states or local governments could authorize the facilities and operate them without violating federal law. Such facilities could be established on an experimental basis for the purpose of estimating the effectiveness and cost of such programs.

Drug Checking

The heroin that the individuals in Huntington, West Virginia, had injected, as described earlier in Box 5-5, was found to be mixed with fentanyl (an opioid 50–100 times stronger than morphine) and carfentanil (an opioid used for tranquilizing elephants that is 10,000 times stronger than morphine) (Joseph, 2016). Drug checking services are designed to avert these kinds of tragedies by analyzing the purity of drugs and identifying the presence of adulterants; in addition, the services use this information to monitor the drug market and identify new or lethal drugs. Drug checking services have existed in Europe for several decades but are scarcer in the United States, consisting of only a handful of online services that test anonymously sent drug samples or provide at-home test kits (Johnson, 2016).

Behavioral Interventions

The medications and services discussed above often are offered in tandem with behavioral interventions, although the latter interventions may also be offered solo. Evidence suggests that behavioral interventions—such as trainings, education about safe injection practices, and motivational counseling—can result in increased knowledge, safer and/or reduced drug use, and lower risk of overdose or transmission of disease. Research has shown, for example, that opioid overdose training that includes information about how to recognize an overdose and administer naloxone significantly increases knowledge and confidence in administration (Ashrafioun et al., 2016).

Behavioral interventions can be delivered in a variety of settings, including the community, syringe exchange facilities, clinics, and pharmacies.

One particularly promising setting for such interventions is the emergency department. People who seek help at an emergency department for opioid-related issues, including overdose, are in a prime position to be receptive to behavioral interventions, including education and treatment. Intervention in the emergency department is a fairly new strategy, so data on its effectiveness are limited, but early research suggests that this strategy can result in long-term behavior changes. A program begun in August 2014, for example, targets patients presenting with an opioid overdose in Rhode Island hospitals. Patients in the emergency department are given a naloxone kit and overdose prevention education, and are paired with a peer recovery coach who offers support and referral to addiction treatment (Samuels et al., 2014). The coaches are trained and certified by the Anchor Recovery Community Center, a peer-to-peer recovery support organization. Since the program's inception, 82 percent of people who have overdosed and been seen in Rhode Island hospitals have accepted a recovery coach, and 87 percent of them have remained engaged at the 30-day mark. Six months after their emergency department visit, 33 percent were still engaged and on the path to recovery (Goyer, 2016). Other emerging models for these types of interventions include the following:

- Safe Stations (Manchester, New Hampshire)—Fire stations are designated safe spaces for individuals who are seeking assistance on a path to recovery. Such individuals who arrive at fire stations are asked to dispose of needles, paraphernalia, and illegal substances, and then are medically assessed and may speak with recovery coaches and obtain further information about treatment.[20]
- Angel Program (Gloucester, Massachusetts): This program allows individuals to turn in their drugs to the police (without threat of arrest) and assigns them an "angel" to guide them through recovery. Early numbers suggest that the program saves money and may facilitate recovery. Of 100 program participants who answered a survey question, 60 had not returned to using drugs. Similar programs have begun in Chicago and North Carolina (Hasan, 2016).

Summary

Harm reduction strategies such as syringe exchanges, SIFs, and drug checking can not only facilitate safer drug use practices but also serve as a conduit for users to access treatment, medical care, and basic services. Unfortunately, while some strategies have been shown to reduce morbidity and mortality among people who use prescription and/or illicit opioids,

[20]See https://www.manchesternh.gov/Departments/Fire/Safe-Station (accessed April 17, 2017).

there are significant barriers to access to safe injection equipment, most notably state laws.

To reduce the harms of opioid use, including death by overdose and transmission of infectious diseases, the committee recommends that states implement laws and policies that remove barriers to access to naloxone and safe injection equipment by

- **permitting providers and pharmacists to prescribe, dispense, or distribute naloxone to laypersons, third parties, and first responders and by standing order or other mechanism;**
- **ensuring immunity from civil liability or criminal prosecution for prescribers for prescribing, dispensing, or distributing naloxone, and for laypersons for possessing or administering naloxone; and**
- **permitting the sale or distribution of syringes, exempting syringes from laws that prohibit the sale or distribution of drug paraphernalia, and explicitly authorizing syringe exchange (Recommendation 5-10).**

SUMMARY AND RECOMMENDATIONS

Each of the above strategies involves costs and trade-offs. Every policy that aims to curtail opioid-related harms by reducing access to opioids (including reducing "overprescribing") involves a potential therapeutic loss to patients in pain who have no satisfactory alternatives to opioids. The committee believes the restrictions, policies, and practices recommended in this report leave adequate space for responsible prescribing and reasonable access for patients and physicians who believe that an opioid is medically necessary. Another likely effect of restrictions on lawful access to prescription opioids is that some proportion of persons who have developed OUD will seek to satisfy their needs on the illicit market. One way of thinking about the policy trade-off is that curtailing access on the legal market to reduce the incidence of future iatrogenic OUD (and other harms) will drive persons who already have OUD to the illegal market. The committee regards the need to couple the long-run public health gain of reduced access with an investment in treatment for the millions of individuals with OUD as an ethical imperative.

Strategies for Restricting Supply

Recommendation 5-1. Improve access to drug take-back programs. States should convene a public–private partnership to implement drug take-back programs allowing individuals to return drugs to any pharmacy on any day of the year, rather than relying on occasional take-back events.

Strategies for Influencing Prescribing Practices

Recommendation 5-2. Establish comprehensive pain education materials and curricula for health care providers. State medical schools and other health professional schools should coordinate with their state licensing boards for health professionals (e.g., physicians, nurses, dentists, pharmacists), the National Institutes of Health's Pain Consortium, the U.S. Food and Drug Administration, the U.S. Centers for Disease Control and Prevention, and the U.S. Drug Enforcement Administration to develop an evidence-based national approach to pain education encompassing pharmacologic and nonpharmacologic treatments and educational materials on opioid prescribing.

Recommendation 5-3. Facilitate reimbursement for comprehensive pain management. Public and private payers should develop reimbursement models that support evidence-based and cost-effective comprehensive pain management encompassing both pharmacologic and nonpharmacologic treatment modalities.

Recommendation 5-4. Improve the use of prescription drug monitoring program data for surveillance and intervention. The U.S. Department of Health and Human Services, in concert with state organizations that administer prescription drug monitoring programs, should conduct or sponsor research on how data from these programs can best be leveraged for patient safety (e.g., data on drug–drug interactions), for surveillance of policy and other interventions focused on controlled substances (e.g., data on trends in opioid prescribing, effects of prescriber guidelines), for health service planning (e.g., data on discrepancies in dispensing of medications for treatment of opioid use disorder), and for use in clinical care (i.e., in clinical decision making and patient–provider communication).

Strategies for Reducing Demand

Recommendation 5-5. Evaluate the impact of patient and public education about opioids on promoting safe and effective pain management. The nation's public health leadership, including the surgeon general, the U.S. Centers for Disease Control and Prevention, and heads of major foundations and professional organizations, should convene a body of experts in communication and in pain and opioid use disorder to evaluate the likely impact (and cost) of an education program designed to raise awareness among patients with pain and the general public about

the risks and benefits of prescription opioids and to promote safe and effective pain management.

Recommendation 5-6. Expand treatment for opioid use disorder. States, with assistance from relevant federal agencies, particularly the Substance Abuse and Mental Health Services Administration, should provide universal access to evidence-based treatment for opioid use disorder (OUD), including use of medication, in a variety of settings, including hospitals, criminal justice settings, and substance use treatment programs. Efforts to this end should be carried out with particular intensity in communities with a high burden of OUD. State licensing bodies should require training in treatment for OUD for all licensed substance use disorder treatment facilities and providers.

Recommendation 5-7. Improve education in treatment of opioid use disorder for health care providers. Schools for health professional education, professional societies, and state licensing boards should require and provide basic training in the treatment of opioid use disorder for health care providers, including but not limited to physicians, nurses, pharmacists, dentists, physician assistants, psychologists, and social workers.

Recommendation 5-8. Remove barriers to coverage of approved medications for treatment of opioid use disorder. The U.S. Department of Health and Human Services and state health financing agencies should remove impediments to full coverage of medications approved by the U.S. Food and Drug Administration for treatment of opioid use disorder.

Strategies for Reducing Harm

Recommendation 5-9. Leverage prescribers and pharmacists to help address opioid use disorder. State medical and pharmacy boards should educate and train their members in recognizing and counseling patients who are at risk for opioid use disorder and/or overdose, and encourage providers and pharmacists to offer naloxone when an opioid is prescribed to these patients or when a patient seeks treatment for overdose or other opioid-related issues.

Recommendation 5-10. Improve access to naloxone and safe injection equipment. To reduce the harms of opioid use, including death by overdose and transmission of infectious diseases, states should implement

laws and policies that remove barriers to access to naloxone and safe injection equipment by

- permitting providers and pharmacists to prescribe, dispense, or distribute naloxone to laypersons, third parties, and first responders and by standing order or other mechanism;
- ensuring immunity from civil liability or criminal prosecution for prescribers for prescribing, dispensing, or distributing naloxone, and for laypersons for possessing or administering naloxone; and
- permitting the sale or distribution of syringes, exempting syringes from laws that prohibit the sale or distribution of drug paraphernalia, and explicitly authorizing syringe exchange.

REFERENCES

AAFP (American Academy of Family Physicians). 2017. *Chronic pain management and opioid misuse: A public health concern (position paper)*. http://www.aafp.org/about/policies/all/pain-management-opioid.html (accessed March 21, 2017).

Abbasi, J. 2017. CDC says more needle exchange programs needed to prevent HIV. *Journal of the American Medical Association* 317(4):350.

Afsharimani, B., K. Kindl, P. Good, and J. Hardy. 2015. Pharmacological options for the management of refractory cancer pain: What is the evidence? *Supportive Care in Cancer* 23(5):1473-1481.

Alcorn, T. 2014. America embraces treatment for opioid drug overdose. *Lancet* 383(9933): 1957-1958.

Alford, D.P., C.T. LaBelle, N. Kretsch, A. Bergeron, M. Winter, M. Botticelli, and J.H. Samet. 2011. Five year experience with collaborative care of opioid addicted patients using buprenorphine in primary care. *Archives of Internal Medicine* 171(5):425-431.

Alpert A., D. Powell, and A.L. Pacula. 2017. *Supply-side drug policy in the presence of substitutes: Evidence from the introduction of abuse-deterrent opioids*. Working Paper 23031. Cambridge, MA: National Bureau of Economic Research.

Anderson, D.R., I. Zlateva, E.N. Coman, K. Khatri, T. Tian, and R.D. Kerns. 2016. Improving pain care through implementation of the Stepped Care Model at a multisite community health center. *Journal of Pain Research* 9:1021-1029.

AoME (Academy of Medical Educators). 2017. *Professional standards*. http://www.medicaleducators.org/Professional-Standards (accessed March 21, 2017).

APhA (American Pharmacists Association). 1999. *APhA policy manual: Sale of sterile syringes*. http://www.pharmacist.com/policy-manual?page=11&key=pharmacist%20 (accessed January 7, 2017).

APhA. 2015. *Old drug, new life: Naloxone access expands to community pharmacies*. http://www.pharmacist.com/old-drug-new-life-naloxone-access-expands-community-pharmacies (accessed April 17, 2017).

Arlotta, C.J. 2016. *The FDA's support for abuse-deterrent opioids may not be enough*. *Forbes*, March 29. https://www.forbes.com/sites/cjarlotta/2016/03/29/the-fdas-support-for-abuse-deterrent-opioids/#6a872fe64ad6 (accessed April 26, 2017).

ASAM (American Society of Addiction Medicine). 2016. *Summary of the Comprehensive Addiction and Recovery Act*. http://www.asam.org/advocacy/issues/opioids/summary-of-the-comprehensive-addiction-and-recovery-act (accessed April 2, 2017).

ASHP (American Society of Health-System Pharmacists). 2011. *ASHP guidelines on pharmacist-conducted patient education and counseling*. https://www.ashp.org/-/media/assets/policy-guidelines/docs/guidelines-pharmacist-conducted-patient-education-counseling.ashx?la=en (accessed May 29, 2017).

Ashrafioun, L., S. Gamble, M. Herrmann, and G. Baciewicz. 2016. Evaluation of knowledge and confidence following opioid overdose prevention training: A comparison of types of training participants and naloxone administration methods. *Substance Abuse* 37(1):76-81.

Bachhuber, M.A., E.E. McGinty, A. Kennedy-Hendricks, J. Niederdeppe, and C.L. Barry. 2015. Messaging to increase public support for naloxone distribution policies in the United States: Results from a randomized survey experiment. *PLoS One* 10(7):e0130050.

Bachyrycz, A., S. Shrestha, B.E. Bleske, D. Tinker, and L.N. Bakhireva. 2016. Opioid overdose prevention through pharmacy-based naloxone prescription program: Innovations in health care delivery. *Substance Abuse* 38(1):55-60.

Bailey, A.M., and D.P. Wermeling. 2014. Naloxone for opioid overdose prevention: Pharmacists' role in community-based practice settings. *Annals of Pharmacotherapy* 48(5):601-606.

Barber, C., D. Gagnon, J. Fonda, J. Hermos, and M. Miller. 2017. Assessing the impact of prescribing directives on opioid prescribing practices among Veterans Health Administration providers. *Pharmacoepidemiology and Drug Safety* 26(1):40-46.

Bauhoff, S., B.D. Stein, and R.L. Pacula. 2014. *Do substance abuse policies influence opioid agonist therapies in substance abuse treatment facilities?* Paper presented at the Addiction Health Services Research Conference, Boston, MA.

Beaudoin, F.L., G.N. Banerjee, and M.J. Mello. 2016. State-level and system-level opioid prescribing policies: The impact on provider practices and overdose deaths, a systematic review. *Journal of Opioid Management* 12(2):109-118.

Behar, E., C. Rowe, G.M. Santos, S. Murphy, and O. Coffin. 2016. Primary care patient experience with naloxone prescription. *Annals of Family Medicine* 14(5):431-436.

Belenko, S., M. Hiller, and L. Hamilton. 2013. Treating substance use disorders in the criminal justice system. *Current Psychiatry Reports* 15(11):414.

Beletsky, L., C.S. Davis, E. Anderson, and S. Burris. 2008. The law (and politics) of safe injection facilities in the United States. *American Journal of Public Health* 98(2):231-237.

Bertsimas, D., and S.S. Patterson. 1998. The air traffic flow management problem with en route capacities. *Operations Research* 46(3):406-422.

Binswanger, I.A., and J.M. Glanz. 2015. Pharmaceutical opioids in the home and youth: Implications for adult medical practice. *Substance Abuse* 36(2):141-143.

Binswanger, I.A., S. Koester, S.R. Mueller, E.M. Gardner, K. Goddard, and J.M. Glanz. 2015. Overdose education and naloxone for patients prescribed opioids in primary care: A qualitative study of primary care staff. *Journal of General Internal Medicine* 30(12):1837-1844.

Bird, S.M., M.K.B. Parmar, and J. Strang. 2015. Take-home naloxone to prevent fatalities from opiate-overdose: Protocol for Scotland's public health policy evaluation, and a new measure to assess impact. *Drugs: Education Prevention & Policy* 22(1):66-76.

Bjørndal, T., D.E. Lane, and A. Weintraub. 2004. Operational research models and the management of fisheries and aquaculture: A review. *European Journal of Operational Research* 156(3):533-540.

Brandeis PMP COE (Prescription Monitoring Program Center of Excellence). 2012. *Prescription monitoring programs: An effective tool in curbing the prescription drug abuse epidemic*. https://www.bja.gov/publications/brandeis_pmp_effectiveness_brief.pdf (accessed April 17, 2017).

Brandeis PMP COE. 2013. *Using PDMPs to improve medical care: Washington State's data sharing initiative with Medicaid and workers' compensation*. http://www.pdmpassist.org/pdf/COE_documents/Add_to_TTAC/washington_nff_final.pdf (accessed December 6, 2016).

Brandeis PMP COE. 2014. *Using PDMP data to guide interventions with possible at-risk prescribers*. http://www.pdmpassist.org/pdf/COE_documents/Add_to_TTAC/Using_PDMP_Data_Guide_Interventions_at_Risk_Prescribers.pdf (accessed December 6, 2016).

Brandeis PMP COE. 2015. *Use of PDMP data by opioid addiction treatment programs*. http://www.pdmpassist.org/pdf/COE_documents/Add_to_TTAC/Use%20of%20PDMP%20data%20by%20opioid%20treatment%20programs.pdf (accessed December 6, 2016).

Brandeis PDMP TTAC (Prescription Drug Monitoring Program Training and Technical Assistance). 2017. *Prescription drug monitoring frequently asked questions*. http://www.pdmpassist.org/content/prescription-drug-monitoring-frequently-asked-questions-faq (accessed February 1, 2017).

Burns, R.M., R.L. Pacula, S. Bauhoff, H. Hendrikson, D.L. Leslie, and B.D. Stein. 2015. Policies related to opioid agonist therapy for opioid use disorders: The evolution of state policies from 2004 to 2013. *Substance Abuse* 37(1):63-69.

Bushak, L. 2016. Portugal's drug experiment: Tackling heroin addiction by decriminalizing drugs and focusing on health. *Medical Daily*, April 21. http://www.medicaldaily.com/portugal-drug-experiment-heroin-decriminalizing-drugs-382598 (accessed March 1, 2017).

Campanella, P.E., E. Lovato, C. Marone, L. Fallacara, A. Mancuso, W. Ricciardi, and M.L. Speccia. 2016. The impact of electronic health records on healthcare quality: A systematic review and meta-analysis. *European Journal of Public Health* 26(1):60-64.

Cassidy, T.A., P. DasMahapatra, R.A. Black, M.S. Wieman, and S.F. Butler. 2014. Changes in prevalence of prescription opioid abuse after introduction of an abuse-deterrent opioid formulation. *Pain Medicine* 15(3):440-451.

Caulkins, J.P., B. Kilmer, P.H. Reuter, and G. Midgette. 2014. Cocaine's fall and marijuana's rise: Questions and insights based on new estimates of consumption and expenditures in U.S. drug markets. *Addiction* 110(5):728-736.

Caulkins, J.P., E. Disley, M. Tzvetkova, M. Pardal, H. Shah, and X. Zhang. 2016. Modeling the structure and operation of drug supply chains: The case of cocaine and heroin in Italy and Slovenia. *International Journal of Drug Policy* 31:64-73.

CDC (U.S. Centers for Disease Control and Prevention). 2012. Community-based opioid overdose prevention programs providing naloxone—United States, 2010. *Morbidity and Mortality Weekly Report* 61(6):101-105. https://www.cdc.gov/mmwr/pdf/wk/mm6106.pdf (accessed November 12, 2016).

CDC. 2015. *CDC statement on syringe services programs—December 21, 2015*. https://www.cdc.gov/nchhstp/newsroom/2015/syringe_service_statement.html (accessed January 5, 2017).

CDC. 2016a. *Access to clean syringes*. https://www.cdc.gov/policy/hst/hi5/cleansyringes/index.html (accessed May 22, 2017).

CDC. 2016b. *Guideline information for patients. Safer, more effective pain management*. https://www.cdc.gov/drugoverdose/prescribing/patients.html (accessed February 17, 2017).

Chang, H.Y., T. Lyapustina, L. Rutkow, M. Daubresse, M. Richey, M. Faul, E.A. Stuart, and G.C. Alexander. 2016. Impact of prescription drug monitoring programs and pill mill laws on high-risk opioid prescribers: A comparative interrupted time series analysis. *Drug and Alcohol Dependence* 165:1-8.

Chen, J.H., J. Hom, I. Richman, S.M. Asch, T. Podchiyska, and N.A. Johansen, 2016. Effect of opioid prescribing guidelines in primary care. *Medicine (Baltimore)* 95(35):e4760.

Childress, S. 2016. Veterans face greater risks amid opioid crisis. *PBS Frontline*, March 28. http://www.pbs.org/wgbh/frontline/article/veterans-face-greater-risks-amid-opioid-crisis (accessed January 10, 2017).

Cicero, T.J., M.S. Ellis, and H.L. Surrat. 2012. Effect of abuse-deterrent formulation of OxyContin. *New England Journal of Medicine* 367(2):187-189.

Cigna. 2016. *Chronic pain: Policy overview.* https://www.cigna.com/healthwellness/hw/medical-topics/chronic-pain-cpain (accessed April 28, 2017).

City of Ithaca. 2016. *The Ithaca plan: A public health and safety approach to drugs and drug policy.* http://www.cityofithaca.org/documentcenter/view/4224 (accessed June 22, 2017).

Clark, A.K., C.M. Wilder, and E.L. Winstanley. 2014. A systematic review of community opioid overdose prevention and naloxone distribution programs. *Journal of Addiction Medicine* 8(3):153-163.

Clark, C. 1990. *Mathematical bioeconomics: The optimal management of renewable resources* (2nd edition). New York: John Wiley & Sons, Inc.

Clark, T., J. Eadie, P. Kreiner, and G. Strickler. 2013. *Prescription drug monitoring programs: An assessment of the evidence for best practices*. http://www.pewtrusts.org/~/media/assets/0001/pdmp_update_1312013.pdf (accessed December 6, 2016).

Cochella, S., and K. Bateman. 2011. Provider detailing: An intervention to decrease prescription opioid deaths in Utah. *Pain Medicine* 12(Suppl. 2):S73-S76.

Coe, M.A., and S.L. Walsh. 2015. Distribution of naloxone for overdose prevention to chronic pain patients. *Preventive Medicine* 80:41-43.

Coffin, P.O., and S.D. Sullivan. 2013. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. *Annals of Internal Medicine* 158(1):1-9.

Coffin, P.O., E. Behar, C. Rowe, G.M. Santos, D. Coffa, M. Bald, and E. Vittinghoff. 2016. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. *Annals of Internal Medicine* 165(4):245-252.

Coplan, P.M., H. Kale, L. Sandstrom, C. Landau, and H.D. Chilcoat. 2013. Changes in oxycodone and heroin exposures in the National Poison Data System after introduction of extended-release oxycodone with abuse-deterrent characteristics. *Pharmacoepidemiology and Drug Safety* 22(12):1274-1282.

Coplan, P.M., H.D. Chilcoat, S.F. Butler, E.M. Sellers, A. Kadakia, V. Harikrishnan, J.D. Haddox, and R.C. Dart. 2016. The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting. *Clinical Pharmacology and Therapeutics* 100(3):275-286.

Craig, B.M., and S.A. Strassels. 2010. Out-of-pocket prices of opioid analgesics in the United States, 1999-2004. *Pain Medicine* 11(2):240-247.

Cunningham, J.K., R.C. Callaghan, and L.M. Liu. 2015. U.S. federal cocaine essential ("precursor") chemical regulation impacts on U.S. cocaine availability: An intervention time-series analysis with temporal replication. *Addiction* 110(5):805-820.

Cunningham, J.K., L. Liu, and R.C. Callaghan. 2016. Essential/precursor chemicals and drug consumption: Impacts of U.S. sodium permanganate and Mexico pseudoephedrine controls on the numbers of U.S. cocaine and methamphetamine users. *Addiction* 111(11):1999-2009.

Cyclamed. 2014. *Annual report*. http://www.cyclamed.org/wp-content/uploads/2015/06/Rapport-annuel-v-anglaiseHD-.pdf (accessed February 24, 2017).

Daughton, C.G. 2003. Cradle to cradle stewardship of drugs for minimizing their environmental disposition while promoting human health—rationale for and avenues toward a green pharmacy. *Environmental Health Perspectives* 111(5):757-774.

Daughton, C.G. 2007. Pharmaceuticals in the environment: Sources and their management. In *Analysis, fate and removal of pharmaceuticals in the water cycle*, Vol. 50, Ch. 1, edited by M. Petrović and D. Barceló. Amsterdam, The Netherlands: Elsevier Science. Pp. 1-58.

Davis, C.S., M. Pierce, and N. Dasgupta. 2014. Evolution and convergence of state laws governing controlled substance prescription monitoring programs, 1988–2011. *American Journal of Public Health* 104(8):1389-1395.

Davis, C.S., N. Zaller, and T.C. Green. 2015. Addressing the overdose epidemic requires timely access to data to guide interventions. *Drug and Alcohol Review* 35(4):383-386.

de la Cruz, M., A. Reddy, V. Balankari, M. Epner, S. Frisbee-Hume, J. Wu, D. Liu, S. Yennuraialingam, H. Cantu, J. Williams, and E. Bruera. 2017. The impact of an educational program on patient practices of safe use, storage, and disposal of opioids at a comprehensive cancer center. *Oncologist* 22(1):115-121.

DEA (U.S. Drug Enforcement Administration). 2014. *Letter to registrants*. https://www.deadiversion.usdoj.gov/drug_disposal/dear_registrant_disposal.pdf (accessed November 15, 2016)

DEA. 2015a. *DEA announces largest-ever prescription drug operation*. Press Release. Washington, DC: DEA. https://www.dea.gov/divisions/no/2015/no052015.shtml (accessed March 1, 2017).

DEA. 2015b. *DEA'S Prescription Drug Take-Back Effort—A Big Success*. DEA Press Release, Washington, DC. https://www.dea.gov/divisions/hq/2015/hq100115.shtml (accessed November 12, 2016).

DEA. 2016a. *Counterfeit prescription pills containing fentanyls: A global threat*. DEA Intelligence Brief. Washington, DC: U.S. Department of Justice. https://www.dea.gov/docs/Counterfeit%20Prescription%20Pills.pdf (accessed April 17, 2017).

DEA. 2016b. *2016 national drug threat assessment summary*. https://www.dea.gov/resource-center/2016%20NDTA%20Summary.pdf (accessed April 23, 2017).

del Portal, D.A., M.E. Healy, W.A. Satz, and R.M. McNamara. 2016. Impact of an opioid prescribing guideline in the acute care setting. *Journal of Emergency Medicine* 50(1):21-27.

Delcher, C., A.C. Wagenaar, B.A. Goldberger, R.L. Cook, and M.M. Maldonado-Molina. 2015. Abrupt decline in oxycodone-caused mortality after implementation of Florida's Prescription Drug Monitoring Program. *Drug and Alcohol Dependence* 150:63-68.

Dobkin, C., and N. Nicosia. 2009. The war on drugs: Methamphetamine, public health, and crime. *The American Economic Review* 99(1):324-349.

Doe-Simkins, M., E. Quinn, Z. Xuan, A. Sorensen-Alawad, H. Hackman, A. Ozonoff, and A. Y. Walley. 2014. Overdose rescues by trained and untrained participants and change in opioid use among substance-using participants in overdose education and naloxone distribution programs: A retrospective cohort study. *BMC Public Health* 14:297.

DOJ (U.S. Department of Justice). 2016. *United States reaches $8 million settlement agreement with CVS for unlawful distribution of controlled substances*. https://www.justice.gov/usao-md/pr/united-states-reaches-8-million-settlement-agreement-cvs-unlawful-distribution-controlled (accessed March 21, 2017).

D'Onofrio, G., P.G. O'Connor, M.V. Pantalon, M.C. Chawarski, S.H. Busch, P.H. Owens, S.L. Bernstein, and D.A. Fiellin. 2015. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: A randomized clinical trial. *Journal of the American Medical Association* 313(16):1636-1644.

Doorenbos, A.Z., D.B. Gordon, D. Tauben, J. Palisoc, M. Drangsholt, T. Lindhorst, J. Danielson, J. Spector, R. Ballweg, L. Vorvick, and J.D. Loeser. 2013. A blueprint of pain curriculum across prelicensure health sciences programs: One NIH Pain Consortium Center of Excellence in Pain Education (CoEPE) experience. *The Journal of Pain* 14(12):1533-1538.

Dowell, D., T. Haegerich, and R. Chou. 2016. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *Journal of the American Medical Association* 315(15):1624-1645.

Du Pen, S.L., A.R. Du Pen, N. Polissar, J. Hansberry, B.M. Kraybill, M. Stillman, J. Panke, R. Everly, and K. Syrjala. 1999. Implementing guidelines for cancer pain management: Results of a randomized controlled clinical trial. *Journal of Clinical Oncology* 17(1):361-370.

Ducharme, L.J., and A.J. Abraham. 2008. State policy influence on the early diffusion of buprenorphine in community treatment programs. *Substance Abuse Treatment, Prevention, and Policy* 3:17.

Egan, K.L., E. Gregory, M. Sparks, and M. Wolfson. 2017. From dispensed to disposed: Evaluating the effectiveness of disposal programs through a comparison with prescription drug monitoring program data. *American Journal of Drug and Alcohol Dependence* 43(1):69-77.

EMCDDA (European Monitoring Centre for Drugs and Drug Addiction). 2015. *Preventing overdose deaths in Europe.* Lisbon, Portugal: EMCDDA.

Eyre, E. 2016. Drug firms poured 780M painkillers into WV amid rise of overdoses. *Charleston Gazette-Mail*, December 17. http://www.wvgazettemail.com/news-health/20161217/drug-firms-poured-780m-painkillers-into-wv-amid-rise-of-overdoses#sthash.Lyer58dK.dpuf (accessed March 1, 2017).

FBM (Florida Board of Medicine). 2010. *Standards for the use of controlled substances for the treatment of pain.* http://www.painpolicy.wisc.edu/sites/www.painpolicy.wisc.edu/files/Florida%20Medical%20Board%20Regulations_1.pdf (accessed February 25, 2017).

FDA (U.S. Food and Drug Administration). 2015a. *Abuse-deterrent opioids—evaluation and labeling: Guidance for industry*. https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf (accessed February 24, 2017).

FDA. 2015b. *History.* https://www.fda.gov/AboutFDA/WhatWeDo/History (accessed March 21, 2017).

FDA. 2016a. *Training and continuing education*. https://www.fda.gov/Training (accessed March 21, 2017).

FDA. 2016b. *Summary minutes of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee joint meeting May 3-4, 2016*. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM509895.pdf (accessed April 21, 2017).

FDA. 2016c. *What to ask your doctor before taking opioids*. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm529517.htm (accessed February 17, 2017).

FDA. 2017a. *2017 meeting materials, Drug Safety and Risk Management Advisory Committee*. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm536632.htm (accessed March 15, 2017).

FDA. 2017b. *Introduction for the FDA blueprint for prescriber education for extended-release and long-acting opioid analgesics*. https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM515636.pdf (accessed February 5, 2017).

Fleming, E., S. Proescholdbell, N. Sachdeva, A.A. Alexandridis, L. Margolis, and K. Ransdell. 2016. North Carolina's Operation Medicine Drop: Results from one of the nation's largest drug disposal programs. *North Carolina Medical Journal* 77(1):59-62.

FSMB (Federation of State Medical Boards). 2013. *Model policy on the use of opioid analgesics in the treatment of chronic pain.* http://www.fsmb.org/Media/Default/PDF/FSMB/Advocacy/pain_policy_july2013.pdf (accessed January 10, 2017).

FSMB. 2017. *Guidelines for the chronic use of opioid analgesics.* https://www.fsmb.org/Media/Default/PDF/Advocacy/Opioid%20Guidelines%20As%20Adopted%20April%202017_FINAL.pdf (accessed May 28, 2017).

Garg, R.K., J.A. Turner, A.M. Bauer, T. Wickizer, M.D. Sullivan, and G.M. Franklin. 2013. Changes in opioid prescribing for Washington workers' compensation claimants after implementation of an opioid dosing guideline for chronic noncancer pain: 2004 to 2010. *The Journal of Pain* 14(12):1620-1628.

Gau, J.M., and E.J. Brooke. 2016. An assessment of the impact of a multipronged approach to reducing problematic pain clinics in Florida. *Journal of Drug Issues* 47(2).

GCOAT (Governor's Cabinet Opiate Action Team). 2013. *Ohio guidelines for prescribing opioids for the treatment of chronic, non-terminal pain 80 mg of a morphine equivalent daily dose (MED) "trigger point."* http://mha.ohio.gov/Portals/0/assets/Initiatives/GCOAT/Guidelines-Chronic-Pain.pdf (accessed February 25, 2017).

Gladden, R.M., P. Martinez, and P. Seth. 2016. Fentanyl law enforcement submissions and increases in synthetic opioid–involved overdose deaths—27 states, 2013–2014. *Morbidity and Mortality Weekly Report* 65(33):837-843.

Glassmeyer, S.T., E.K. Hinchey, S.E. Boehme, C.G. Daughton, I.S. Ruhoy, O. Conerly, R.L. Daniels, L. Lauer, M. McCarthy, T.G. Nettesheim, K. Sykes, and V.G. Thompson. 2009. Disposal practices for unwanted residential medications in the United States. *Environment International* 35(3):566-572.

Goldstein, S.T., Z. Fangjun, S.C. Hadler, B.P. Bell, E.E. Mast, and H.S. Margolis. 2005. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. *International Journal of Epidemiology* 34(6):1329-1339.

Gordon, M.S., T.W. Kinlock, R.P. Schwartz, T.T. Fitzgerald, K.E. O'Grady, and F.J. Vocci. 2014. A randomized controlled trial of prison-initiated buprenorphine: Prison outcomes and community treatment entry. *Drug and Alcohol Dependence* 142:33-40.

Goyer, J. 2016. Presentation to the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse, Washington, DC, September 22.

Gray, J.A., and N.E. Hagemeier. 2012. Prescription drug abuse and DEA-sanctioned drug take-back events: Characteristics and outcomes in rural Appalachia. *Archives of Internal Medicine* 172(15):1186-1187.

Gray, J.A., N. Hagemeier, B. Brooks, and A. Alamian. 2015. Prescription disposal practices: A 2-year ecological study of drug drop box donations in Appalachia. *American Journal of Public Health* 105(9):e89-e94.

Green, L.W., and M.W. Kreuter. 2010. Evidence hierarchies versus synergistic interventions. *American Journal of Public Health* 100(10):1824-1825.

Green, T.C., N. Zaller, J. Rich, S. Bowman, and P. Friedmann. 2011. Revisiting Paulozzi et al.'s "Prescription drug monitoring programs and death rates from drug overdose." *Pain Medicine* 12(6):982-985.

Green, T.C., S. Bowman, C.S. Davis, and P. Friedmann. 2015a. Discrepancies in addressing overdose prevention through prescription drug monitoring programs. *Drug Alcohol and Dependence* 153:355-358.

Green, T.C., E.F. Dauria, J. Bratberg, C.S. Davis, and A.Y. Walley. 2015b. Orienting patients to greater opioid safety: Models of community pharmacy-based naloxone. *Harm Reduction Journal* 12:25.

Haddad, M.S., A. Zelenev, and F.L. Altice. 2013. Integrating buprenorphine maintenance therapy into federally qualified health centers: Real-world substance abuse treatment outcomes. *Drug and Alcohol Dependence* 131(1-2):127-135.

Haddad, M.S., A. Zelenev, and F.L. Altice. 2015. Buprenorphine maintenance treatment retention improves nationally recommended preventive primary care screenings when integrated into urban federally qualified health centers. *Journal of Urban Health* 92(1): 193-213.

Haegerich, T.M. 2016. *Prescription drug monitoring programs and other state level strategies*. Presentation to the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse, Washington, DC, September 22. http://www.nationalacademies.org/hmd/Activities/PublicHealth/AddressPrescriptionOpioidAbuse/2016-SEP-22/Videos/Session%204/19-haegerich-video.aspx.

Haegerich, T.M., L.J. Paulozzi, B.J. Manns, and C.M. Jones. 2014. What we know, and don't know, about the impact of state policy and systems-level interventions on prescription drug overdose. *Drug and Alcohol Dependence* 145:34-47.

Hagan, H., E.R. Pouget, and D.C. Des Jarlais. 2011. A systematic review and meta-analysis of interventions to prevent hepatitis C virus infection in people who inject drugs. *Journal of Infectious Diseases* 204(1):74-83.

Hansen, H., C. Siegel, J. Wanderling, and D. DiRocco. 2016. Buprenorphine and methadone treatment for opioid dependence by income, ethnicity and race of neighborhoods in New York City. *Drug and Alcohol Dependence* 164:14-21.

Harle, C.A., R.L. Cook, H.S. Kinsell, and J.S. Harman. 2014. Opioid prescribing by physicians with and without electronic health records. *Journal of Medical Systems* 38(11):138.

Harris, K., J. Curtis, B. Larsen, S. Calder, K. Duffy, G. Bown, M. Hadley, and P. Tristani-Firouzi. 2013. Opioid pain medication use after dermatologic surgery: A prospective observational study of 212 dermatologic surgery patients. *JAMA Dermatology* 149(3):317-321.

Hasan, S. 2016. One year later: Gloucester's opioid program inspires policy reform. *NPQ: Nonprofit Quarterly*, June 3. https://nonprofitquarterly.org/2016/06/03/one-year-later-gloucesters-opioid-program-inspires-policy-reform (accessed April 17, 2017).

Haynes, A., K. Kleinschmidt, M.B. Forrester, and A. Young. 2016. Trends in analgesic exposures reported to Texas Poison Centers following increased regulation of hydrocodone. *Clinical Toxicology* 54(5):434-440.

HHS (U.S. Department of Health and Human Services). 2016. *Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health*. HHS Publication SMA 16-4984, NSDUH Series H-51. Rockville, MD: Substance Abuse and Mental Health Services Administration.

Hill, C.S. 1996. Government regulatory influences on opioid prescribing and their impact on the treatment of pain of nonmalignant origin. *Journal of Pain and Symptom Management* 11(5):287-298.

Hill, M.V., M.L. McMahon, R.S. Stucke, and R.J. Barth, Jr. 2017. Wide variation and excessive dosage of opioid prescriptions for common general surgical procedures. *Annals of Surgery* 265(4):709-714.

Holliday, S.M., C. Hayes, A.J. Dunlop, S. Morgan, A. Tapley, K.M. Henderson, M.L. van Driel, E.G. Holliday, J.I. Ball, A. Davey, N.A. Spike, L.A. McArthur, and P.J. Magin. 2017. Does brief chronic pain management education change opioid prescribing rates? A pragmatic trial in Australian early-career general practitioners. *Pain* 158(2):278-288.

Hser, Y.I., V. Hoffman, C.E. Grella, and M.D. Anglin. 2001. A 33-year follow-up of narcotics addicts. *Archives of General Psychiatry* 58(5):503-508.

Hughes, C.E., and A. Stevens. 2010. What can we learn from the Portuguese decriminalization of illicit drugs? *The British Journal of Criminology* 50(6):999-1022.

Humphries, C.A., D.J. Counsell, R.C. Pediani, and S.L. Close. 1997. Audit of opioid prescribing: The effect of hospital guidelines. *Anaesthesia* 52(8):745-749.

Hunt, E., R.H. Peters, and J. Kremling. 2015. Behavioral health treatment history among persons in the justice system: Findings from the arrestee drug abuse monitoring II program. *Psychiatric Rehabilitation Journal* 38(1):7-15.

Inciardi, J.A., H.L. Surratt, S.P. Kurtz, and T.J. Cicero. 2007. Mechanisms of prescription drug diversion among drug-involved club- and street-based populations. *Pain Medicine* 8(2):171-183.

IOM (Institute of Medicine). 2007. *Ending the tobacco problem: A blueprint for the nation*. Washington, DC: The National Academies Press.

IOM. 2011. *Relieving pain in America: A blueprint for transforming prevention, care, education, and research*. Washington, DC: The National Academies Press.

IOM. 2015. *Public health implications of raising the minimum age of legal access to tobacco products*. Washington, DC: The National Academies Press.

Jann, M., W.K. Kennedy, and G. Lopez. 2014. Benzodiazepines: A major component in unintentional prescription drug overdoses with opioid analgesics. *Journal of Pharmacy Practice* 27(1):5-16.

Johnson, C.K. 2016. Could drug checking have prevented Prince's overdose death? *The Big Story*, October 4. http://bigstory.ap.org/article/df36569d11294d918572d3edf5428cbe/could-drug-checking-have-prevented-princes-overdose-death (accessed January 7, 2017).

Johnson, H., L. Paulozzi, C. Porucznik, K. Mack, and B. Herter. 2014. Decline in drug overdose deaths after state policy changes—Florida, 2010–2012. *Morbidity and Mortality Weekly Report* 63(26):569-574.

Jones, C.M., M. Campopiano, G. Baldwin, and E. McCance-Katz. 2015. National and state treatment need and capacity for opioid agonist medication-assisted treatment. *American Journal of Public Health* 105(8):e55-e63.

Joseph, A. 2016. 26 overdoses in just hours: Inside a community on the front lines of the opioid epidemic. *STAT*, August 22. https://www.statnews.com/2016/08/22/heroin-huntington-west-virginia-overdoses/ (accessed March 1, 2017).

Kaplan, E.H., D.L. Craft, and L.M. Wein. 2002. Emergency response to a smallpox attack: The case for mass vaccination. *Proceedings of the National Academy of Sciences of the United States of America* 99(16):10935-10940.

KBML (Kentucky Board of Medical Licensure). 2003. *Guidelines for the use of controlled substances in pain treatment*. http://www.kentucky.com/latest-news/article40998984.ece/BINARY/Kentucky%20Board%20of%20Medical%20Licensure's%20guidelines%20for%20the%20use%20of%20controlled%20substances%20in%20pain%20treatment (accessed February 25, 2017).

Kennedy-Hendricks, A., A. Gielen, E. McDonald, E.E. McGinty, W. Shields, and C.L. Barry. 2016. Medication sharing, storage, and disposal practices for opioid medications among U.S. adults. *JAMA Internal Medicine* 176(7):1027-1029.

Kerlikowske, G., C.M. Jones, R.M. Labelle, and T.P. Condon. 2011. Prescription drug monitoring programs—lack of effectiveness or a call to action. *Pain Medicine* 12(5):687-689.

Kim, N., J.L. Matzon, J. Abboudi, C. Jones, W. Kirkpatrick, C.F. Leinberry, F.E. Liss, K.F. Lutsky, M.L. Wang, M. Maltenfort, and A.M. Ilyas. 2016. A prospective evaluation of opioid utilization after upper-extremity surgical procedures: Identifying consumption patterns and determining prescribing guidelines. *Journal of Bone and Joint Surgery. American Volume* 98(20):e89.

Knudsen, H.K. 2015. The supply of physicians waivered to prescribe buprenorphine for opioid use disorders in the United States: A state-level analysis. *Journal of Studies on Alcohol and Drugs* 76(4):644-654.

Knudsen, H.K., A.J. Abraham, and P.M. Roman. 2011. Adoption and implementation of medications in addiction treatment programs. *Journal of Addiction Medicine* 5(1):21-27.

LaBelle, C.T., S.C. Han, A. Bergeron, and J.H. Samet. 2016. Office-based opioid treatment with buprenorphine (OBOT-B): Statewide implementation of the Massachusetts Collaborative Care Model in Community Health Centers. *Journal of Substance Abuse Treatment* 60:6-13.

Laqueur, H. 2015. Uses and abuses of drug decriminalization in Portugal. *Law & Social Inquiry* 40(3):746-781.

Larney, S., W. Lai, K. Dolan, and D. Zador. 2016. Monitoring a prison opioid treatment program over a period of change to clinical governance arrangements, 2007–2013. *Journal of Substance Abuse Treatment* 70:58-63.

Law, A.V., P. Sakharkar, A. Zargarzadeh, B.W. Bilvick, K. Hess, M. Hata, R. Mireles, C. Ha, and T.J. Park. 2015. Taking stock of medication wastage: Unused medications in U.S. households. *Research in Social and Administrative Pharmacy* 11(2015):571-578.

Lerner, A.M. 1966. The abuse of paregoric in Detroit Michigan (1956–1965). *Bulletin on Narcotics* 3:13-19.

Levy, D.T., L. Nikolayev, and E. Mumford. 2005. Recent trends in smoking and the role of public policies: Results from the SimSmoke tobacco control policy simulation model. *Addiction* 100(10):1526-1536.

Li, G., J.E. Brady, B.H. Lang, J. Giglio, H. Wunsch, and C. DiMaggio. 2014. Prescription drug monitoring and drug overdose mortality. *Injury Epidemiology* 1(1):9.

Liebling, E.J., J.L. Yedinak, T.C. Green, S.E. Hadland, M.A. Clark, and B.D. Marshall. 2016. Access to substance use treatment among young adults who use prescription opioids nonmedically. *Substance Abuse Treatment, Prevention, and Policy* 11(1):38.

Loeffler, G., and C. Craig. 2013. The effect of legal bans on poison control center contacts regarding "legal highs." *Addiction* 108(7):1348-1349.

Logan, K., and S. Deutsch. 2015. Room for improvement in the New York State pharmacy-based syringe access program. *Columbia Medical Rev*iew 1(1):40-50.

Long, D., D. Lee., J. Johnson, E. Gaier, and P. Kostiuk. 1999. *Modeling air traffic management technologies with a queuing network model of the national airspace system*. https://pdfs.semanticscholar.org/b9c8/3126afb91cc91887c02e8d540a07e8063565.pdf (accessed January 6, 2017).

Lyapustina, T., L. Rutkow, H.Y. Chang, M. Daubresse, A.F. Ramji, M. Faul, E.A. Stuart, and G.C. Alexander. 2016. Effect of a "pill mill" law on opioid prescribing and utilization: The case of Texas. *Drug and Alcohol Dependence* 159:190-197.

Maeng, D.D., R.C. Snyder, C.J. Medico, W.M. Mold, and J.E. Maneval. 2016. Unused medications and disposal patterns at home: Findings from a Medicare patient survey and claims data. *Journal of the American Pharmacists Association* 56(1):41-46.

Mai, J., G. Franklin, and D. Tauben. 2015. Guideline for prescribing opioids to treat pain in injured workers. *Physical Medicine and Rehabilitation Clinics of North America* 26(3):453-465.

Mancini, M.A., C.P. Salas-Wright, and M.G. Vaughn. 2015. Drug use and service utilization among Hispanics in the United States. *Social Psychiatry and Psychiatric Epidemiology* 50(11):1679-1689.

Mark, T.L., R. Lubran, E.F. McCance-Katz, M. Chalk, and J. Richardson. 2015. Medicaid coverage of medications to treat alcohol and opioid dependence. *Journal of Substance Abuse Treatment* 55:1-5.

Maughan, B.C., E.V. Hersh, F.S. Shofer, K.J. Wanner, E. Archer, L.R. Carraso, and K.V. Rhodes. 2016. Unused opioid analgesics and drug disposal following outpatient dental surgery: A randomized controlled trial. *Drug and Alcohol Dependence* 168:328-334.

MBC (Medical Board of California). 2014. *Guidelines for prescribing controlled substances for pain*. http://www.mbc.ca.gov/licensees/prescribing/pain_guidelines.pdf (accessed February 25, 2017).

McCance-Katz, E.F., P. George, N.A. Scott, R. Dollase, A.R. Tunkel, and J. McDonald. 2017. Access to treatment for opioid use disorders: Medical student preparation. *American Journal on Addictions* 26(4):316-318.

McCauley, J.L., S.E. Back, and K.T. Brady, 2013. Pilot of a brief, web-based educational intervention targeting safe storage and disposal of prescription opioids. *Addictive Behaviors* 38(6):2230-2235.

McKetin, R., R. Sutherland, D.A. Bright, and M.M. Norberg. 2011. A systematic review of methamphetamine precursor regulations. *Addiction* 106(11):1911-1924.

McLaughlin, K. 2016. *Oregon health plan opens door to back-pain treatment*. http://www.bendbulletin.com/home/3363729-151/oregon-health-plan-opens-door-to-back-pain-treatment (accessed May 22, 2017).

Meara, E., J.R. Horwitz, W. Powell, L. McClelland, W. Zhou, A.J. O'Malley, and N.E. Morden. 2016. State legal restrictions and prescription-opioid use among disabled adults. *New England Journal of Medicine* 375(1):44-53.

Mearis, M., J.W. Shega, and R.W. Knoebel. 2014. Does adherence to National Comprehensive Cancer Network guidelines improve pain-related outcomes? An evaluation of inpatient cancer pain management at an academic medical center. *Journal of Pain and Symptom Management* 48(3):451-458.

Medlock, J., and A.P. Galvani. 2009. Optimizing influenza vaccine distribution. *Science* 325(5948):1705-1708.

Megrey, B.A. 1988. *A review and comparison of age-structured stock assessment models from theoretical and applied points of view*. Seattle, WA: U.S. Department of Commerce, National Oceanic and Atmospheric Administration, National Marine Fisheries Service, Northwest and Alaska Fisheries Center. https://docs.lib.noaa.gov/noaa_documents/NMFS/AFSC/NWAFC_processed_report/NWAFC_PR_88-21.pdf (accessed April 17, 2017).

Meinhofer, A. 2016. *The war on drugs: Estimating the effect of prescription drug supply-side interventions (September 7, 2016)*. https://ssrn.com/abstract=2716974 (accessed February 24, 2017).

Mennis, J., and G.J. Stahler. 2016. Racial and ethnic disparities in outpatient substance use disorder treatment episode completion for different substances. *Journal of Substance Abuse Treatment* 63:25-33.

Miaskowski, C., M.J. Dodd, C. West, S.M. Paul, D. Tripathy, P. Koo, and K. Schumacher. 2001. Lack of adherence with the analgesic regimen: A significant barrier to effective cancer pain management. *Journal of Clinical Oncology* 19(23):4275-4279.

Michna, E., W.Y. Cheng, C. Korves, H. Birnbaum, R. Andrews, Z. Zhou, A.V. Joshi, D. Schaaf, J. Mardekian, and M. Sheng. 2014. Systematic literature review and meta-analysis of the efficacy and safety of prescription opioids, including abuse-deterrent formulations, in non-cancer pain management. *Pain Medicine* 15(1):79-92.

Mohlman, M.K., B. Tanzman, K. Finison, M. Pinette, and C. Jones. 2016. Impact of the medication-assisted treatment for opioid addiction on Medicaid expenditures and health services utilization rates in Vermont. *Journal of Substance Abuse Treatment* 67:9-14.

Moore, R.A. 2013. What works for whom? Determining the efficacy and harm of treatments for pain. *Pain* 154(1):S77-S86.

Morden, N.E., J.T. Zerzan, T.C. Rue, P J. Heagerty, E.E. Roughead, S.B. Soumerai, D. Ross-Degnan, and S.D. Sullivan. 2008. Medicaid prior authorization and controlled-release oxycodone. *Medical Care* 46(6):573-580.

Mueller, S.R., A.Y. Walley, S.L. Calcaterra, J.M. Glanz, and L.A. Binswanger. 2015. A review of opioid overdose prevention and naloxone prescribing: Implications for translating community programming into clinical practice. *Substance Abuse* 36(2):240-253.

Murnion, B.P., D. Gnjidic, and S.N. Hilmer. 2010. Prescription and administration of opioids to hospital in-patients, and barriers to effective use. *Pain Medicine* 11(1):58-66.

NAMSDL (National Alliance for Model State Drug Laws). 2016. *Compilation of prescription monitoring program maps*. http://www.namsdl.org/library/CAE654BF-BBEA-211E-694C755E16C2DD21 (accessed January 18, 2017).

NAMSDL. 2017. *Frequency of prescription drug monitoring program (PMP) data reporting—Map*. http://www.namsdl.org/library/D33048BB-E629-981F-648E746714E2A194 (accessed July 10, 2017).

Network for Public Health Law. 2016. *Legal interventions to reduce overdose mortality: Naloxone access and overdose Good Samaritan laws*. https://www.networkforphl.org/_asset/qz5pvn/network-naloxone-10-4.pdf (accessed May 25, 2017).

Nielsen, S., S. Larney, M. Farrell, and L. Degenhardt. 2016. Community pharmacist knowledge, attitudes and confidence regarding naloxone for overdose reversal. *Addiction* 111(12):2177-2186.

NIH (National Institutes of Health). 2017. *Centers of Excellence in Pain Education (CoEPEs)*. https://painconsortium.nih.gov/nih_pain_programs/coepes.html (accessed March 21, 2017).

NRC (National Research Council). 2001. *Informing America's policy on illegal drugs: What we don't know keeps hurting us*. Washington, DC: National Academy Press.

Oehler, E.C., R.L. Day, D.B. Robinson, and L.H. Brown. 2016. Has the rescheduling of hydrocodone changed ED prescribing practices? *American Journal of Emergency Medicine* 34(12):2388-2391.

Oregon Health Plan. 2016. *Back policy changes fact sheet*. https://www.oregon.gov/oha/herc/FactSheet/Back-policy-changes-fact-sheet.pdf (accessed May 22, 2017).

Paone, D., E. Tuazon, J. Kattan, M.L. Nolan, D.B. O'Brien, D. Dowell, T.A. Farley, and H.V. Kunins. 2015. Decrease in rate of opioid analgesic overdose deaths—Staten Island, New York City, 2011–2013. *Morbidity and Mortality Weekly Report* 64(18):491-494.

Parmar, M.K.B., J. Strang, L. Choo, A.M. Meade, and S.M. Bird. 2017. Randomized controlled pilot trial of naloxone-on-release to prevent post-prison opioid overdose deaths. *Addiction* 112(3):502-515.

Patrick, S.W., C.E. Fry, T.F. Jones, and M.B. Buntin. 2016. Implementation of prescription drug monitoring programs associated with reductions in opioid-related death rates. *Health Affairs* 35(7):1324-1332.

Paulozzi, L.J., E.M. Kilbourne, and H.A. Desai. 2011. Prescription drug monitoring programs and death rates from drug overdose. *Pain Medicine* 12(5):747-754.

Pergolizzi, J.V., Jr., R.B. Raffa, and J.A. LeQuang. 2016. The Centers for Disease Control and Prevention opioid guidelines: Potential for unintended consequences and will they be abused? *Journal of Clinical Pharmacy and Therapeutics* 41(6):592-593.

Petry, N.M., and W.K. Bickel. 1998. Polydrug abuse in heroin addicts: A behavioral economic analysis. *Addiction* 93(3):321-335.

Pew Charitable Trusts. 2016. *Curbing prescription drug abuse with patient review and restriction programs: Learning from Medicaid agencies*. http://www.pewtrusts.org/~/media/assets/2016/03/curbing_prescription_drug_abuse_with_patient_review_and_restriction_programs.pdf (accessed March 21, 2017).

Policy Surveillance Program. 2012. *Syringe distribution laws*. http://lawatlas.org/datasets/syringe-policies-laws-regulating-non-retail-distribution-of-drug-parapherna (accessed April 17, 2017).

Poncelet, A., S. Bokser, B. Calton, K.E. Hauer, H. Kirsch, T. Jones, C.J. Lai, L. Mazotti, W. Shore, A. Teherani, L. Tong, M. Wamsley, and P. Robertson. 2011. Development of a longitudinal integrated clerkship at an academic medical center. *Medical Education Online* 16.

Qaseem, A., T.J. Wilt, R.M. McLean, and M.A. 2017. Noninvasive treatments for acute, subacute, and chronic low back pain: A clinical practice guideline from the American College of Physicians. *Annals of Internal Medicine* 166(7):I20-I21.

Qureshi, N., L.A. Wesolowicz, C.M. Liu, and L.A. Tungol. 2015. Effectiveness of a retrospective drug utilization review on potentially unsafe opioid and central nervous system combination therapy. *Journal of Managed Care and Specialty Pharmacy* 21(10):938-944.

Rathlev, N., R. Almomen, A. Deutsch, H. Smithline, H. Li, and P. Visintainer. 2016. Randomized controlled trial of electronic care plan alerts and resource utilization by high frequency emergency department users with opioid use disorder. *Western Journal of Emergency Medicine* 17(1):28-34.

Reddy, A., M. de la Cruz, E.M. Rodriguez, J. Thames, J. Wu, G. Chisholm, D. Liu, S. Frisbee-Hume, S. Yennurajalingam, D. Hui, H. Cantu, A. Marin, V. Gayle, N. Shinn, A. Xu, J. Williams, and E. Bruera. 2014. Patterns of storage, use, and disposal of opioids among cancer outpatients. *The Oncologist* 19(7):780-785.

Rees, D.I., J.J. Sabia, L.M. Argys, J. Latshaw, and D. Dave. 2017. *With a little help from my friends: The effects of naloxone access and good Samaritan laws on opioid-related deaths*. Working Paper 23171. Cambridge, MA: National Bureau of Economic Research. http://www.nber.org/papers/w23171 (accessed February 23, 2017).

Relman, A.S. 2001. Separating continuing medical education from pharmaceutical marketing. *Journal of the American Medical Association* 285(15):2009-2012.

Reuter, P., and M. Kleiman. 1986. Risks and prices: An economic analysis of drug enforcement. In *Crime and justice: A review of research*, Vol. 7, edited by M. Tonry and N. Morris. Chicago, IL: University of Chicago Press.

Rocheleau, A.M., and D. Boyum. 1994. *Measuring heroin availability in three cities*. Washington, DC: Office of National Drug Control Policy.

Rowe, C., M. Santos, E. Wheeler, E. Vittinghoff, P. Davidson, and P.O. Coffin. 2015. Predictors of participant engagement and naloxone utilization in a community-based naloxone distribution program. *Addiction* 110(8):1301-1310.

Rudd, R.A., P. Seth, F. David, and L. Scholl. 2016. Increases in drug and opioid-involved overdose deaths—United States, 2010–2015. *Morbidity and Mortality Weekly Report* 65:1445-1452.

Rutkow, L., H.Y. Chang, M. Daubreese, D.W. Webster, E.A. Stuart, and G.C. Alexander. 2015. Effect of Florida's prescription drug monitoring program and pill mill laws on opioid prescribing and use. *JAMA Internal Medicine* 175(10):1642-1649.

SAMHSA (Substance Abuse and Mental Health Services Administration). 2011. *Bibliographic support for the Syringe Services Program (SSP)*. http://archive.samhsa.gov/ssp/ (accessed January 5, 2017).

SAMHSA. 2012. *A treatment improvement protocol: Managing chronic pain in adults with or in recovery from substance use disorders*. http://store.samhsa.gov/shin/content/SMA12-4671/TIP54.pdf (accessed March 21, 2017).

Samuels, E. 2014. Emergency department naloxone distribution: A Rhode Island department of health, recovery community, and emergency department partnership to reduce opioid overdose deaths. *Rhode Island Medical Journal (2013)* 97(10):38-39.

Sapienza, F.L. 2006. Abuse deterrent formulations and the Controlled Substances Act (CSA). *Drug & Alcohol Dependence* 83:S23-S30.

Satterfield, J.M., L.S. Mitteness, M. Tervalon, and N. Adler. 2004. Integrating the social and behavioral sciences in an undergraduate medical curriculum: The UCSF essential core. *Academic Medicine* 79(1):6-15.

Schwartz, R.P., J. Gryczynski, K.E. O'Grady, J.M. Sharfstein, G. Warren, Y. Olsen, S.G. Mitchell, and J.H. Jaffe. 2013. Opioid agonist treatments and heroin overdose deaths in Baltimore, Maryland, 1995–2009. *American Journal of Public Health* 103(5):917-922.

ScienceDaily. 2016. Opening a supervised injection facility for people who inject drugs could save millions. *ScienceDaily*, December 14. https://www.sciencedaily.com/releases/2016/12/161214115102.htm (accessed April 17, 2017).

Seago, S., A. Hayek, J. Pruszynski, and M.G. Newman. 2016. Change in prescription habits after federal rescheduling of hydrocodone combination products. *Proceedings (Baylor University. Medical Center)* 29(3):268.

Severtson, S.G., B.B. Bartelson, J.M. Davis, A. Munoz, M.F. Schneider, H. Chilcoat, P.M. Coplan, H. Surratt, and R.C. Dart. 2013. Reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. *The Journal of Pain* 14(10):1122-1130.

Silverman, E. 2016. Senators ask drug makers to explain prices for opioid overdose antidote. *STAT*, June 7. https://www.statnews.com/pharmalot/2016/06/07/naloxone-opioids-heroin-drug-prices/ (accessed November 4, 2016).

Spiller, H.A., J.M. Scaglione, A. Aleguas, H. Foster, L. Durback-Morris, E.J. Scharman, and S.D. Baker. 2010. Effect of scheduling tramadol as a controlled substance on poison center exposures to tramadol. *Annals of Pharmacotherapy* 44(6):1016-1021.

Stein, M.D., B.J. Anderson, P. Thurmond, and G.L. Bailey. 2015. Comparing the life concerns of prescription opioid and heroin users. *Journal of Substance Abuse Treatment* 48(1):43-48.

Stewart, H., A. Malinowski, L. Ochs, J. Jaramillo, K. McCall, and M. Sullivan. 2015. Inside Maine's medicine cabinet: Findings from the Drug Enforcement Administration's medication take-back events. *American Journal of Public Health* 105(1):e65-e71.

Stogner, J., D.N. Khey, O.H. Griffin, B.L. Miller, and J.H. Boman. 2012. Regulating a novel drug: An evaluation of changes in use of Salvia divinorum in the first year of Florida's ban. *International Journal of Drug Policy* 23(6):512-521.

Strang, J., B. Powis, D. Best, L. Vingoe, P. Griffiths, C. Taylor, S. Welch, and M. Gossop. 1999. Preventing opiate overdose fatalities with take-home naloxone: Pre-launch study of possible impact and acceptability. *Addiction* 94(2):199-204.

Sullivan, M.D., A.M. Bauer, D. Fulton-Kehoe, R.G. Garg, J.A. Turner, T. Wickizer, and G.M. Franklin. 2016. Trends in opioid dosing among Washington State Medicaid patients before and after opioid dosing guideline implementation. *The Journal of Pain* 17(5):561-568.

Sun, E.C., B.D. Darnall, L.C. Baker, and S. Mackey. 2016. Incidence of and risk factors for chronic opioid use among opioid-naive patients in the postoperative period. *JAMA Internal Medicine* 176(9):1286-1293.

Surratt, H.L., C. O'Grady, S.P. Kurtz, Y. Stivers, T.J. Cicero, R.C. Dart, and M. Chen. 2014. Reductions in prescription opioid diversion following recent legislative interventions in Florida. *Pharmacoepidemiology and Drug Safety* 23(3):314-320.

Terrab, M., and A.R. Odoni. 1993. Strategic flow management for air traffic control. *Operations Research* 41(1):138-152.

Thomas, K. 2014a. Doubts raised about off-label use of Subsys, a strong painkiller. *The New York Times*, May 13. https://www.nytimes.com/2014/05/14/business/doubts-raised-about-off-label-use-of-subsys-a-strong-painkiller.html (accessed January 5, 2017).

Thomas, K. 2014b. Using doctors with troubled pasts to market a painkiller. *The New York Times*, November 27. https://www.nytimes.com/2014/11/28/business/drug-maker-gave-large-payments-to-doctors-with-troubled-track-records.html (accessed January 5, 2017).

Thomas, K. 2015. Nurse pleads guilty to taking kickbacks from drug maker. *The New York Times*, June 25. https://www.nytimes.com/2015/06/26/business/nurse-pleads-guilty-to-taking-kickbacks-from-drug-maker.html (accessed January 5, 2017).

Thomas, K. 2016a. Drug maker's former employees accused of shady dealings with doctors. *The New York Times*, June 10. https://www.nytimes.com/2016/06/11/business/drug-makers-former-employees-accused-of-shady-dealings-with-doctors.html (accessed January 5, 2017).

Thomas, K. 2016b. Former Insys officials charged in scheme to push its painkiller. *The New York Times*, December 8. https://www.nytimes.com/2016/12/08/business/insys-therapeutics-arrests-fentanyl.html (accessed January 5, 2017).

Trafton, J., S. Martins, M. Michel, E. Lewis, D. Wang, A. Combs, N. Scates, S. Tu, and M.K. Goldstein. 2010. Evaluation of the acceptability and usability of a decision support system to encourage safe and effective use of opioid therapy for chronic, noncancer pain by primary care providers. *Pain Medicine* 11:575-585.

Traynor, K. 2016. Maine enacts statewide limits on opioid prescribing. *American Journal of Health- System Pharmacy* 73(12):854-856.

Turk, D., and T. Burwinkle. 2005. Clinical outcomes, cost-effectiveness, and the role of psychology in treatments for chronic pain sufferers. *Professional Psychology: Research and Practice* 36(6):602-610.

UCSF (University of California, San Francisco). 2017. *Biopsychosocial and cultural issues in action: Mr. Danovic outpatient case and review.* http://www.osher.ucsf.edu/education/integrative-medicine-curriculum/required-curriculum/#Danovic (accessed April 26, 2017).

VA (U.S. Department of Veterans Affairs). 2016. *Recommendations for issuing naloxone rescue for the VA Opioid Overdose Education and Naloxone Distribution (OEND) program.* https://www.pbm.va.gov/PBM/clinicalguidance/clinicalrecommendations/Naloxone_HCl_Rescue_Kits_Recommendations_for_Use.pdf (accessed December 5, 2016).

VA and DoD (U.S. Department of Defense). 2017. *VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain.* https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPGProviderSummary022817.pdf (accessed August 16, 2017).

Volkow, N.D., T.R. Frieden, P.S. Hyde, and S.S. Cha 2014. Medication-assisted therapies—tackling the opioid-overdose epidemic. *New England Journal of Medicine* 370(22): 2063-2066.

Wakeland, W., A. Nielsen, and P. Geissert. 2015. Dynamic model of nonmedical opioid use trajectories and potential policy interventions. *The American Journal of Drug and Alcohol Abuse* 41(6):508-518.

Walgreens. 2016. *Walgreens expands availability of naloxone without a prescription to 33 states and Washington D.C.* Press Release. http://news.walgreens.com/press-releases/general-news/walgreens-expands-availability-of-naloxone-without-a-prescription-to-33-states-and-washington-dc.htm (accessed April 17, 2017).

Walgreens. 2017. *Walgreens medication disposal program collects 72 tons of unused medications in first year; opioid antidote medication naloxone available without prescription at Walgreens in 44 states.* Press Release. http://news.walgreens.com/press-releases/general-news/walgreens-medication-disposal-program-collects-72-tons-of-unused-medications-in-first-year-opioid-antidote-medication-naloxone-available-without-prescription-at-walgreens-in-44-states.htm (accessed May 5, 2017).

Walley, A.Y., Z. Xuan, H.H. Hackman, E. Quinn, M. Doe-Simkins, A. Sorensen-Alawad, S. Ruiz, and A. Ozonoff. 2013. Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: Interrupted time series analysis. *British Medical Journal* 346:f174.

Wang, V. 2016. *CVS pays $3.5m to settle claims it filled fake painkiller prescriptions.* https://www.bostonglobe.com/metro/2016/06/30/cvs-pays-million-settle-federal-probe-that-found-pharmacists-filled-forged-prescriptions/btKqNm4tYmglO3s8qm8V3I/story.html (accessed March 21, 2017).

We are the Drug Policy Alliance. 2017. *Supervised injection facilities.* http://www.drugpolicy.org/supervised-injection-facilities (accessed April 17, 2017).

Webster, B.S., S.K. Verma, and R.J. Gatchel. 2007. Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. *Spine* 32(19):2127-2132.

Welham, G.C., J.K. Mount, and A.M. Gilson. 2015. Type and frequency of opioid pain medications returned for disposal. *Drugs-Real World Outcomes* 2(2):129-135.

Wen, H., B.R. Schackman, B. Aden, and Y. Bao. 2017. States with prescription drug monitoring mandates saw a reduction in opioids prescribed to Medicaid enrollees. *Health Affairs* 36(4):733-741.

WHO (World Health Organization). 1986. *Cancer pain relief*. Geneva, Switzerland: WHO.

WSAMDG (Washington State Agency Medical Directors' Group). 2015. *Interagency guideline on prescribing opioids for pain*. http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf (accessed February 25, 2017).

WSIN (Western States Information Network). 2016. *Drug price and purity guide, 2016*. Sacramento, CA: WSIN.

Wu, L.T., H. Zhu, and M.S. Swartz. 2016. Treatment utilization among persons with opioid use disorder in the United States. *Drug and Alcohol Dependence* 169:117-127.

Yanovitsky, I. 2016. The American medicine chest challenge: Evaluation of a drug take-back and disposal campaign. *Journal of Studies on Alcohol and Drugs* 77(4):549-555.

Zeppetella, G., and A.N. Davies. 2013. Opioids for the management of breakthrough pain in cancer patients. *Cochrane Database of Systematic Reviews* 10:CD004311.

Zerzan, J.T., N.E. Morden, S. Soumerai, D. Ross-Degnan, E. Roughead, F. Zhang, L. Simoni-Wastila, and S.D. Sullivan. 2006. Trends and geographic variation of opiate medication use in state Medicaid fee-for-service programs, 1996 to 2002. *Medical Care* 44(11):1005-1010.

6

Opioid Approval and Monitoring by the U.S. Food and Drug Administration

As the federal agency responsible for protecting the public's health by assuring the safety, efficacy, and security of drugs, the U.S. Food and Drug Administration (FDA) has a central role to play in addressing the opioid epidemic. The agency is responsible for approving new drugs and reformulations, giving it an important gatekeeping function, and also, along with the U.S. Drug Enforcement Administration (DEA), helps monitor the use of available opioid products. In this chapter, the committee provides recommendations aimed at improving the FDA's regulation of opioid analgesics, including by informing the agency's development of a framework for opioid approval and monitoring that takes into account the range of benefits and harms associated with the use of opioid analgesics, incorporating both the needs of pain patients and the relevant public health considerations.

Federal regulation of opioid medications has a long history. The original Pure Food and Drug Act of 1906—the first piece of U.S. federal legislation regulating the pharmaceutical marketplace—was passed in part because of widespread use of morphine in the so-called patent medicines of the 1800s, particularly in products aimed at children, such as Mrs. Winslow's Soothing Syrup, which was promoted for treating colic. The Pure Food and Drug Act required that products containing morphine indicate the quantity of the drug on their labels. The 1938 Food, Drug, and Cosmetic Act (FDCA) built on these rules by additionally requiring manufacturers to test their products for safety in human patients prior to approval. In the 1962 Kefauver-Harris Amendments, the FDA was given the further authority to ensure that drugs showed substantial evidence of efficacy from adequate and well-controlled investigations prior to approval.

As the FDA's authorities have evolved over the past century, so have the types of opioids available to U.S. patients. After the first synthetic opioid medications were developed in the 1910s, manufacturers continued to develop new products and formulations. In the 1960s and 1970s, the FDA approved short-acting combination products such as oxycodone/acetaminophen (Percocet, 1976). In the late 1980s and early 1990s, the FDA approved long-acting formulations of older opioid products, such as morphine (MS Contin in 1985) and oxycodone extended-release (ER) (OxyContin, 1995). Most recently, starting around 2010, the FDA has approved a cohort of opioids with supposedly abuse-deterrent properties, including tapentadol ER (Nucynta ER, 2011) and hydromorphone ER (Exalgo ER, 2010), although controversy arose when the agency approved hydrocodone ER (Zohydro ER) around this time without an abuse-deterrent formulation (ADF) (see Box 6-1).

Throughout all of these approvals, as well as other regulatory actions, the FDA generally has reviewed opioids through the same lens used for

BOX 6-1
Approval of Zohydro Extended-Release

The first stand-alone hydrocodone product approved by the U.S. Food and Drug Administration (FDA), hydrocodone extended-release (ER) (Zohydro) was approved on the basis of a single randomized, placebo-controlled, double-blind pivotal trial lasting 12 weeks and involving 183 subjects with moderate to severe chronic lower back pain. The primary endpoint was mean change in average 24-hour pain scores (at 12 weeks compared with baseline) with hydrocodone ER, leading to a statistically significant mean decrease of less than 1 point on an 11-point scale (the overall pain scores in both groups worsened over the 12-week period). The safety of the drug was studied in 1,512 subjects, both inside and outside the trial, 332 of whom were exposed for more than 6 months. Adverse events consistent with other ER opioid analgesics, such as constipation and somnolence, were noted, as were some episodes of study drug diversion and hoarding, despite the particular care taken to minimize such events. The FDA convened an outside expert advisory committee, which voted 11-2 (with 1 abstention) against approval of the drug given the high probability of opioid use disorder and diversion for a hydrocodone-containing product without an abuse-deterrent formulation (ADF). Nonetheless, the FDA approved the product in 2013, instituting a post-approval Risk Evaluation and Mitigation Strategy that included voluntary prescriber education and close surveillance. An ADF version of hydrocodone ER was introduced to replace the original version in 2015.

SOURCE: FDA, 2017b.

other drugs. The committee believes that the preceding chapters of this report establish a scientific and epidemiological basis for special treatment of opioids by the FDA that would involve greater integration of public health considerations at the time of preapproval testing, during regulatory review and approval, and during routine post-approval oversight.

In making the case for this approach, this chapter begins with an overview of the FDA's current regulatory oversight of prescription drugs. This overview is followed by a discussion of public health dimensions of FDA drug regulation, which includes examples of previous cases in which the agency has successfully incorporated public health considerations into its regulatory decision making and an examination of those public health considerations specifically relevant to the approval and monitoring of opioids. Next, the chapter lays out the key elements of an integrated framework for opioid regulation that incorporates these considerations. Finally, the chapter presents the committee's recommendations for the implementation of such a framework; these recommendations are summarized at the end of the chapter.

OVERVIEW OF THE FDA'S REGULATORY PROCESS FOR PRESCRIPTION DRUGS AND ITS APPLICATION TO OPIOIDS

This section of the report briefly reviews the key principles of FDA drug regulation and their application to opioids.

FDA Review and Approval of Prescription Drugs

Drug development often begins with the identification of cellular targets and corresponding candidate compounds, with the most promising compounds moving on to preclinical studies. Preclinical in vitro and in vivo animal studies seek to establish initial pharmacologic activity and, importantly, potential for toxicity. FDA oversight at this stage is limited,[1] although the agency has promulgated requirements for good laboratory practice.[2]

Once a compound has demonstrated sufficient preclinical activity to warrant investigation in humans, an Investigational New Drug (IND) application is filed with the FDA. Information required in an IND application includes drug chemical and manufacturing information, pharmacologic and toxicologic information from preclinical data, a summary of any prior human data, a protocol for each planned study, and a brief outline of the

[1] 7 U.S.C. § 2131.

[2] See http://www.ecfr.gov/cgi-bin/text-idx?SID=a3db503068f5f3b0ec5abcbcf360940f&mc=true&tpl=/ecfrbrowse/Title21/21cfr58_main_02.tpl (accessed June 27, 2017).

clinical study plan. The FDA reviews the application, which goes into effect 30 days after being submitted unless the FDA imposes a clinical hold. Once the IND has gone into effect, clinical studies may proceed, typically occurring in three phases. Phase 1 studies usually enroll a few, often healthy, volunteers to explore pharmacokinetic and pharmacodynamic parameters of the drug based on a small number of doses. Phase 2 studies begin to test the drug's optimal dosage in patients with the condition of interest, and may provide a first look at the drug's therapeutic potential.[3] Phase 3 studies (if they are performed) enroll hundreds or thousands of patients and may require years to complete, although one review found that two-thirds of all new drugs are approved on the basis of trials lasting 6 months or less (Downing et al., 2014). These latter studies account for the majority of the spending on drug development, and "are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling."[4] While the manufacturer controls the organization and execution of the trials, manufacturers can, and frequently do, consult with FDA staff at various times to receive advice on trial design and outcomes.[5]

At the conclusion of the clinical trials, the manufacturer submits a New Drug Application (NDA). There is a 60-day filing review period during which the FDA ensures that all the necessary information is organized within the NDA. The drug is reviewed under a standard 10-month pathway; however, drugs that appear to represent therapeutic advances may be granted a 6-month priority review schedule (FDA, 2014c). The raw data and the study reports submitted in the NDA are reviewed by teams of FDA staff with expertise in chemistry and manufacturing, pharmacology, toxicology, statistics, clinical medicine, and any other relevant fields to determine whether the data show that the drug is safe and that there is substantial evidence of its effectiveness. To meet the substantial evidence standard, the FDA traditionally interpreted its statute as requiring two adequate and well-controlled studies, each convincing on its own, because results from any single trial "may be subject to unanticipated, undetected

[3] 21 C.F.R. § 312.21(b).

[4] 21 C.F.R. § 312.21(c).

[5] Note that "manufacturer" refers to an entity engaged in manufacturing, preparing, propagating, compounding, processing, packaging, or labeling of a product (e.g., a drug), while "sponsor" is defined in the regulations for Investigational New Drug applications as the pharmaceutical company, government agency, academic institution, private organization, or other entity that takes responsibility for and initiates a clinical investigation (21 C.F.R. 312.3). Although a drug's manufacturer may not be its sponsor, for simplicity, and because in the context of unapproved investigational opioids the committee expects that the sponsor will frequently be the manufacturer, the committee uses the term "manufacturer" throughout this chapter.

systematic biases" (FDA, 1998). However, the Food and Drug Administration Modernization Act of 1997[6] amended the FDCA to allow efficacy to be demonstrated by one adequate and well-controlled trial under certain circumstances, and about one-third of all drugs are currently approved on the basis of a single pivotal trial (Downing et al., 2014).

The FDA synthesizes the efficacy and safety data that make up the NDA into a structured qualitative benefit-risk assessment (discussed in detail later in this section), leading to a determination as to whether the benefits of approval outweigh the risks for the particular clinical indication sought by the manufacturer. During the review process, the FDA may engage advisory committees of outside experts to obtain additional input and to provide a public forum for discussion of the drug. These committees also include at least one consumer representative and one nonvoting industry representative. One study examining more than 200 advisory committees between 2008 and 2012 found that approval was recommended 74 percent of the time, and approval subsequently was granted by the FDA in 79 percent of those cases (Ciociola et al., 2014).

The FDA also reviews the manufacturer's proposed labeling describing use related to the indications sought, and this labeling is finalized at the time of approval. This labeling contains, among other things, the drug's approved indications, directions for use, dosing frequency and duration, and route of administration and preparation, as well as clinically significant adverse reactions, safety hazards, or other limitations on its use. The labeling must be revised to include warnings of new, clinically significant hazards as soon as reasonable evidence of a causal association with the drug exists.[7]

Drug Reformulations

Many drugs approved by the FDA are reformulations of previously approved products. Reformulated drugs, which include nearly every opioid product approved in the past few decades, can be approved via an abbreviated pathway described in section 505(b)(2) of the FDCA through which the application relies on published literature or on an FDA finding of safety and/or effectiveness for an approved drug product. In these cases, the manufacturer provides data to bridge to the FDA's prior findings for the approved product, as well as data necessary to support any differences between the two formulations (FDA, 1999).[8] The FDA can require studies

[6]Public Law 105-115.

[7]See FDCA 502(f)(2) for specific statutory language and 21 C.F.R. § 201.57(c)(6) for relevant regulations.

[8]21 C.F.R. § 201.57.

to establish efficacy and safety, as well as additional safety studies should unforeseen safety signals arise (FDA, 2014b).

Application to Opioid Approval

The requirement that prescription drugs be subject to prospective clinical trials that provide data on their safety and efficacy is an essential component of the regulatory apparatus that protects patients, allows for collection of rigorous data that can guide clinical practice, and promotes a well-functioning prescription drug marketplace by preventing the widespread use of ineffective products. The FDA's standards for new drug approval, therefore, serve a key public health function. However, the investigational drug evaluation process also has important limitations, particularly with respect to the approval of opioids.

For example, showing that a drug has substantial evidence of efficacy does not necessarily mean that the drug is more effective than currently available therapies, or that the efficacy demonstrated is clinically meaningful. In the case of hydrocodone ER (see Box 6-1), the drug was tested against a placebo. Also, while the hydrocodone ER case showed a statistically significant improvement in pain outcomes, it is not clear whether the slight numeric difference in the pain scale is clinically meaningful for patients with pain, particularly since pain worsened overall over the course of the trial among both the subjects receiving hydrocodone ER and those receiving placebo (FDA, 2017b).

In addition, clinical trials sufficient to meet the FDA's efficacy standard can be conducted in a brief, highly protocolized setting and often exclude many patients who would be expected to get the drug following its approval. In the case of hydrocodone ER, the entire pivotal study was conducted among patients with lower back pain, and did not include patients with cancer, arthritis, or other conditions who may receive opioid medications for pain (FDA, 2017b). Clinical trials could be designed with more robust follow-up periods or be prospectively powered to ensure that well-known side effects are adequately measured. However, the FDA bases its approval decision on the data provided by the manufacturer at the time of the NDA and does not require that trials of investigational drugs be conducted with particular characteristics.

Post-Approval FDA Authorities

The FDA's regulatory authority continues following the initial marketing approval of a drug. Pre-approval prospective clinical trials cannot comprehensively assess the risks of drugs. Therefore, it is not unusual for specific questions to arise that do not preclude marketing but nevertheless

warrant further investigation after approval. Additionally, risks observed in the clinical trials may require ongoing evaluation and mitigation, and post-approval monitoring may necessitate timely communication with health care providers and the public. These activities take place against a backdrop of industry activities promoting use of the drug to providers and patients.

Spontaneous Adverse Event Reporting and Active Surveillance

Traditionally, the FDA has relied on passive collection of spontaneous adverse event reports submitted by health care facilities, providers, drug manufacturers, patients, and others as its primary source of information about post-approval drug safety. Manufacturers are required to submit to the FDA within 15 days any reports of adverse events that are both serious and unexpected. Other reports manufacturers receive are to be submitted to the FDA quarterly for the first 3 years post-approval and annually thereafter. The FDA's Adverse Event Reporting System (FAERS) database stores all such reports. Physicians and patients may also submit reports to FAERS, but do so voluntarily (and rarely). FAERS data are available to the public, but often contain less information than may be needed to fully assess the relationship between the drug and the event in question (Findlay, 2015). Nevertheless, past examples of FAERS data being used to identify safety signals provide evidence that this type of passive post-approval surveillance does have some value (FDA, 2014d).

In addition to receiving and processing adverse event reports, nearly all brand-name manufacturers conduct active post-market surveillance of their products, which may include observational studies or other safety-related research. They report results of these pharmacovigilance activities to the FDA, along with their adverse event reports, in Periodic Adverse Drug Experience Reports, Periodic Safety Update Reports, or Periodic Benefit-Risk Evaluation Reports. The FDA now also has the capacity to actively monitor safety outcomes related to drugs in the post-approval setting. Based on a pilot program launched in 2008, the Sentinel System allows the agency, through an independent contractor that has established a secure distributed data network, to assess an emerging drug risk using data from a broad array of electronic health care data. While Sentinel has not yet facilitated rapid drug safety assessment and improved regulation, it holds promise for regulatory decisions to be based on big-data tools that help in organizing and evaluating evidence (FDA, 2015a).

Post-Market Commitments and Requirements

At the time a product is granted marketing approval, the FDA can impose various post-market requirements, or the agency and the manu-

facturer can agree on post-market commitments, intended to help address questions that arise during the review of the pre-approval data, to help assess a known serious risk or a signal of a serious risk, or to identify an unexpected serious risk when data suggest the potential for such a risk. These requirements and commitments can include clinical trials, observational studies, or the creation of patient registries, which can be used to help adjust the labeled indication or safety warnings, and even can lead to withdrawal of the approved indication (OIG, 2016). Yet despite additional authorities granted to the FDA in 2007,[9] post-market requirements and commitments often are delayed or not completed (Fain et al., 2013).

Risk Evaluation and Mitigation Strategies

One particularly important type of post-market requirement is a Risk Evaluation and Mitigation Strategy (REMS). The FDA can require that a manufacturer develop a REMS to provide safeguards for the use of high-risk medications when the FDA determines that such safeguards are necessary to ensure that benefits of a drug outweigh its risks (Sarpatwari et al., 2014). A REMS may simply involve disseminating means of educating prescribers and patients about the drug, but it may also require manufacturers to implement "elements to assure safe use," such as mandatory training or certification for prescribers and pharmacies, restrictions on dispensing, and targeted patient follow-up and testing that can rely on the establishment of registries (Sarpatwari et al., 2014). Although elements to assure safe use often target prescribing and dispensing practices, it is drug manufacturers, not health care providers, that are responsible for ensuring that REMS requirements are met (Zettler, 2015). Brand-name manufacturers also are required to periodically monitor and assess the success of their REMS.[10]

Evidence about whether REMS can substantially affect prescribing and dispensing practices is conflicting. In a 2013 report, the U.S. Department of Health and Human Services (HHS) Office of the Inspector General raised concerns about the effectiveness of REMS in improving safe use of drugs (HHS OIG, 2013). An evaluation of post-FDA approval use of bosentan (Tracleer), a treatment for pulmonary hypertension, uncovered a high level of nonadherence to liver function tests required among the elements to assure safe use in the REMS for the drug (Blanchette et al., 2015). On the other hand, some REMS with elements to assure safe use may be effective in reducing non-evidence-based off-label drug prescribing. One rigorous study found that the REMS for the thrombopoietin agonist eltrombopag (Promacta), which before the FDA eliminated the REMS required such

[9]Public Law 110-85.
[10]21 U.S.C. § 355-1(d).

elements to assure safe use as a signed acknowledgment of drug risks and semiannual patient monitoring, decreased off-label use of the drug (for an indication later approved by the FDA) (Sarpatwari et al., 2015). As mentioned previously in this report, the FDA has required a REMS with elements to assure safe use for ER/long-acting (LA) opioids, which currently requires manufacturers of these drugs to provide education to prescribers based on an FDA prescriber education "blueprint" (FDA, 2017e).

Individual professional schools have produced their own online REMS teaching modules based on the FDA REMS blueprint for ER/LA opioids. Boston University's SCOPE (Safe and Competent Opioid Prescribing Education) of Pain program was funded by an independent education grant awarded by the manufacturers of ER/LA opioid analgesics, known collectively as the REMS Program Companies or RPC.[11] Boston University School of Medicine partnered with the Federation of State Medical Boards and the Council of Medical Specialty Societies in the development, execution, and promotion of the SCOPE of Pain program (Alford et al., 2015). The committee notes that education through REMS represents one source of education on safe opioid prescribing, but is not a substitute for fundamental knowledge of multidisciplinary pain care that utilizes nonopioid and nonpharmacologic strategies for managing acute pain and especially chronic painful conditions.

Communicating Drug Safety Information

The combination of data from passive adverse event reporting, the Sentinel System, and other surveillance activities conducted by the FDA and manufacturers, together with post-market commitments and requirements, can point to the need to update a drug's labeling. While the FDA can, under certain conditions, require the manufacturer to update the label with new safety information, primary responsibility for keeping labeling up to date for brand-name drugs lies with the manufacturer.[12]

A boxed warning (also called a black-box warning)—the most prominent safety warning on a drug's label—is appropriate when an identified hazard poses a risk of death or serious injury.[13] A boxed warning can be required at the time of drug approval or after a drug is already on the market and, in tandem with the media coverage it inevitably generates, can reduce prescribing (Dorsey et al., 2010). However, some boxed warnings fail to change practice as substantially as expected, and physicians com-

[11]For more information, see http://www.er-la-opioidrems.com/IwgUI/rems/home.action (accessed June 27, 2017).

[12]21 C.F.R. § 201.57(c)(6).

[13]21 C.F.R. § 201.57(c)(1).

monly prescribe drugs without regard to information in these warnings (Lasser et al., 2006).

When a label change is made after a drug's approval, it is often accompanied by a Drug Safety Communication. Between 2010 and 2016, 233 Drug Safety Communications were issued (39 in 2010, 66 in 2011, 29 in 2012, 32 in 2013, 16 in 2014, 30 in 2015, and 21 in 2016) (FDA, 2017c). One review found little impact of FDA drug risk communications on prescribing behaviors (Dusetzina et al., 2012).

Regulating Industry Promotion

After a drug has been approved, its manufacturer promotes it to prescribers and patients. Promotion to prescribers includes detailing (face-to-face interactions between a sales representative and a prescriber); educational programing; provision of drug samples; and direct financial incentives, such as meals, travel expenses, grants, and consulting fees (Pew Charitable Trusts, 2013). Research shows that pharmaceutical marketing to physicians has a strong, consistent, and specific effect on driving prescribing practices toward the product being promoted, particularly when it is not necessarily the first-line or most cost-effective therapeutic option available (Avorn et al., 1982; Manchanda and Honka, 2005). Similarly, direct-to-consumer (DTC) promotion affects prescribing by changing how patients interact with their health care providers—for example, by prompting patients to ask for a particular drug and increasing the likelihood that patients will be prescribed both appropriate and inappropriate medications (Kravitz et al., 2005; Skeldon et al., 2015; Spence et al., 2005). In the opioid context, McKinlay and colleagues (2014) conducted a study that involved showing primary care physicians two different video-based scenarios in which actors played patients with sciatica-like symptoms. In one of the scenarios, the "patients" requested oxycodone; in the other, they requested no specific pain medication. After viewing each scenario, physicians were interviewed about how they would manage the case: after viewing the scenario in which the "patients" specifically requested oxycodone, 19.8 percent of physicians prescribed that drug, compared with 1 percent following viewing of the scenario in which no specific pain medication was requested (McKinlay et al., 2014).

The FDCA prohibits false or misleading prescription drug labeling and advertising,[14] and the FDA regulates the promotion of prescription medications and certain medical devices to both prescribers and patients by encouraging companies to portray products in a way that is truthful, balanced, and accurate (FDA, 2010b). Advertisements must provide fair

[14] 21 U.S.C. §§ 321(n), 352.

and balanced information with respect to the risks and benefits of a drug, reveal material facts related to the representations in the advertisement, give comparable prominence to risk and benefit information, and not overstate efficacy or safety.[15] If the FDA becomes aware of promotional material that it believes violates the law (e.g., states or implies that a drug can treat a condition when the FDA has not approved it for such use, overstates a drug's benefits, omits or downplays information about a drug's risks), it sends the company a letter asking that the promotional material be removed and/or corrected (FDA, 2015b). Improper prescription drug marketing also can violate other laws, including the federal antikickback statute; state consumer fraud statutes; and federal and state false claims acts, which permit the government to recover payments made for prescriptions (such as through Medicare or Medicaid) as a result of fraudulent advertising.

After a drug has been approved, prescribers ordinarily may use it in ways that the FDA has not approved (known as "off-label" use), a practice that is common in the field of pain medicine (Radley et al., 2006). When an off-label use is particularly risky and non-evidence-based, the FDA can factor this consideration into its post-approval regulatory decisions. For example, when data emerged showing that antipsychotics used off-label in elderly patients with dementia increased the risk of mortality, the FDA added a boxed warning that helped reduce such dangerous prescribing. Off-label use for opioids contributes to misuse and opioid use disorder (OUD), and the inevitability of such off-label use of opioids is another justification for the development of an opioid-specific FDA review framework (discussed later in this chapter).

While off-label use is common, industry promotion of off-label uses violates the FDCA by causing the drug to be misbranded or to be an unapproved new drug (Cortez, 2016). In recent years, constitutional questions have been raised about the FDA's ability to limit manufacturers' off-label marketing.[16] In test cases, the drug industry and libertarian advocacy organizations have had some success in persuading courts that the FDA violates industry's First Amendment rights when enforcing its policies against off-label promotion.[17] The agency is "currently engaged in a comprehensive review" of its regulatory framework for medical product promotion.[18]

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[15] 21 C.F.R. § 202.1.

[16] *Virginia State Board of Pharmacy v. Virginia Consumer Council*, 425 U.S. 748, 748 (1976); *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002); *Sorrell v. IMS Health Inc.*, 131 S. Ct. 2653, 2670 (2011).

[17] *United States v. Caronia*, 703 F.3d 149 (2d Cir. 2012); *Washington Legal Found. v. Henney*, 202 F.3d 331 (D.C. Cir. 2000); *Amarin Pharma, Inc. v. FDA*, 119 F. Supp. 3d 196, 224 (S.D.N.Y. 2015).

[18] See https://www.federalregister.gov/documents/2017/01/19/2017-01013/manufacturer-communications-regarding-unapproved-uses-of-approved-or-cleared-medical-products (accessed June 27, 2017).

Drug Quality and Supply Chain Security

Another key area of oversight for the FDA is drug quality and security. The primary means through which the FDA regulates drug quality is its Current Good Manufacturing Practice (CGMP) requirements. The agency's CGMP regulations cover the methods, facilities, and controls used for the manufacture, processing, packing, holding, or preparation of a drug.[19] These requirements include standards for the qualifications of the personnel involved in drug manufacturing, for the design of facilities and equipment, and for sanitation and cleaning. The purpose of these regulations is to help ensure that a drug is safe and has the identity, strength, quality, and purity that it is represented as possessing. Before approving a drug, the FDA reviews compliance with CGMP requirements,[20] and it continues to monitor compliance after approval.[21]

The FDA also oversees the security of the drug supply chain. The 2013 Drug Quality and Security Act amended the FDCA to create an electronic, interoperable system to "track and trace" many prescription drugs throughout the supply chain.[22] Once fully in effect in 2023, the system will include product identifiers for certain prescription drug packages; information on who handles a drug each time it is sold in the United States; requirements that industry stakeholders investigate products suspected to be counterfeit, substandard, or otherwise illegitimate; and processes for notifying the FDA and others when illegitimate drugs are found.[23] Various requirements will apply to drug manufacturers, wholesale drug distributors, repackagers, third-party logistics providers (entities that help coordinate distribution of a drug but never take ownership of it), and dispensers. The intent of this expansive system is to enable the FDA and industry to verify the legitimacy of drug products; enhance detection of counterfeit, substandard, or otherwise illegitimate products; and more easily conduct drug recalls.[24] Although the track and trace system is designed to prevent illegal drugs from entering the pharmaceutical supply chain, it may help identify some instances of opioid diversion by providing more information about drug distribution.

[19]21 C.F.R. § 210.1–211.1.
[20]21 U.S.C. § 355(d), 355(j)(4)(A).
[21]21 U.S.C. § 351(a)(2)(B).
[22]Public Law 113-54 127 Stat. 587 (2013).
[23]Public Law 113-54 127 Stat. 587 (2013).
[24]*Federal Register*, Vol 81, No. 181, September 19, 2016: 64175–64177, https://www.gpo.gov/fdsys/pkg/FR-2016-09-19/pdf/2016-22441.pdf (accessed June 27, 2017).

Application to Safety Monitoring of Opioids

Opioids have been the subject of numerous post-approval strategies to address the serious safety concerns associated with these products, although thus far these approaches have had little effect in terms of stemming harms. For example, as reports of misuse and diversion of oxycodone controlled-release mounted, Purdue Pharma and the FDA fashioned a risk management plan in 2001 encouraging improved surveillance and the education of prescribers about the risks of the drug. In addition, the label was updated to include a boxed warning calling attention to the potential for misuse and diversion. But neither of these interventions appeared to have much effect on diminishing the rate of opioid overdose, which crested over the next decade.

Recent actions by the FDA have included requiring manufacturers of immediate-release (IR) opioid analgesic products to update the safety information in their product labeling (FDA, 2016b) and requiring additional warnings about interactions between opioids and benzodiazepines (FDA, 2016c). In 2012, the FDA imposed a REMS for all ER/LA opioid analgesics. As discussed in Chapter 5, the REMS requires manufacturers to provide unrestricted education grants to accredited continuing education providers to develop and provide voluntary prescriber education programs. To date there has been little evidence that the REMS has had much effect on prescribing practice or on curbing opioid-related harms. The current opioid REMS also has been criticized for providing inadequate checks on unsafe opioid prescribing practices (FDA, 2016d). Propelled by the unrelenting increase in opioid-related deaths in the United States, one element of the FDA's Opioid Action Plan, launched in 2016, is to expand the REMS for opioids to incorporate pain management, include a broader range of health care professionals involved in the management of patients with pain, include IR opioid analgesic manufacturers, and evaluate approaches for implementing mandatory pain management education for prescribers (FDA, 2017e).

Similarly, passive adverse event surveillance and active use of such systems as Sentinel have proven insufficient with respect to opioids or medications to treat substance use disorder (SUD), because of delay in reporting and detecting problems. The *International Classification of Diseases* (ICD) has multiple ICD codes for chronic pain, and there are known challenges with diagnosis and documentation in medical records and billing for stigmatized conditions. The most recent post-marketing requirements for ER/LA opioids include studies to validate better mechanisms for extracting these data from medical records (FDA, 2014e).

Recent efforts to augment the post-market surveillance of opioid medications include, but are not limited to, the development of the Researched

Abuse, Diversion and Addiction-Related Surveillance (RADARS) system for active, real-time surveillance, with the aim of using this information to guide risk reduction interventions. Developed by Purdue Pharma after the FDA provided suggestions and comments, it collects this information through regular surveys of individuals entering or being assessed for SUD treatment, experts in SUD, and law enforcement agencies, as well as analysis of exposure calls to poison control centers pertaining to misuse and diversion of licit and illicit drugs, including prescription opioid analgesics (Cicero et al., 2007). Around the same time, the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) was developed to provide post-marketing surveillance, signal detection, signal verification, and prevention and intervention programs for scheduled therapeutics. The surveillance component of NAVIPPRO integrates multiple data streams to monitor drug use both temporally and spatially at a product-specific level, in part by collecting data from a national network of SUD treatment centers on substances used by adult individuals entering treatment (Butler et al., 2008).

Another recent step taken by the FDA was to update the shared list of post-marketing requirements for all ER/LA opioid analgesics in 2014 (see Annex Table 6-1 at the end of the chapter), such that the holders of the NDAs for the entire class would be responsible for performing 10 observational studies to assess the known serious risks of misuse, OUD, overdose, and death associated with these products, as well as one clinical trial to assess the risk of hyperalgesia associated with long-term, high-dose opioid therapy (FDA, 2014e). These required observational studies focus on the development and validation of algorithms or measures to identify patients exhibiting signs of SUD, including through electronic health records and other data, and the use of these algorithms to support studies of patients prescribed these products long-term to determine the risk and risk factors for the known serious adverse events. Beyond these class-wide studies, manufacturers of individual opioid analgesics can be subject to additional requirements related to safety signals and other issues that arose during NDA review or have arisen in the post-market context.

Finally, the FDA's rules concerning marketing and promotion did not stop manufacturers from engaging in illegal off-label marketing, as well as dissemination of advertisements that overstated the benefits of opioids and downplayed the risks of addiction.[25] As discussed in Chapter 1, one well-publicized example involved Purdue Pharma's marketing of oxycodone ER for chronic noncancer pain during the years after its approval.

[25]U.S. House of Representatives Committee on Governmental Reform—Minority Staff Special Investigations Division, *FDA Enforcement Actions Against False and Misleading Prescription Drug Advertisements Declined in 2003* (Washington, DC: Government Printing Office, January 2004).

During that marketing campaign, Purdue Pharma promoted oxycodone ER to prescribers and also engaged in DTC promotion through brochures, videotapes, and a "Partners Against Pain" website (VanZee, 2009). That marketing effort drove oxycodone ER sales from $48 million to more than $1 billion as the drug became the most prescribed brand name opioid for moderate to severe pain. Therefore these promotional practices were a strong contributor to the subsequent and ongoing increase in oxycodone misuse and oxycodone-related deaths (Dhalla et al., 2011; GAO, 2003). State and federal prosecutors have sued opioid manufacturers for allegedly fraudulent marketing in violation of the law.[26] However, the penalties imposed in these cases invariably fall well short of the billions of dollars in revenues earned by opioid manufacturers as a result of these marketing campaigns.

Scheduling of Opioids Under the Controlled Substances Act

As discussed in Chapter 5, the five schedules for drugs covered by the Controlled Substances Act (CSA) (see Table 6-1) were designed to provide a structure for balancing the nuanced requirements of perceived safety, medical utility, and "abuse potential" (Spillane, 2004). Scheduling status affects prescribing authority (e.g., manner of prescribing and limits on refills), triggers requirements for supply chain record keeping, and determines the degree of criminal punishment for illicit trafficking. The most restrictive controls on use cover Schedule I and II substances.

Decision Making About Scheduling

The CSA allows the DEA to place a drug temporarily in Schedule I when it believes the drug may pose "imminent hazards to public safety." The substance may be retained in Schedule I for up to 3 years, after which it must be removed or permanently scheduled.[27] The DEA has used this temporary scheduling authority for more than 35 synthetic drugs since 2002. Most recently, the DEA has used it to place several synthetic opioids temporarily in Schedule I.[28]

[26]Kentucky Settlement, http://ag.ky.gov/pdf_news/purduepharmaoxycontin.pdf (accessed June 27, 2017); http://www.latimes.com/local/california/la-me-pharma-20150828-story.html (accessed June 27, 2017).

[27]21 U.S.C. § 811 (h) CSA and amendments Synthetic Drug Abuse Prevention Act of 2012, Subtitle D of Title XI FDASIA (P.L. 112-144).

[28]An example is synthetic opioid 3,4-dichloro-N-[2-(dimethylamino)cyclohexyl]-N-methylbenzamide (also known as U-47700), placed in Schedule I in 2016. The DEA announced and then later withdrew temporarily the placement of kratom in Schedule I through this authority.

TABLE 6-1 Schedules Under the Controlled Substances Act

Schedule	Definition	Prescribing Restrictions[a]	Examples
Schedule I	Substances in this schedule have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse.	Not applicable.	Heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), peyote, methaqualone, and 3,4-methylenedioxy-methamphetamine (ecstasy)
Schedule II/IIN	Substances in this schedule have a high potential for abuse that may lead to severe psychological or physical dependence.	Prescriptions must be written and signed by the prescriber. Telephone prescriptions are permitted only in emergencies,[b] and only when followed by a written version within 7 days. No prescription refills permitted.	II: hydromorphone, methadone, meperidine, oxycodone, fentanyl, morphine, opium, codeine, and hydrocodone; IIN: amphetamine, methamphetamine
Schedule III/IIIN	Substances in this schedule have a potential for abuse less than that of substances in Schedules I or II; abuse may lead to moderate or low physical dependence or high psychological dependence.	Prescriptions may be written, oral, or transmitted by fax. Five refills are allowed every 6 months.	III: products containing not more than 90 milligrams of codeine per dosage unit (Tylenol with Codeine®) and buprenorphine; IIIN: benzphetamine, phendimetrazine, ketamine, and anabolic steroids
Schedule IV	Substances in this schedule have a low potential for abuse relative to substances in Schedule III.	Prescriptions may be written, oral, or transmitted by fax. Five refills are allowed every 6 months.	Alprazolam, carisoprodol, clonazepam, clorazepate, diazepam, lorazepam, midazolam, temazepam, and triazolam

TABLE 6-1 Continued

Schedule	Definition	Prescribing Restrictions[a]	Examples
Schedule V	Substances in this schedule have a low potential for abuse relative to substances listed in Schedule IV and consist primarily of preparations containing limited quantities of certain narcotics.	Prescriptions may be written, oral, or transmitted by fax. Refills are allowed as authorized by the prescriber.	Cough preparations containing not more than 200 milligrams of codeine per 100 milliliters or per 100 grams, and ezogabine

[a]All Schedule II–V substances can be prescribed electronically through systems that meet U.S. Drug Enforcement Administration requirements, and are also subject to any additional state-level regulations.

[b]An exception also exists for hospice care programs, where Schedule II controlled substances may be prescribed via telephone or fax.

SOURCES: DEA, 2017a,b.

The CSA's somewhat ambiguous designation of authority to make permanent scheduling decisions is the result of a compromise that was reached at the time of its passage. The American Medical Association (AMA) resisted providing broad regulatory authority to the regulatory agencies, preferring that particularized decisions be made for each drug, similar to the approach of drug-by-drug approval used under the FDCA. Physicians distrusted the ability of federal regulatory agencies to accurately assess the therapeutic and research value of any given drug (Spillane, 2004), and pharmaceutical manufacturers feared that strict controls could have a serious impact on profitability. The FDA was uncomfortable with wielding enforcement power and ceded that power to the U.S. Department of Justice (DOJ). DOJ wanted to have the authority to control a drug quickly to address incipient issues of abuse. The resulting shared authority reflects an attempt to address all of those concerns.

Under the CSA, "If, at the time a NDA is submitted to the Secretary for any drug having stimulant, depressant or hallucinogenic effect on the central nervous system, it appears that such drug has an abuse potential, such information shall by forwarded by the Secretary to the Attorney General."[29] That determination by the FDA triggers a coordinated response

[29]21 U.S.C. § 811(f). Since 1973, the attorney general has subdelegated authority for drug scheduling to the administrator of the DEA. See Exec. Order No. 11,727, 38 Fed. Reg. 18,357

by the FDA and the DEA designed to limit the potential for such abuse by assigning the drug to an appropriate "schedule."[30] The CSA requires HHS and the attorney general (usually acting through the FDA and the DEA) to consider eight factors in determining whether and at what level to schedule a drug: "(1) the drug's actual or potential for abuse, (2) scientific evidence of the drug's pharmacologic effect, (3) the state of current scientific knowledge regarding the drug, (4) the drug's history and current pattern of abuse, (5) the scope, duration and significance of abuse, (6) risk to public health, (7) the drug's psychic or physiologic dependence liability and (8) whether the substance is an immediate precursor of a substance already controlled under the CSA."[31]

The FDA begins the process by making a recommendation as to whether the drug should be "controlled or removed as a controlled substance" and if so, "the appropriate schedule, if any under which such drug . . . should be listed."[32] In so doing, the FDA is directed to consider factors (2), (3), (6), (7), and (8) above, as well as any other relevant scientific or medical considerations.[33] The FDA may require the drug's manufacturer to provide relevant data pertaining to its abuse potential as part of the NDA requirements.[34] The FDA's recommendation is binding on the DEA, although any specific scheduling recommendation is not.[35] If the FDA has recommended that the drug be controlled as a scheduled drug, the baton passes to the DEA administrator for consideration of the above eight factors in the context of appropriate scheduling.[36]

The FDA and the DEA thus play different roles in their evaluation pursuant to the CSA. The FDA's role is to perform a risk assessment of the drug's abuse potential. If the FDA determines that such a potential exists, it may require appropriate labeling for both physicians and patients. As dis-

(July 10, 1973); 28 C.F.R. § 0.100 (2003). Under the CSA, a scheduling proceeding "may be initiated by the Attorney General (1) on her own motion, (2) at the request of the Secretary [of Health and Human Services (HHS)], or (3) on the petition of any interested party." 21 U.S.C. § 811(a).

[30]As noted previously, there are five scheduled classifications under the CSA based on potential for abuse. Schedule I drugs are those that have high abuse potential and are not approved in the United States. Schedule II–V drugs are allowed to be marketed under restrictions depending on their potential (high to limited) for physical or psychological dependence (see Table 6-1 for further information).

[31]21 U.S.C. § 811(c).

[32]21 U.S.C. § 811(b). The FDA has a manual that outlines these procedures: MAPP 4200.3, *Consulting the Controlled Substance Staff on Abuse Liability, Drug Dependence, Risk Management and Drug Scheduling.*

[33]21 U.S.C. § 811(c).

[34]21 C.F.R. § 314.50(d)(5)(vii). This includes a proposal for scheduling under the CSA.

[35]21 U.S.C. § 811(c).

[36]21 U.S.C. § 811(c).

cussed above, under the REMS authority, the FDA may also require various measures intended to ensure safe use of the drug, including the provision of patient medication guides, prescriber and/or patient agreements, and prospective registries. It can recommend extensive education for prescribers and counseling for patients as well. The DEA may also have input into the drug's labeling, and is responsible for licensing manufacturers of scheduled drugs and prescribers and for setting quotas for Schedule I and II drug production. The DEA has enforcement authority for violations under the CSA.

Once a drug has been placed in a schedule, that placement is unlikely to be changed (Henningfield and Schuster, 2009). "Down-scheduling," or moving a drug to a tier with fewer controls, is very rare; however, "up-scheduling" has occurred in recent years in the context of increased prescribing and misuse of opioids. Schedule changes may be initiated by the FDA, the DEA, Congress, or any other interested party.[37] In such cases, as in the original scheduling, the DEA seeks scientific and medical advice from the FDA and then acts through formal rulemaking. In the case of hydrocodone combination products, for example, a physician specializing in treatment of SUD petitioned the DEA to reschedule those products from Schedule III to Schedule II in 1999 (DEA, 2014). Five years later, following its review of the abuse potential of the drug, the DEA forwarded relevant data on the petition to the FDA for a scientific and medical evaluation. When the FDA undertook a review based on the eight factors listed earlier in 2008, it paid special attention to how rescheduling might affect prescribing practices. It found, for example, that rescheduling might result in the need for additional physician visits, that prescribers might then opt for oxycodone rather than hydrocodone combination products since they were in the same schedule, and that patients might receive inadequate pain relief (FDA, 2012). The FDA then recommended that hydrocodone combination products be maintained as Schedule III drugs. In 2009, after receiving another petition for rescheduling, the DEA sent additional data to the FDA providing further information about misuse in 2009, and the FDA undertook another review. In 2013, after an advisory committee voted 19-10 to recommend a scheduling change, the FDA forwarded a letter to the DEA recommending the rescheduling of hydrocodone combination products to Schedule II. The DEA issued a final rule to that effect in 2014.

[37] 21 U.S.C. § 811(a). Congress can and does insert itself into this process. In 2000, Congress legislatively required emergency scheduling of GHB (liquid ecstasy), and the 2012 Synthetic Drug Abuse Prevention Act required permanent scheduling of a number of synthetic stimulants and opiates.

Effects of Scheduling on Medical Practice

The design of the CSA reflects the inherent tension between optimizing the medical benefits of the controlled drugs and minimizing the dangers associated with their misuse. This tension is reflected in the CSA's tiered classification scheme, which anticipates that the responsible agencies will balance these considerations in making scheduling decisions. The tension is also evident at the level of the individual prescriber, given that placing a drug in the higher schedules can have a chilling effect on medically appropriate prescribing. As discussed in Chapters 2 and 5, prudent clinical judgment is required in deciding whether, when, and how to taper or terminate prescribing of opioids for patients reporting chronic pain. Well-meaning providers may be concerned about whether continued prescribing over the long term might be regarded by law enforcement or licensing agencies as being without "legitimate medical purpose" on the part of a practitioner "acting in the usual course of his professional practice," and therefore in violation of the federal or state CSA.

Despite a DEA guidance document that attempts to clarify those terms,[38] they may create enough concern that providers may choose not to prescribe controlled substances at all. For providers who do prescribe controlled substances, the CSA's tiered scheduling has had a more nuanced effect. Schedule tiers impose different prescribing requirements; CSA scheduling also affects how state law may impose additional requirements on prescribing of drugs assigned to the various tiers. Schedules III–V do not impose stringent prescribing limitations, but for Schedule II substances, prescriptions may not be refilled, the amount of drug or duration of use that may be prescribed on a single prescription is limited, and the prescription is required to be in written form. Many states require triplicate forms for Schedule II drugs and limit prescriptions to a short duration.

Schedule II requirements may increase providers' reluctance to prescribe substances that are so classified. Scheduling requirements do not provide incentives for providers to find other avenues for treatment, and they are not coupled with education. Making prescribing difficult for all providers, regardless of patient population, may result in denying access to individuals who need these drugs (Noah, 2003). The reclassification of hydrocodone combination products in 2014 has provided a natural experiment with which to study the effect of moving a drug to Schedule II. As noted in Chapter 5, early evidence shows that the reclassification substantially reduced the prescribing of these drugs (Chumpitazi et al., 2016; Jones et al., 2016), but whether health outcomes have improved as a result remains to be seen.

[38]DEA Docket No. DEA-286P, Dispensing Controlled Substances for the Treatment of Pain (2006).

Indeed, concern has been raised that rescheduling opioids to Schedule II is an unduly blunt instrument with which to limit overprescribing, and that it may have serious offsetting effects for individuals who need adequate pain treatment (Dineen, 2016). If rescheduling were simply to deter prescribing, the objection raised by the AMA when the CSA was adopted would be validated. More research is needed to study the effect of scheduling to Schedule II on pain treatment.

Three points emerge from the committee's review of CSA scheduling. First, the CSA requires explicit trade-offs between the effects of regulatory decisions on legitimate medical use and the harms associated with misuse and OUD. Second, the rescheduling of hydrocodone combination products reveals the diverging perspectives of the FDA and the DEA in exercising regulatory judgment on these issues and the inefficiency thus produced. Finally, because the FDA has many tools available under the FDCA for balancing these interests, the experience with hydrocodone combination products highlights the virtues of harmonizing the regulatory analysis undertaken under the two statutes, especially in relation to opioids.

Current FDA Benefit-Risk Framework

Currently, after the FDA reviews an NDA, it lays out the key details to help guide its decision making. The benefit-risk table shown in Figure 6-1 had its origins in an FDA initiative of 2009 "to develop a structured approach for drug benefit-risk assessments that could serve as a template for product reviews, as well as a vehicle for explaining the basis for the FDA's regulatory decisions in drug approvals" (FDA, 2013, p. 1). In 2012, section 905 of the FDA Safety and Innovation Act formalized this commitment by requiring the agency to implement a structured benefit-risk framework in its new drug approval process.[39] The FDA states that while "quantitative assessments certainly underpin" any regulatory decisions, this approach is "designed to support the identification and communication of the key considerations in FDA's benefit-risk assessment and how that information led to the regulatory decision" (FDA, 2013, p. 4).

The framework displayed in Figure 6-1 has been applied explicitly in a number of cases since 2012, although not yet for an opioid product. For one product, pimavanserin (Nuplazid), a treatment for the hallucinations and delusions of Parkinson's disease, the framework revealed that the FDA considered the unmet clinical need for a treatment in the "Analysis of Condition" row, the on- and off-label use of other available drugs for this purpose (and their outcomes) in the "Current Treatment Options" row, summaries of the pivotal efficacy trial ("Benefit" row) and serious adverse

[39]Public Law 112-144.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		

FIGURE 6-1 Current FDA benefit-risk framework.
SOURCE: FDA, 2013.

event profile ("Risk" row), and any key post-market surveillance activities in the "Risk Management" row (FDA, 2017a).

The committee believes that this framework was developed thoughtfully and that it achieves its patient-centered goals by clearly organizing the components of the benefit-risk decision leading to a drug's approval. The committee also believes that this framework can be adapted to specifically integrate public health considerations, and can be incorporated into a much more comprehensive approach to gathering and reviewing the available information and making decisions accordingly to guide the FDA's regulation of opioids. As described below, the FDA routinely considers broader public health goals in its assessment of drugs, and the committee believes there is a growing public health mandate to apply this flexibility in certain ways to the approval and oversight of opioids.

PUBLIC HEALTH DIMENSIONS OF FDA DRUG REGULATION

To approve a drug, the FDA must determine that the drug is safe and efficacious "under the conditions prescribed, recommended, or suggested in the proposed labeling."[40] The FDA has long interpreted this approval standard as meaning that a drug's benefits must outweigh its risks. Since at least the early 1990s, the agency also has acknowledged that it has "flexibility" in applying the approval standard, and in "determin[ing] the kind and quantity of data and information an applicant is required to provide" to demonstrate that a drug meets the standard.[41]

[40] 21 U.S.C. § 355(d).
[41] 21 C.F.R. § 314.105(c).

One of the ways in which the FDA exercises this flexibility is by integrating public health considerations into its benefit-risk determinations. Public health considerations may include how the availability or use of the product will affect an unintended population or the broad public health impact resulting from the aggregated effects on patients taking the drug. For drugs with the potential for misuse, for example, NDAs must include "studies or information related to abuse of the drug,"[42] which, of course, is not information about the use of the drug as directed in the proposed labeling. The FDA's authority to consider the broad impact of its pre- and post-approval decisions on the health and well-being of American patients and consumers is an extension of the FDA's primary role as a public health agency.[43]

Indeed, various provisions of the FDCA and FDA regulations make clear that the FDA has considerable discretion in determining what information is relevant to its regulatory decisions. Consistent with this flexibility, the FDA considers the public health consequences of its approval decisions in many aspects of its oversight of prescription drugs. For example, it may require a REMS, safety labeling changes, or post-market studies or trials to address risks of misuse, SUD, and overdose associated with a drug.[44] When requiring a REMS, the agency also must consider the broad context within which the drug will be used, including the burden on patient access and the health care delivery system.[45] As another example, as noted earlier, the FDCA requires holders of approved NDAs to report to the agency any adverse drug experiences, regardless of whether the drug was used as directed.[46] Likewise, the FDA's Sentinel initiative is intended to identify and analyze a broad range of drug risks, not limited to those associated with the intended patient population using the drug as directed.[47]

The following examples of FDA decision making with respect to testosterone products, transmucosal IR fentanyl (TIRF) products, antibiotics, and prescription acetaminophen products further illustrate that the FDA is able to integrate, and has integrated, public health considerations into its drug approval and withdrawal decisions pursuant to its existing authority under the FDCA. In addition, this integration of public health considerations into regulatory decisions has encompassed decisions regarding the content that must be in drug labeling and REMS requirements. The following examples are not exhaustive. The FDA has incorporated public health considerations into numerous other decisions not described in depth in this report, includ-

[42] 21 C.F.R. § 314.50(c)(5)(vii).
[43] 21 U.S.C. § 393 (1997).
[44] FDCA Sections 505(o)(3) and (4); 505-1(2)(b).
[45] FDCA Section 505-1(f)(2).
[46] 21 C.F.R. § 314.80.
[47] FDCA Section 505(k)(3).

ing its approval of vaccines, requirements for misuse warnings on all opioid labeling, and certain requirements for labeling of over-the-counter (OTC) drug products, among others. Since the agency already incorporates these issues into its decision making in various contexts, integrating public health considerations into its regulation of opioids—including its approval decisions on new opioids—would be consistent with both its past practice and a generally accepted understanding of its statutory authority.

Examples of the FDA's Taking a Public Health Approach to Regulation

Example 1: Testosterone Products

In 2009, the FDA received a series of adverse event reports of children who had not been prescribed testosterone gel suffering serious side effects after inadvertent exposure to the products. After reviewing these cases, the FDA determined that the labeling for the products failed to adequately protect children from unintended side effects because some patients for whom they were being prescribed did not follow instructions, and as a result, children were coming into direct contact with the patients' treated skin (FDA, 2009b). In response, the FDA required manufacturers of certain formulations to include a boxed warning on the products' labels and implement a REMS that included a medication guide providing more thorough instructions for the user. At the time, this regulatory action drew some attention because it was the first instance of the FDA's requiring a REMS designed exclusively to protect a third party rather than the patient. (The manufacturers did not contest the label changes.)

Example 2: Transmucosal Immediate-Release Fentanyl Products

TIRF products are intended to manage breakthrough pain in adults with cancer who are already taking, and are tolerant to, other opioids for their consistent pain. TIRF products, however, pose significant public health risks, including diversion, misuse, and overdose.[48] These risks are particularly acute for off-label use among nonopioid-tolerant patients and for accidental exposure and toxicity in children, because TIRF products come in a variety of easy-to-ingest forms, including sublingual and buccal tablets, lozenges, nasal sprays, and buccal soluble films.[49]

[48]Actiq Medical Reviews, http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20747_Actiq.cfm (accessed June 27, 2017).

[49]Actiq Medical Reviews, http://www.accessdata.fda.gov/drugsatfda_docs/nda/98/20747_Actiq.cfm (accessed June 27, 2017).

Because of these risks, FDA regulation of TIRF products provides an example of how the agency has dealt with concerns about the use of a drug in unintended populations. The FDA reviews published at the time of the TIRF product approvals address the risks of use in nonopioid-tolerant populations and accidental exposure and overdose in children, suggesting that the agency considered those risks as part of its approval decisions.[50] That the agency considered these risks in its approval decisions is further apparent from the TIRF products' approved labeling. All TIRF product labeling contains a contraindication for nonopioid-tolerant patients and a warning explaining that TIRF products contain fentanyl in a dose that can be fatal to a child, and advising that patients ensure the products' proper storage and disposal.[51]

Beyond these measures, the TIRF REMS is designed to mitigate the risk of exposure to nonopioid-tolerant patients and children. Express goals of the TIRF REMS include "prescribing and dispensing TIRF medicines only to . . . opioid-tolerant patients" and "preventing accidental exposure to children and others for whom [the TIRF product] was not prescribed" (FDA, 2015c). To accomplish the first of these goals, the REMS requires prescribers, dispensers, and patients to confirm that they are aware of the risk of TIRF products for nonopioid-tolerant patients and the contraindication for that population. To accomplish the second goal, the REMS requires a prescriber–patient agreement form in which the prescriber documents that she or he has counseled the patient on the risk that TIRF products pose to children and on proper storage, and in which the patient documents that she or he understands this information. In sum, the FDA has considered the risks of the use of TIRF products by unintended patient populations in its approval and labeling decisions, as well as in the design of the REMS, for these products.

Example 3: Antibiotics and Resistance

Antibiotic resistance has been recognized as a problem since the late 1960s (Swann et al., 1969), and the FDA has struggled with how best to regulate antibiotic use in humans and animals in light of this problem, which poses risks not only for the patient or animal being treated but also for the population broadly. Use of antibiotics in animals has been widespread, not only for treatment or prevention of illness but also because such

[50]Abstral, Actiq, Fentora, Lazanda, Onsolis, and Subsys reviews, http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60 (accessed June 27, 2017).

[51]See, e.g., Abstral Labeling at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022510s000lbl.pdf (accessed June 27, 2017).

drugs promote weight gain and feed efficiency. The FDA has been legitimately concerned that such use of antibiotics in animals leads to greater antibiotic resistance in humans.

The FDA first announced its intent to withdraw approval for penicillin and tetracycline for livestock production uses in 1977, but for decades, the agency struggled to provide conclusive evidence that such use posed risks to humans. Finally, in 2003 the FDA determined that while it did not have full proof of the resistance risks posed by livestock production use of antibiotics, it could not conclude that such use was safe. Accordingly, it issued a guidance document describing a risk-based assessment process for new antimicrobial animal drug applications (FDA, 2003). This document explained that the FDA expected new animal antimicrobial drug applications to demonstrate not only safety and efficacy for the intended animal use but also "reasonable certainty of no harm to human health" from that use. The document was followed by additional guidance further explaining the agency's thinking on mitigating the risks of resistance associated with use of antibiotics in animals.

With respect to human use, in 2003 the FDA published a final rule[52] requiring specific language on labels for human antibiotics encouraging providers to limit prescription of the drugs. This language advises providers to prescribe antibiotics only when bacterial infection is strongly suspected and warns against the potential for antibiotic resistance. These admonitions appear at least four times on each label: at the beginning of the label, in the section on indications and usage, and twice in the precautions section. The precautions section also provides specific guidance for physicians in counseling their patients about the proper use of antibiotics. Additionally, the 21st Century Cures Act, enacted in 2016, amended the FDCA to create an approval pathway for antibiotic drugs intended for patients with unmet medical needs that would require the drugs' labeling to caution prescribers that the drug is intended only for a limited population."[53]

Example 4: Prescription Acetaminophen Products

Acetaminophen is an active ingredient in many prescription combination drug products for pain, such as hydrocodone/acetaminophen (Vicodin), as well as in OTC pain relievers, such as Tylenol. It has been a persistent cause of liver injury, and acetaminophen overdoses—both intentional and unintentional—are a leading cause of acute liver failure in the United States. The FDA has taken numerous steps to address the problem, including working with the National Association of State Boards of Pharmacy

[52]21 C.F.R. 201.24.

[53]Sec. 3042 of the 21st Century Cures Act.

to label prescription medications containing acetaminophen more clearly, organizing a 2002 advisory committee meeting regarding OTC acetaminophen products, launching a patient education campaign in 2004, initiating an internal agency working group on acetaminophen in 2007, requiring changes to OTC drug labeling in 2009, and holding another advisory committee meeting in 2009 focused on both OTC and prescription products (FDA, 2009a).

In January 2011, the FDA published a *Federal Register* notice announcing that it was taking two additional steps;[54] requiring a warning about hepatoxicity on the labeling of prescription drugs containing acetaminophen[55] and asking prescription drug manufacturers to limit the maximum amount of acetaminophen per dosage unit to 325 mg (previously, some products had dosage units with as much as 750 mg). The agency explained that if manufacturers did not comply voluntarily within 3 years, it would use its authority under section 505(e) of the FDCA to withdraw approval of any prescription acetaminophen products that exceeded the new maximum dosage unit strength. The agency ultimately was successful in removing all high-dose acetaminophen products from the market by March 2014 (FDA, 2014a).

These actions all involved consideration of the broader public health implications of acetaminophen use. In particular, in explaining its rationale for planning to withdraw approval of prescription acetaminophen products that did not comply with the new maximum dosage unit strength, the agency pointed to some conventional individual health considerations, including the lack of evidence suggesting that the benefits of the higher-strength products outweigh their risks and the need to establish a larger margin of safety because of uncertainty about the precise toxicity threshold for different patient populations. But the agency also discussed various public health considerations. One basis for its decision was the high risk of unintentional overdose—in other words, the risks associated with the drugs when patients do not use them as directed. The FDA also discussed some of the societal impacts of acetaminophen-associated overdoses, including the estimated 56,000 emergency room visits, 26,000 hospitalizations, and 456 deaths per year caused by such overdoses (numbers far lower than those for opioid overdoses) (Nourjah et al., 2006). Additionally, the agency pointed to the contribution of prescription acetaminophen products to the high incidence of acetaminophen-related liver injury as another reason for withdrawing approval of the higher-dose products.

[54]76 Fed. Reg. 2691 (Jan. 14, 2011).

[55]Section 505(o)(4) of the FDCA (added by the Food and Drug Administration Amendments Act of 2007 [FDAAA]).

Public Health Considerations Relevant to Opioid Regulation

Some reasons why opioid analgesics warrant a unique regulatory approach are summarized in Table 6-2. As discussed in previous chapters, in addition to pain relief, opioids can produce feelings of pleasure, relaxation, and contentment (NIDA, 2017). Misuse and diversion associated with seeking these effects, facilitated to some degree by variability in prescribing practices and suboptimal management of pain, have fueled the development of black markets for opioids and counterfeiters.

Accordingly, a public health orientation assumes particular importance in the case of opioids and opioid derivatives, which are associated with nonmedical use and OUD and often are diverted from the lawful system of medical distribution. Related problems arise for opioid agonists and partial agonists (e.g., medication-assisted treatment for OUD), which share many of the same chemical properties and, like opioids, are diverted from lawful medical distribution or used by others beyond the patients for whom they are prescribed. Even opioid antagonists (e.g., the overdose reversal drug naloxone) are used legally and regularly to great benefit beyond the individuals to whom they are prescribed, and sometimes must be administered to the individuals to whom they were prescribed by other persons.

As discussed in Chapter 4, an approach to opioid regulation that actively takes public health considerations into account also requires the recognition that actions taken with respect to one opioid will affect the use and misuse of other opioids, opioid derivatives, and forms of pain management and consideration of the social system shaping use of those drugs.

TABLE 6-2 Special Biological and Social Characteristics of Opioids and Opioid Derivatives

Characteristic	Opioids	Opioid Agonists/ Partial Agonists	Opioid Antagonists
Genetic predisposition to misuse	X	X	
Repeated exposure alters neurobiology of brain	X	X	
Licit/illicit product replacement capacity	X	X	
Reinforcing effects due to chemical properties	X	X	
Clinical need is great	X	X	X
Unintentional/intentional harm or benefit from exposure is great	X	X	X
Exposure or availability can cause risks or benefits to others besides the patient	X	X	X

The interrelations among regulatory decisions concerning different drugs are a prominent feature of the opioid marketplace. The FDA recognizes that continued decisions about drug A require updating the information about the benefits and risks of drug A and its alternatives. For example, in the wake of placebo-controlled randomized trials linking the nonsteroidal anti-inflammatory drugs (NSAIDs) rofecoxib (Vioxx) and celecoxib (Celebrex) to increased cardiovascular risk, the FDA required that new boxed warnings about cardiovascular risk also be added to the labels for older, nonspecific NSAIDs, even though the strength of the evidence implicating those drugs was based on observational data. In the case of opioids, the various drugs in the class interact in the legal and illegal markets and often substitute for one another, so regulatory decisions about opioid A should not be based solely on predicted outcomes among users of opioid A. As an extreme example, it might be excellent policy to approve a new opioid formulation that was expected to cause 500 overdose deaths per year if that new opioid reduced overdose deaths from all other opioids by 5,000 per year. Likewise, randomized clinical trials might show that an ADF of opioid B was safer than an ADF of opioid C, but for various reasons, opioid B would achieve little market penetration and would be used primarily by people who would not develop OUD in any case, while opioid C was positioned to displace use of the current dangerous non-ADF more successfully. Opioid B might win a head-to-head competition in a traditional clinical trial, but a more circumspect decision to instead approve opioid C would save more lives.

Finally, the social system surrounding opioids is a key driver of the committee's recommendations in this report. Integrating public health considerations into regulatory decision making helps in considering distributional effects of those decisions over time. Important state-to-state and regional differences in opioid prescribing and problems have been observed since oxycodone ER was introduced in 1995 (Cicero, 2005). Thus, an optimal regulatory process will consider not only what is best for the country as a whole but also the possibility that what is best for the country as a whole might create unacceptable problems in certain states or regions that are more vulnerable because of established opioid trafficking routes, migration patterns, poverty and unemployment, and other social determinants of opioid misuse and OUD. Similar logic applies to key subpopulations, such as pregnant women (see the discussion in Chapter 4) and persons with mental health conditions that historically have been heavily impacted by SUD (Edlund et al., 2010). The effects of a policy action on the health and welfare of these subpopulations could also serve as a "warning signal" for the population at large.

KEY ELEMENTS OF AN INTEGRATED DECISION-MAKING FRAMEWORK FOR OPIOID REGULATION

A public health perspective is necessary but not sufficient for rational opioid regulation. Rather, as reflected in the committee's recommendations in this chapter, public health considerations need to be embedded in a regulatory framework that is flexible enough to capture and weigh an array of diverse outcomes occurring at multiple levels, from individual to societal. This integrated framework needs to facilitate informed regulatory decisions throughout a drug's life cycle, and include built-in periodic monitoring of each decision's consequences instead of decisions being treated primarily as self-contained events. If correctly formulated, this integrated framework will minimize mistakes and allow the community to recover expeditiously from any that are made. This is the ideal scenario for decision making in the face of uncertainty, which is the hallmark of regulating new drugs. This approach may also be applicable to other drug classes with similar concerns related to risk of misuse, SUD, diversion, and illicit market–based substitutes, likely with some alterations for the specific issues those drug classes present, although in the context of this report the discussion is focused on opioids.

The starting point for the development of an integrated decision-making framework for the FDA's regulation of opioids is recognition that attempting to introduce considerations beyond the clinical trial and other scientific data presented in the NDA will substantially increase the complexity of the agency's decision-making process. To promote rational, data-driven, and transparent decision making under such conditions, the FDA would need to (1) identify all relevant outcomes; (2) quantify those outcomes to the extent feasible; and (3) integrate those outcomes into an evaluative framework, including a common metric that would facilitate comparison and balancing.

Step 1: Identifying All Relevant Outcomes

An integrated framework for opioid regulation would include all relevant outcomes with an impact on public health. For most drugs, these outcomes are adequately summarized by the potential benefits and risks for individuals for whom the drug is indicated in the labeling. For example, a regulatory analysis of a cholesterol-lowering statin drug would need to consider its impact on users' cardiovascular risk reduction (the potential benefits) and on the development of diabetes and muscle and liver injury (the potential risks), as well as any other outcomes that are anticipated to affect the health of the drug's users. Another important consideration in the regulation of many drugs is the quantification of "risk compensation." For example, if statins make users feel less concerned about their diets, they

may revert to less healthy eating habits, therefore partially offsetting the hoped-for benefits of the drug.

As discussed in more depth in the next section, application of this step to an opioid would involve consideration of its impact on such outcomes as users' short- and long-term pain relief and functional improvements (the potential benefits); hyperalgesia, misuse, OUD, overdose, and death (the potential risks); and the possibility of risk compensation. It could also include outcomes that are not directly experienced by the drug's users but affect families, communities, and society as a whole.

Other outcomes that might need to be considered include illegal markets for diverted prescription opioids, illegal opioids such as heroin and illicitly manufactured fentanyl, and counterfeit pills that look like prescription opioids. Approval or withdrawal of a prescription opioid on the legal market can affect levels of use of black market opioids such that the total net effect on mortality may be very different from the apparent effect if one considers only outcomes directly related to the approved or withdrawn opioid. Indeed, one survey found that roughly three-quarters of people who used heroin in the past year misused prescription opioids first, and seven of ten people who used heroin in the past year also misused prescription opioids over the same period (Jones, 2013). The challenge of monitoring indirect effects also is illustrated by the introduction of ADFs, which may prevent misuse through specific modes of administration (e.g., injection or insufflation) but may have unintended impacts (see discussions in Chapters 4 and 5).

Step 2: Quantifying the Outcomes

Traditionally, the FDA appropriately relies on randomized trials, observational studies, and other patient experiences to quantify drugs' benefit-risk profiles. However, because supplying opioids for long-term use outside of medical facilities creates additional risks from misuse and diversion, many of the relevant outcomes cannot be identified or quantified using the FDA's usual research tools. In these situations, regulation would need to be informed by data on behaviors of intended users or others designed to evade or neutralize desired outcomes (including intentional efforts to defeat the system, such as by physician shopping or operating "pill mills" in the case of opioids). To accomplish this important task, the FDA might need to monitor nontraditional data sources (e.g., prescription drug monitoring programs, relevant online message forums, and special populations such as people in treatment for OUD) to quantify the extent of these behaviors in support of its regulatory decisions.

Evaluation of this full spectrum of outcomes is an inherently interdisciplinary task that requires alternative data sources and inputs from

experts in epidemiology, economics, and other social and behavioral sciences. Although improvements in measurement and surveillance are under way, the precision and completeness of the tools available to measure the many relevant outcomes are not ideal (Secora et al., 2014), and may never be given the illicit nature of most opioid misuse. However, sound regulatory decisions need not overlook important benefits and risks just because they are difficult to quantify. In addition, incorporation of the full range of considerations need not be postponed until all pertinent data sources have been developed, but may proceed tactically and strategically, incorporating available outcomes and data sources as they are developed and improved.

The outcomes would ideally be measurable in at least one extant surveillance system. Risks could generally reflect mortality (e.g., risk of fatal overdose) or substantial morbidity (e.g., measures of OUD among women of childbearing age). A denominator reflecting the drug's availability or its potential for misuse or diversion at the local level could be applied to aid in comparing across the components (Butler et al., 2008; Secora et al., 2014). Because geographic trends could be especially useful in risk-benefit considerations, preservation of the lowest possible geographic unit for numerator and denominator might be optimal. Another important choice would be what to consider as the denominator. For example, morphine milligram equivalent (MME) availability could be used because data on dispensed medications are readily available at high levels of specificity (zip code, county), and because availability of illicit drugs can be captured at this geographic unit level and equated with prescription opioid–generated MME to provide a more accurate measure of the relevant health outcomes. Diversion and corruption of the drug's access mechanisms could be anticipated based on information on comparable products captured by government and private datasets. These "secondary" outcomes of the opioid under consideration could be estimated at the patient, provider, manufacturer, and distribution levels.

One of the FDA's major challenges would be to evaluate the currently available data sources addressing these outcomes and to work with the sponsoring agencies or institutions to improve these sources, such as by identifying gaps in the data and collaborating with partners to close those gaps or generate new datasets. Appendix C of this report provides a tabular summary of current data sources, as well as their strengths and limitations.

Step 3: Integrating Outcomes into an Evaluative Framework

Beyond creating a comprehensive list of outcomes and quantifying those outcomes, a key conceptual challenge is determining how to integrate many outcomes into a single framework that permits a transparent comparison of policies with differential effects on each outcome.

For most drugs, the procedure for weighing benefits and risks typically involves a mix of quantitative estimates (e.g., findings from clinical studies) and qualitative judgments (e.g., opinions of advisory committees). A 2012 Institute of Medicine report proposes a framework for assessing a drug's benefit-risk profile (IOM, 2012). For opioids, however, the weighing of benefits and risks is more complex than is the case for other drugs because the relevant consequences affect intended and unintended users as well as third parties, operate at multiple levels (individual, household, community), and encompass a wide array of fatal and nonfatal outcomes. Weighing benefits and risks in this context requires a decision-analysis framework that can adequately capture the dynamic interrelations among the many variables involved. One possibility, discussed briefly in Chapter 5, is building a mathematical model of the opioid system that simulates the expected outcomes. However, developing and testing such a model is likely to take several years, and the committee believes the need to expand the FDA's regulatory framework, including by incorporating unquantified elements and "best estimates," warrants action to meet that need in the meantime.

Another challenge is to weigh the risks avoided by tighter regulation of an opioid against the pain, functional limitations, and other adverse effects experienced by patients who would benefit from that drug if its access were not restricted. The FDA's current approach informally weighs the available measures of pain utilized in clinical trials against estimated increases in misuse and OUD and the derivative risks. Although this approach will remain necessary for the immediate future, the committee also encourages and expects the FDA to explore use of a common yardstick (e.g., quality-adjusted life years) to incorporate all the outcomes of interest within a single metric.

The committee recognizes that no single quantitative exercise, even an integrated one using a common metric, can replace the agency's regulatory judgment for every decision. However, the FDA could quantify the outcomes as fully as possible given the available data and integrate these outcomes into a transparent framework that utilizes a common metric for measurement to the extent feasible. In the next section, the committee provides its recommendations for how this transparent framework might look and how it might be implemented.

IMPLEMENTATION OF AN INTEGRATED FRAMEWORK FOR OPIOID REGULATION

In the committee's judgment, the FDA should take steps toward the implementation of an integrated, transparent framework for opioid regulation at three different stages of its decision-making process: clinical develop-

ment, drug approval, and post-approval monitoring. Box 6-2 contains the committee's overarching recommendation framing this discussion.

Stage 1: The Clinical Development Stage

The FDA can first intervene to implement a new approach to opioid regulation after the submission of the IND application. During the investigational clinical trial period that follows submission of an IND application, crucial data currently are collected on the drug's pharmacodynamics, safety, and efficacy for intended users, but data also could be collected on its potential public health consequences. To date, evidence generation for opioids, as for many drugs, often has involved short-term trials involving narrowly defined patient populations (e.g., patients with back pain). A more comprehensive approach to organizing pre-approval trials could encompass

- testing the drug in subpopulations at high risk of harmful outcomes, including those in locations of the country with high rates of misuse, OUD, or diversion;
- including patients with mental health disorders and OUD and other populations in which opioid drugs are known to be widely used to ensure a representative sample of patients in the pivotal clinical trials;
- measuring outcomes reported by household members or other third parties expected to be affected by the product (to partially overcome underreporting of misuse and OUD);
- conducting continued testing of ADFs to understand the mechanisms of manipulation that might be used to defeat them; and
- understanding interactions with other drugs (both prescription and illicit) commonly used with opioids or by people who use opioids illicitly, including how the drug interacts with antiretrovirals or anti–hepatitis C virus (HCV) medications.

While the committee understands that not all of these outcomes could be collected for every opioid being tested, this also may not be a comprehensive list—the particular public health outcomes would need to be specific to the opioid and its predicted effects. To that end, the FDA could issue a guidance document delineating the specific public health data that are likely to be most relevant to different types of opioids and that would need to be collected during pre-market clinical trials. This guidance document would explain the agency's current thinking on the overall development program and clinical trial design for opioids intended to treat acute and chronic pain. In addition to commenting on public health outcomes, the guidance could address the current state of the evidence on the essential

BOX 6-2
Overarching Recommendation for Development of an Integrated Framework for Regulation of Opioids

Recommendation 6-1. Incorporate public health considerations into opioid-related regulatory decisions. The U.S. Food and Drug Administration (FDA) should utilize a comprehensive, systems approach for incorporating public health considerations into its current framework for making regulatory decisions regarding opioids. The agency should use this approach, in conjunction with advisory committee input, to evaluate every aspect of its oversight of prescription opioid products in order to ensure that opioids are safely prescribed to patients with legitimate pain needs and that, as actually used, the drugs provide benefits that clearly outweigh their harms. When recommending plans for opioids under investigation; making approval decisions on applications for new opioids, new opioid formulations, or new indications for approved opioids; and monitoring opioids on the U.S. market, the FDA should explicitly consider

- benefits and risks to individual patients, including pain relief, functional improvement, the impact of off-label use, incident opioid use disorder (OUD), respiratory depression, and death;
- benefits and risks to members of a patient's household, as well as community health and welfare, such as effects on family well-being, crime, and unemployment;
- effects on the overall market for legal opioids and, to the extent possible, impacts on illicit opioid markets;
- risks associated with existing and potential levels of diversion of all prescription opioids;
- risks associated with the transition to illicit opioids (e.g., heroin), including unsafe routes of administration, injection-related harms (e.g., HIV and hepatitis C virus), and OUD; and
- specific subpopulations or geographic areas that may present distinct benefit-risk profiles.

Subpopulations and geographic areas that may present distinct benefit-risk profiles include, but are not limited to, pregnant women, individuals with a history of SUD/OUD or other mental health conditions, and geographic areas with high rates of unemployment or SUD/OUD.

features of trials for new opioids or opioid formulations, such as the duration necessary to collect appropriate outcomes. Such a document could also specifically address how the agency will handle new applications through the 505(b)(2) pathway frequently used for opioid reformulations or dosing changes. While reformulations may undergo less drug efficacy and safety testing, they may entail important public health considerations based on

ongoing experience with the formulations that are currently being marketed. Similarly, studies have documented a positive opioid dose–harm relationship (with respect to OUD and death in particular). FDA approval of opioids through the 505(b)(2) process would need to involve the same rigorous data evaluation process as that used for approvals made under the traditional pathway.

Communication of the types of public health outcomes sought by the FDA for a particular opioid could be communicated during the meetings that manufacturers are permitted to have with the FDA after each stage of testing, and at other times with sufficient notice. At these meetings, manufacturers may discuss plans for the design and outcomes of their trials, as well as the early evidence on the drug that has emerged. The FDA can impart useful advice during these meetings on optimal trial designs that can meet the considerations outlined in this chapter; indeed, according to one review, manufacturers that had an end-of-phase-2 meeting were far more likely to have their drugs approved than those that did not (Booz Allen Hamilton, 2006). Some manufacturers are diligent about having these meetings, while others are not. These meetings could serve as a useful mechanism for encouraging a new paradigm for opioid testing. The FDA guidance could suggest that manufacturers developing new opioids or new opioid formulations request a certain number of pre-approval meetings before submitting an NDA. These meetings could also help build a paper trail to inform FDA post-approval surveillance and help regulators understand why any recommendations about measurement of public health outcomes are not being implemented.

While the committee did not wish to make specific recommendations on what the FDA should do if manufacturers' development plans were to diverge substantially from the above guidance or if signals of potential problematic public health outcomes were to arise (such as evidence of diversion or misuse even in the highly structured environment of a clinical trial), issuance of a clinical hold is a strategy the FDA can use to delay additional proposed clinical studies or suspend an ongoing study. Reasons why a clinical hold may be issued under the current regulations include an unreasonable risk for subjects participating in the clinical research or a protocol for a phase 2 or phase 3 trial that is clearly deficient in design to meet its stated goals.[56] Twenty-nine clinical holds were issued between 2008 and 2014 (Boudes, 2015), a remarkably low number given the number of investigational drugs being tested during those years. A clinical hold, if needed, could be issued as soon as possible after the IND was submitted or after the FDA received new information about ongoing opioid development trials, thereby reducing disruption for manufacturers and clinical trial enrollees.

[56] 21 C.F.R. § 312.42.

For example, if a manufacturer sought to bring a new LA formulation of an opioid to market without a tamper-resistant formulation, the FDA could decide to act at this point to hold the clinical trial until the company's rationale could be assessed. In this case, the proposed formulation could present an unreasonable risk of contributing to harmful outcomes among the subjects of the trial, and the trial would clearly be deficient in design, assuming that one of its stated goals would be to obtain FDA approval of the product.

As another example, if the FDA observed that a proposed pivotal trial for a new opioid or opioid formulation had not been designed to be of sufficient duration to enable collection of the necessary public health outcomes, this could be the basis for issuing a clinical hold until the trial had been redesigned. In this case, the agency might conclude that the trial was clearly deficient in design, assuming that one goal of the trial was to support FDA approval. The FDA could create an internal system to prioritize review of opioid INDs to facilitate the issuance of clinical holds, when warranted, and develop a similar system for integrating new information it received about opioids later in the development process to help in deciding whether clinical holds would be needed at any point.

The FDA could also specially consider the public health implications of opioid approval when making use of the multiple pathways leading to approval of investigational drugs. In addition to the 6-month priority review option, drugs can receive four other special designations to expedite their development or approval (see Table 6-3). While the expedited access provided by these pathways can be highly useful in cases of transformative new products or drugs intended to serve an unmet medical need, shortened development and review times have also been associated with negative public health outcomes. Drugs approved shortly before their regulatory deadlines have been found to be more likely to have post-marketing safety problems—including safety-related withdrawals and the need for added boxed warnings—relative to drugs approved at any other time (Carpenter et al., 2008, 2012). Drugs receiving faster reviews also have more spontaneous reports of drug-related adverse events (Lexchin, 2012; Olson, 2008; Reaves, 2009).

In the case of opioids, it would be inadvisable to truncate the development time in the absence of extraordinary circumstances. Instead, opioids and their secondary effects need to be fully investigated and the normal amount of time allotted to reanalyze the results of that investigation (currently 10 months for standard-review drugs). Because it is highly unlikely that a new opioid would satisfy the criteria for an expedited review or development pathway (e.g., fills an unmet medical need or offers a substantial improvement over available treatments for a serious condition), guidance might be issued defining how these pathways apply to opioids and

TABLE 6-3 The U.S. Food and Drug Administration's Expedited Drug Development and Approval Pathways

Special Designation (Year Initiated)	Criteria and Notable Pathway Features
Orphan Drug (1983)	Applies to drugs intended to treat diseases affecting <200,000 people per year. Such drugs often are approved based on smaller trials with few rigorous features (controlled, randomized, testing a real clinical outcome versus a surrogate measure).
Fast Track (1988)	One phase 2 trial is sufficient to demonstrate safety and efficacy.
Accelerated Approval (1992)	Approval is based on a surrogate or intermediate endpoint "reasonably likely to predict clinical benefit."
Priority Review (1992)	The new drug should "significantly improve" safety or effectiveness; FDA review is shorter (6 months versus the 10-month standard).
Breakthrough Therapy (2012)	Based on preliminary clinical evidence with clinically significant endpoint(s), the drug offers "substantial improvement" over existing therapy; intensive guidance is intended to expedite development.

SOURCE: Darrow et al., 2014.

other drugs with addiction potential. Recently, the 21st Century Cures Act of 2016 permitted supplemental approvals—for newly approved indications for drugs already on the market—to be granted on the basis of summaries of the data, rather than full FDA review of the underlying data. Again, the committee believes this truncated pathway is inappropriate for opioids, and instead review of the underlying data for supplemental NDAs for these drugs is necessary in all cases. Box 6-3 contains the committee's recommendations to the FDA for the clinical development stage.

Stage 2: Drug Approval

The next major intervention point for the FDA in its regulation of opioids is the time of market authorization, when it is considering an NDA for a new opioid molecule or formulation. As indicated above, a decision usually is made at this stage based on the efficacy and safety data related to the specific drug for the intended clinical use. In making this decision, the

BOX 6-3
Recommendations for the Clinical Development Stage

Recommendation 6-2. Require additional studies and the collection and analysis of data needed for a thorough assessment of broad public health considerations. To utilize a systems approach that adequately assesses the public health benefits and risks described in Recommendation 6-1, the U.S. Food and Drug Administration (FDA) should continue to require safety and efficacy evidence from well-designed clinical trials while also seeking data from less traditional data sources, including nonhealth data, that pertain to real-world impacts of the availability and use of the approved drug on all relevant outcomes. The FDA should develop guidelines for the collection of these less traditional data sources and their integration in a systems approach.

Recommendation 6-3. Ensure that public health considerations are adequately incorporated into clinical development. The U.S. Food and Drug Administration (FDA) should create an internal system to scrutinize all Investigational New Drug (IND) applications for opioids. This review should examine whether public health considerations are adequately incorporated into clinical development (e.g., satisfactory trial design; see Recommendation 6-2). In implementing this recommendation, the FDA should rarely, if ever, use expedited development or review pathways or designations for opioid drugs and should review each application in its entirety.

FDA conducts a formal, qualitative benefit-risk assessment and ultimately arrives at a decision as to whether a drug's benefits to patients for whom it is prescribed outweigh its risks. The committee believes, given the evidence presented thus far in the report, that formal incorporation of public health considerations into the existing assessment process is warranted since the risks of opioids are so profound, and their diversion is so prevalent. To this end, using its existing legal authority to take into account the public health considerations outlined in Recommendation 6-1, the FDA would consider use by the individual patient (including, for example, the possibility that the drug would not be used as intended) or by unintended persons (such as household members), as well as the broader societal consequences of likely use, such as the scale of diversion and the overall impact of addiction on the health and well-being of patients who develop OUD. One would expect a thorough regulatory analysis of a new opioid within this framework to consider the drug's broad impact on untreated pain, the risk of diversion/OUD, the risk of overdose/death, and an assessment of the expected number of persons who would experience each of these outcomes. Relevant considerations for each of these factors could include the following:

- Impact on untreated pain
  - expected prevalence of patients who would be served by the drug in question (versus with other opioids or with nonopioid treatment regimens);
  - pain relief observed in clinical trials (number of people benefiting and average improvement on pain and/or functioning scales);
  - differences between short-term effectiveness in highly protocolized clinical trials with selected patients and long-term effectiveness in health care settings (i.e., avoiding assuming that real-world impact on pain relief will correspond directly with outcomes of randomized controlled trials); and
  - prevalence of untreated pain if the drug were not approved and prescribed for the desired indication.
- Impact on diversion/OUD
  - expected prevalence and frequency of nonmedical use, which could be extrapolated from data on people currently using a related compound nonmedically;
  - expected diversion and impact on existing black markets, again extrapolated from data on people diverting (e.g., giving, selling, exchanging, buying, or otherwise receiving from someone other than one doctor/one pharmacy) related drugs that have already been approved; and
  - expected prevalence and frequency of SUD involving the drug in question if approved and involving use of substitute opioids (e.g., other prescription opioids or illicit opioids).
- Impact on overdose/death—estimated rates of fatal and nonfatal overdoses associated with or involving (1) the drug in question, (2) the compound in question, (3) other prescription opioids not of the same compound, and (4) illicit opioids.
- Other public health outcomes—if the drug is injectable, the risk of transmission of infectious diseases (e.g., HIV and HCV) caused by such use.

Potential effects of the drug on individuals for whom it is indicated and prescribed—as well as those whose use of the drug is unintended and not as prescribed—can be anticipated during the pre-approval stage and, if the drug is approved, can then be monitored post-approval. The factors outlined above could fit into an opioid-specific expansion of the FDA's current benefit-risk framework presented earlier in Figure 6-1 (see example Table 6-4), used when making approval decisions on applications for new opioids, new opioid formulations, or new indications for approved opioids.

The proposed expanded framework includes measurable, opioid-specific considerations relevant to public health, including patient and public safety. Should the information thus amassed suggest to the FDA that an opioid product should not be granted marketing approval, the committee believes the current FDA practice of providing a response letter complete with the rationale for the decision and suggestions for positioning the application for subsequent approval would remain appropriate. Complete response letters traditionally are not made public, but recent research has shown that manufacturers' press releases often misstate the reasons for disapproval. Because of the significant public health concerns associated with opioids and the need to be able to evaluate the FDA's new regulatory

TABLE 6-4 Example of an Adapted Benefit-Risk Framework for Approval of Opioid Products

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Characteristics of Opioid		
How Opioid Fits Among Currently Available Pain Treatment Options		
Benefits Observed in Clinical Trials, Overall • Benefits to patients • Public health benefits		
Risks Observed in Clinical Trials • Risks to patients • Public health risks		
Predicted Benefits/Risks to Families of Patients		
Predicted Benefits/Risks to Society, Overall • Special communities • Subpopulations		
Diversion Potential		
Predicted Effects on Use of Other Opioids or Illicit Drugs		
Risk Management, Overall • Potential for off-label use • Advertising/promotion		

BOX 6-4
Recommendation for the Approval Stage

Recommendation 6-4. Increase the transparency of regulatory decisions for opioids in light of the committee's proposed systems approach (Recommendation 6-1). The U.S. Food and Drug Administration should commit to increasing the transparency of its regulatory decisions for opioids to better inform manufacturers and the public about optimal incorporation of public health considerations into the clinical development and use of opioid products.

Steps that the FDA might take to implement this recommendation include

- Issuing a guidance document that outlines opioid-specific clinical development considerations, including how the new guidance differs from existing analgesic development guidance and relates to public health.
- Releasing summary versions of complete response letters for opioid products to inform the public about the public health considerations that the FDA has determined would preclude marketing approval.

processes accurately, the FDA may want to reexamine its policies relating to publication of complete response letters and consider what steps it needs to take to ensure that all complete response letters related to opioids are publicly released at the time of issuance. Notably, an FDA Transparency Task Force in 2010 proposed that releasing certain relevant documents currently kept confidential, including the agency's letters to drug, biologic, and device manufacturers when their products are not approved, would be consistent with existing agency rules related to safeguarding commercial information (FDA, 2010a).

The final rows in the opioid-specific framework in Table 6-4 relate to post-approval mitigation strategies, which are discussed in the following section. Box 6-4 contains the committee's formal recommendation to the FDA for the drug approval stage.

Stage 3: Post-Approval Monitoring

When the FDA makes an approval decision or after a drug is on the market, the agency can establish post-approval commitments and requirements, including whether the opioid requires a REMS. As detailed in prior chapters, prescribing of opioids for long-term use for chronic pain has led to numerous safety concerns that cannot be adequately addressed or anticipated in limited, prospective pre-approval trials. For this reason, the

committee believes that rigorous, active post-approval monitoring of the ongoing safety and effectiveness of opioids is essential.

The key question is through what mechanisms optimal monitoring can occur such that the benefits of opioids are maximized and their risks minimized. As the FDA considers how to optimize its current post-approval monitoring authority for opioids, a useful way to integrate the review of the collected pre-approval data with the prospect of post-approval monitoring can be found in a three-step decision-making process previously proposed by an Institute of Medicine committee (IOM, 2012). In that process, each step corresponds to one of the three fundamental requirements for rational decision analysis under uncertainty reviewed in the previous section:

- In the first step of the analysis, the FDA would define the public health question that prompted the need for a regulatory decision under the applicable statute. This step would include identifying the specific characteristics of the drug and the health problem at issue, available information about the drug, alternative treatments that are available, and plausible regulatory actions and their potential consequences. This stage would be aimed at identifying the information needed for a regulatory decision.
- In the second step of the analysis, the FDA would evaluate the quality of evidence on both the benefits and the risks associated with the drug, including any new information that has triggered the need to consider regulatory action. The output of this step would include estimates of the likelihood and magnitude of a drug's benefits and risks and a characterization of the scientific evidence on which the estimates are based.
- The third step of the analysis would involve synthesizing and integrating the estimates of benefits and risks and the quality of the evidence on which these estimates are based (Step 2) with the public health question (as specified in Step 1); deciding on the appropriate regulatory actions, including whether further study should be required; communicating the decision; implementing the regulatory actions; evaluating the effects of the regulatory actions; and, particularly in the case of complex or difficult decisions, evaluating the decision-making process and the impact of the actions taken on the public's health. Note that this step would involve deciding whether immediate regulatory action is warranted, or holding a decision in abeyance in anticipation of better information from additional study would justify the costs and consequences of further delay.

With this model in mind, the committee suggests a number of specific actions (reflected in Recommendation 6-5 in Box 6-5 at the end of this sec-

tion) relating to the FDA's use of post-approval monitoring for opioids. The first set of actions relates to the use of currently available authorities, such as REMS, safety labeling changes, and risk communications. Currently, ER/LA opioids must be incorporated in a shared REMS, and the FDA has said that it intends to update the opioid REMS requirements to include IR opioids as well (FDA, 2017e) (the committee supports such a step). The current REMS for opioids is intended to reduce the serious risks associated with these formulations while maintaining access to the drugs for patients in need by educating providers about the limitations, benefits, and continued abuse potential of these formulations. However, the REMS may instead provide a false promise of risk mitigation (Nelson and Perrone, 2012). As discussed previously in this report, evidence is conflicting as to whether REMS can substantially affect prescribing and dispensing practices and is lacking on the effectiveness of the REMS for opioids. As part of efforts to improve its post-approval oversight of opioids, the FDA could make better use of REMS components that have been shown to improve prescribing practices (see Recommendation 6-5).

Meanwhile, the FDA could evaluate the data on the performance of the existing REMS, collecting additional data if needed, and change the features of the REMS so it would more optimally ensure the evidence-based use of opioids while reducing unsafe prescribing. For example, the FDA could consider additional supplemental education strategies when strengthening the opioid REMS, similar to the SCOPE of Pain program discussed in the first section of this chapter. Related considerations include how heightened prescribing restrictions might affect the supply of prescribers willing or able to prescribe opioids to patients with legitimate pain needs. Thus, it would be important to actively solicit the perspectives of prescribers and patients who are independent from the pharmaceutical industry in developing an optimal REMS. Development of an optimal opioid REMS also could be facilitated through collaborations between the FDA and other relevant government agency stakeholders, such as the Substance Abuse and Mental Health Services Administration, National Institute on Drug Abuse, U.S. Centers for Disease Control and Prevention, Health Resources and Services Administration, and U.S. Department of Veterans Affairs, among others.

Similarly, the boxed warning on opioids was strengthened in August 2016 to indicate that opioids carry "serious risks, including misuse and abuse." It may be instructive for the FDA to study whether this change and the publicity surrounding it helped more prescribers and patients better balance the benefits and risks of opioid prescribing. For example, FDA efforts to communicate risk and safety information to providers and the public through advisories and warning labels appear to have variable impact (Dusetzina et al., 2012). If no clear effects are observed, the FDA could further modify opioid labels to include more specific statements about

particular clinical situations, such as the management of chronic noncancer pain, in which there is clear evidence that the risks of opioids outweigh their benefits. These enhanced warnings could be included in the boxed warning, or disseminated through Drug Safety Communications and other media intended for a broad audience of prescribers and patients.

When new opioids are approved, requirements for boxed warnings or post-approval monitoring strategies such as REMS could be used as a way of justifying approval of a drug with an important safety risk, recognizing that the heightened post-approval surveillance or data from additional tests could inform changes to the label or even the marketing status of the product that might prove necessary. Before the FDA relied on such a strategy, however, the committee believes it would be best to study such post-approval actions as applied to opioids rigorously to ensure that they offer the real prospect of safety protections or timely acquisition of necessary data.

Another component of the committee's recommendation concerning post-approval monitoring pertains to the gathering of emerging information about the use of prescription opioids and how they are being used in both safe and unsafe ways. The collection of such information is part of the FDA's oversight of the safety and effectiveness of drugs in widespread use. Following approval of a new opioid or opioid formulation, initial estimates of the drug's risks and benefits would be informed and updated by data on the cumulative impacts of the drug as used in the community. As indicated above, the FDA might seek to impose post-marketing commitments or requirements to conduct ongoing studies. As the committee proposes in Recommendation 6-5, the FDA should engage in active surveillance of data on the use and misuse of approved opioids. This surveillance might include monitoring of new data that emerge from post-market commitments or requirements or the REMS program, which could be acted on efficiently and integrated with spontaneous adverse event reports and other observational data conducted through the Sentinel System. Other mechanisms for monitoring and generating new data might include periodic literature searches for independent reports of potential concern and the organization of prospective studies to respond to safety or other signals that might arise. Given the unique considerations related to opioids outlined in this report, the FDA might consider establishing a special center for opioid oversight to coordinate these activities in the Office of Surveillance and Epidemiology and work with the secretary of HHS to ensure adequate funding for its work. Newly emerging information might require changes to an opioid's labeling, although decisions to change the label wording or add safety warnings would ideally be guided by knowledge of whether past changes to opioid labeling have positively affected prescribing practices. Should such changes be deemed necessary, clear information dissemination plans that

go beyond the Drug Safety Communication mechanism currently in place, for which there is insufficient evidence of effectiveness, would be essential.

Recommendation 6-5 includes establishing a new post-approval monitoring structure for opioids to promote adequate post-approval oversight that would include periodic follow-up. During these formal re-reviews, the totality of the pre- and post-approval data available at the time could be collected and an advisory committee convened to help the FDA review the drug's real-world use and outcomes. The FDA could develop guidance on the types of data that would lead to withdrawal of the drug, the requirements to revise the label, initiation of other REMS or monitoring pathways, or other outcomes of this review process. The progress of such post-market commitments or requirements could be reviewed, giving the FDA an opportunity to examine preliminary data. Conversely, if warranted, the FDA could take an enforcement action, including imposing civil monetary penalties authorized under the FDA Amendments Act, if a manufacturer failed to comply with post-market requirements (including by failing to comply with the timetable for a study or trial).

In extreme cases, after the formal re-review, the FDA might conclude that withdrawal of an opioid was necessary because its benefits no longer outweighed its risks. Notably, the FDA cannot require a mandatory recall of an approved prescription drug. If an approved prescription opioid were later found to be unsafe because it was contributing excessively to misuse and OUD, a recall would have to be initiated voluntarily by the manufacturer in response to an FDA request. The FDA could request a voluntary recall in such extreme circumstances, or other federal or state enforcement authorities could evaluate their potential enforcement roles.

A third component of the committee's recommendation on post-approval oversight of opioids is more effective regulation of industry promotional activities. The committee bases this part of the recommendation on the fact that, as discussed earlier in this chapter, decades of research have shown that industry promotion of prescription drugs to physicians and consumers influences prescribing practices (Robertson et al., 2012). The FDA could issue new guidance outlining what it views as responsible advertising and promotion of opioids to prescribers. Just as the FDA should move to incorporate public health considerations in its approval-related decisions for opioid drugs, it should incorporate such considerations into its review of industry promotional strategies for these products. Requiring that advertising of a drug explicitly mention these public health considerations might be necessary for the advertising of approved opioids to be considered accurate, truthful, and not misleading. For example, the FDA might require that advertising mention the risk that someone in the patient's household might misuse or sell the drug if it is not safely stored, or that it include specific statements about the risks of developing tolerance and OUD

BOX 6-5
Recommendation for the Post-Approval Monitoring Stage

Recommendation 6-5. Strengthen the post-approval oversight of opioids. The U.S. Food and Drug Administration should take steps to improve post-approval monitoring of opioids and ensure the drugs' favorable benefit-risk ratio on an ongoing basis. Steps to this end should include use of Risk Evaluation and Mitigation Strategies that have been demonstrated to improve prescribing practices, close active surveillance of the use and misuse of approved opioids, periodic formal reevaluation of opioid approval decisions, and aggressive regulation of advertising and promotion to curtail their harmful public health effects.

More specific actions under this recommendation might include the following

- Maximizing the use of REMS with elements to assure safe use, boxed warnings, and other available risk communication methods in an evidence-based way to help influence safe and appropriate prescribing and dispensing practices. These tools could be implemented with input from prescribers and patients.
- Actively seeking emerging data on actual use and misuse of opioids through the Sentinel System and other methods to identify safety issues, and then act on them with all deliberate speed.
- Formal reevaluation of opioid approval decisions on a periodic basis based on the totality of the evidence, including evidence of public health outcomes, at that point.
- Restricting advertising and promotion of opioids to the fullest extent possible under existing rules, including prohibiting off-label marketing, to curtail practices inimical to the public health.

after unduly prolonged use for alleviating pain. More significantly, the FDA could find that there is no way to incorporate such broader considerations fairly into broadcast media advertising, ending the practice of DTC advertising of opioids via these media. The committee urges the FDA to issue guidance on responsible practices of DTC advertising and promotion as expeditiously as possible. Violations of promotional rules related to opioids should be pursued to the fullest extent of the government's current powers; in particular, off-label marketing of opioids should be carefully scrutinized.

Box 6-5 contains the committee's formal recommendation for post-approval monitoring.

Implications for Other Regulatory Decisions

The framework outlined in this section was designed for new opioid products and formulations, but can be applied with equal force to

opioids already on the market. Thus, in Recommendation 6-6 (presented in Box 6-6 at the end of this section), the committee recommends that the FDA conduct a full review of currently marketed/approved opioids. Such a review could be carried out by an expert panel that would systematically examine the current range of approved brand-name and generic opioids to determine which of these drugs remained effective and safe; which might need revised labels, formulations, or post-market requirements; and which should be withdrawn from the market entirely. Such a model could be modeled on the Drug Efficacy Study Implementation (DESI) of the 1960s and 1970s, in which the FDA worked in concert with the National Academy of Sciences/National Research Council to classify the risk-benefit ratios of the purported indications for drugs approved between 1938 and 1962 (NAS, 2017), ultimately finding that more than 300 products were ineffective for all indications and had to be withdrawn from the market, and more than 2,400 products had labels for indications for which they were ineffective. Although modeled on DESI, the Opioid Study Implementation (OSI) process envisioned by the committee could be carried out in a much shorter time frame and with far fewer resources than DESI because it would be limited to a single drug class for which the medical literature already provides substantial evidence to help answer the questions about opioids that the expert panel might want to address.

Although the OSI process would not be prohibitively expensive—and should be overall cost-saving to the U.S. health care system given its potential to reduce the substantial costs due to opioid-related harms—it would require sufficient funding sustained until the full range of available opioid products could be reviewed. In addition, several of the ideas offered for how the FDA might implement the committee's recommendations (e.g., the creation of a special center for opioid oversight within the Office of Surveillance and Epidemiology, routine post-approval reviews of new opioid approvals) would require additional regulatory resources. The cost of such interventions could be accounted for without additional legislation as part of the FDA's discretionary budget until the next reauthorization of the Prescription Drug User Fee Act, at which time the user fees applied to NDAs could be adjusted to account for the additional costs of adequate oversight of the prescription opioid market. Funding for this work might also be donated voluntarily by opioid manufacturers interested in helping to ensure a safer opioid marketplace. Another approach, which would require congressional action, would be to add a very small surcharge to each opioid prescription, in the same way that the National Childhood Vaccine Injury Act established a trust fund to compensate those suffering vaccine-related injuries through a $0.75 excise tax on each vaccine dose. All of these approaches warrant study to ensure that the FDA has the funding

it needs to modernize its approach to exercising its vital role in oversight of the opioid market.

The committee recognizes that the OSI process might lead to the removal of some of the opioid formulations or doses currently on the market because it is highly unlikely that all of these products would be judged safe and effective under the new drug approval framework proposed in this chapter should they just now be entering the market. However, the committee does not believe that this process would unduly restrict the availability of opioids for appropriate use in treating pain syndromes overall, since one of the advantages of the proposed OSI process would be its public health scope and the ability to take into account the advantages and disadvantages of removing a product in the context of the current marketplace of pain treatment modalities. Additionally, the FDA could establish reasonable time periods within which manufacturers would have to come into compliance with decisions resulting from the OSI process to minimize any disruption to treatment resulting from changes to marketed opioids (and reduce burdens on industry). Patients also would not need to be concerned that the OSI process would affect the cost of opioids as long as sufficient numbers of generic manufacturers were producing the opioid formulations remaining on the market at the conclusion of the OSI review.

The committee also believes that its recommendations may be relevant to some of the next-generation pain medications outlined in Chapter 3. Many of these products are designed to be nonaddictive, in which case they could be reviewed under the FDA's normal paradigm. But the agency might have lingering doubts about how some products will perform in long-term or widespread use, in which case it might want to apply relevant recommendations detailed in this chapter. When considering the various guidance documents suggested in this report, the FDA could indicate which recommendations it believed would also apply to novel nonopioid pain medications that nonetheless posed a potential risk for misuse, OUD, or illicit use.

Similarly, it is possible that some of the recommendations offered in this chapter could be applied to other controlled substances, such as benzodiazepines, neurostimulants, or other performance-enhancing drugs. This possibility warrants additional study, and the committee expresses no opinion on whether other drug categories should be added to the special focus it proposes for opioids.

The FDA has approved several ADFs of opioids that have physical or chemical properties to prevent misuse, as noted earlier in this chapter. A component of the FDA's Opioid Action Plan is to expand access to ADFs to discourage misuse (FDA, 2016a). While ADFs may have a role in preventing escalation of opioid misuse, as discussed in Chapters 4 and 5, multiple factors will determine the impact of a given ADF on public health. These include such factors as whether shifts in use behaviors that occur as a result

of attempting to defeat the abuse-deterring properties introduce risks and whether substitutions are made for comparably harmful prescription or illicit opioids. Indeed, in June 2017 the FDA requested that the manufacturer of the ADF Opana ER remove the drug from the market because of concern that the drug's ADF properties had led to increased injection of the drug and outbreaks of HIV and HCV, as well as cases of thrombotic microangiopathy (a serious blood disorder) (FDA, 2017d). The evidence on the specific role of ADFs in efforts to curb opioid-related harms is still developing. In light of continuing uncertainty about the benefits and risks of various types of ADFs, the FDA's cautious case-by-case approach appears warranted.

While the committee's recommendations for revised regulatory treatment pertain to brand-name and generic opioid products, many other products relevant to the opioid crisis, particularly opioid reversal agents (such as naloxone) and treatments for OUD, have been discussed in this report. To the extent that these products are intended to alleviate the opioid crisis and themselves present no risk of addiction, the committee favors rigorously testing them for efficacy and safety and making them widely available to patients as expeditiously as possible. In the case of these agents, REMS and other restrictive post-approval prescribing systems might do more harm than good by making them less available to patients and providers. The public health considerations relevant to approval of these drugs are therefore quite different from those outlined in this chapter and would not fit well under the proposed approach for opioid regulation. Thus, a different set of considerations may need to be enumerated in FDA guidance for products intended primarily to treat OUD or manage the opioid crisis rather than to treat pain.

The committee believes further that the process for initial DEA scheduling—and subsequent rescheduling—of drugs also could benefit from implementation of the approach discussed in this chapter. The FDA and the DEA are already required to take "risk to public health" into account in making scheduling decisions, but the considerations included under this heading have not been enumerated in detail. For example, there may be differences in the value placed by the FDA and the DEA on different public health risks, how heavily the two agencies weight these risks, and how they balance these risks against the potential health benefits of opioids. Thus, the committee favors taking the same public health considerations incorporated in the opioid benefit-risk framework into account when the FDA and the DEA evaluate the "risk to public health" criterion in making scheduling—and rescheduling—recommendations and decisions.

Finally, predictions about the various risks of initial scheduling and rescheduling decisions to various public health parameters need to be made based on solid data, and gathering such data will require development of

BOX 6-6
Recommendations for Other Regulatory Decisions

Recommendation 6-6. Conduct a full review of currently marketed/approved opioids. To consistently carry out its public health mission with respect to opioid approval and monitoring, the U.S. Food and Drug Administration should develop a process for reviewing, and complete a review of, the safety and effectiveness of all approved opioids, utilizing the systems approach described in Recommendation 6-1.

Recommendation 6-7. Apply public health considerations to opioid scheduling decisions. To ensure appropriate management of approved opioids, the U.S. Food and Drug Administration and the U.S. Drug Enforcement Administration should apply the same public health considerations outlined in Recommendation 6-1 for approval decisions to scheduling and rescheduling decisions, and study empirically the outcomes of scheduling determinations at the patient and population health levels.

proper methods and data sources. While recognizing that decisions about scheduling of opioids will have to continue based on the best available data while more data are generated, the committee supports a sustained commitment among funders and policy makers in the field to better understanding the outcomes of scheduling decisions.

SUMMARY AND RECOMMENDATIONS

Traditionally, the FDA takes a product-specific approach to drug approval decisions by focusing on the data generated and submitted by the manufacturer on the drug at hand, and balancing the benefits of the drug revealed by those data against the risks known (and unknown) at the time of the review. While this process works well in most cases, the committee believes that the regulatory oversight of opioids needs to be viewed differently. The recommendations offered to the FDA in this chapter are intended to balance manufacturers' ability to introduce new opioid products that hold promise for pain management with the agency's obligation to manage the risks posed by opioids, which extend beyond risks to individual patients. In line with the FDA's public health authorities, mission, and practice, these recommendations focus on incorporating public health considerations into the entire life cycle of drug development to create a safer prescription opioid marketplace. If implemented, these recommendations

will enable both the drug companies and the FDA to evaluate the full range of benefits and risks that need to be reviewed and considered before premarket approval as well as during post-approval surveillance.

Given the well-described individual-, household-, and society-level outcomes that have emerged from decades of experience with opioids, special considerations are necessary in the opioid development, approval, and post-approval stages that incorporate the principles discussed in this report.

Recommendation 6-1. Incorporate public health considerations into opioid-related regulatory decisions. The U.S. Food and Drug Administration (FDA) should utilize a comprehensive, systems approach for incorporating public health considerations into its current framework for making regulatory decisions regarding opioids. The agency should use this approach, in conjunction with advisory committee input, to evaluate every aspect of its oversight of prescription opioid products in order to ensure that opioids are safely prescribed to patients with legitimate pain needs and that, as actually used, the drugs provide benefits that clearly outweigh their harms. When recommending plans for opioids under investigation; making approval decisions on applications for new opioids, new opioid formulations, or new indications for approved opioids; and monitoring opioids on the U.S. market, the FDA should explicitly consider

- benefits and risks to individual patients, including pain relief, functional improvement, the impact of off-label use, incident opioid use disorder (OUD), respiratory depression, and death;
- benefits and risks to members of a patient's household, as well as community health and welfare, such as effects on family well-being, crime, and unemployment;
- effects on the overall market for legal opioids and, to the extent possible, impacts on illicit opioid markets;
- risks associated with existing and potential levels of diversion of all prescription opioids;
- risks associated with the transition to illicit opioids (e.g., heroin), including unsafe routes of administration, injection-related harms (e.g., HIV and hepatitis C virus), and OUD; and
- specific subpopulations or geographic areas that may present distinct benefit-risk profiles.

The committee acknowledges that the quality of data for some of these considerations (e.g., data from nontraditional sources, such as rates of transition from prescription to illicit opioids) is currently suboptimal, but never-

theless stresses the need to include these considerations in a comprehensive public health framework to inform regulatory decision making for opioids.

Implementing this approach successfully will require significant changes in collection and analysis of data. One important implication is that the evidence necessary to demonstrate safety and efficacy for opioid products will necessarily broaden, and this will affect the traditional FDA review and approval process at multiple points. Specific considerations to meet these needs may extend beyond the protocolized setting of traditional clinical trials to encompass use of data from less traditional sources, such as online forums. The agency should include reports from family members or other third parties affected by the drug, as well as data on outcomes in subpopulations at high risk of OUD or with mental health comorbidities common in patients with pain. Outcomes of interest include impact on function and long-term efficacy for pain reduction.

Other data that could inform the agency's decisions include the drug's estimated impact on the demand for and availability of all other prescription and illicit opioids, as well as interactions with other drugs (both prescription and illicit) commonly used with opioids or by people who use opioids illicitly (e.g., considering how the drug interacts with antiretrovirals or anti-HCV medications). Nontraditional data sources will be needed to inform regulatory decisions for opioids. The FDA should also apply these nontraditional study design considerations in the setting of post-marketing requirements imposed as conditions of approval.

As discussed in Chapter 5, another important implication of the need to take a systems approach is that the agency, perhaps in collaboration with the U.S. Centers for Disease Control and Prevention (CDC) or other agencies, will eventually need to develop and implement a quantitative model of the opioid ecosystem and establish the data infrastructure needed to support and apply that model. An explicit model can better integrate information from different sources, articulate assumptions, incorporate dynamic processes, and assess the public health consequences of different decisions and value judgments. However, the committee recognizes that developing such a model will be a challenging task given the complexity of the opioid markets and consumption patterns and the weaknesses of the data currently available to measure several of the outcomes outlined in Recommendation 6-1. To begin the process, the agency could periodically convene experts in policy modeling to review available data and needs pertaining to opioid distribution, use, and consequences—with the eventual objective of formulating a conceptual map and a formal quantitative model of the opioid ecosystem. Doing so would enable the agency to better predict the effects of changes in policy or other changes in the opioid ecosystem.

Recommendation 6-2. Require additional studies and the collection and analysis of data needed for a thorough assessment of broad public health considerations. To utilize a systems approach that adequately assesses the public health benefits and risks described in Recommendation 6-1, the U.S. Food and Drug Administration (FDA) should continue to require safety and efficacy evidence from well-designed clinical trials while also seeking data from less traditional data sources, including nonhealth data, that pertain to real-world impacts of the availability and use of the approved drug on all relevant outcomes. The FDA should develop guidelines for the collection of these less traditional data sources and their integration in a systems approach.

Recommendation 6-3. Ensure that public health considerations are adequately incorporated into clinical development. The U.S. Food and Drug Administration (FDA) should create an internal system to scrutinize all Investigational New Drug (IND) applications for opioids. This review should examine whether public health considerations are adequately incorporated into clinical development (e.g., satisfactory trial design; see Recommendation 6-2). In implementing this recommendation, the FDA should rarely, if ever, use expedited development or review pathways or designations for opioid drugs and should review each application in its entirety.

The committee believes a commitment to transparency is critical to maintain balance between preserving access to opioids when needed by patients experiencing pain and mitigating opioid-related harms. Increased transparency would optimize the clinical development and use of opioids considering the proposed comprehensive systems approach.

Recommendation 6-4. Increase the transparency of regulatory decisions for opioids in light of the committee's proposed systems approach (Recommendation 6-1). The U.S. Food and Drug Administration should commit to increasing the transparency of its regulatory decisions for opioids to better inform manufacturers and the public about optimal incorporation of public health considerations into the clinical development and use of opioid products.

Steps the FDA could take to implement Recommendation 6-4 might include issuing a guidance document that outlines opioid-specific clinical development considerations, or releasing summary versions of complete response letters for opioid products to inform the public about the public health considerations that the FDA has determined would preclude marketing approval.

The committee believes that use of REMS that have been demonstrated to improve prescribing practice, surveillance activities, formal reevaluation of opioid approval decisions, and regulation of advertising and promotion are critical to supporting the safe use of opioids.

Recommendation 6-5. Strengthen the post-approval oversight of opioids. The U.S. Food and Drug Administration should take steps to improve post-approval monitoring of opioids and ensure the drugs' favorable benefit-risk ratio on an ongoing basis. Steps to this end should include use of Risk Evaluation and Mitigation Strategies that have been demonstrated to improve prescribing practices, close active surveillance of the use and misuse of approved opioids, periodic formal reevaluation of opioid approval decisions, and aggressive regulation of advertising and promotion to curtail their harmful public health effects.

Evidence on the effectiveness of the current REMS for opioids is conflicting and limited, and the REMS may provide a false sense of risk mitigation. To improve the data on the existing opioid REMS, the FDA could continue to evaluate the data on its performance, collecting additional data if needed and changing the features of the REMS so it more optimally ensures the evidence-based use of opioids while reducing unsafe prescribing. Maximizing the use of REMS and other post-approval oversight mechanisms for opioids may be facilitated through collaborations among the FDA and other relevant government agency stakeholders, such as the Substance Abuse and Mental Health Services Administration, National Institute on Drug Abuse, Health Resources and Services Administration, and U.S. Department of Veterans Affairs, among others.

The consistent regulatory oversight of opioid products under the committee's proposed systems framework will necessarily raise concerns about the safety and efficacy of products currently approved for market. The committee believes the FDA possesses the authority and responsibility to reexamine the opioid class of drugs, consistent with previous agency actions motivated by public health concerns with a drug class, to ensure that they remain safe and effective. Options for such a large-scale review include a process similar to that used for DESI or a process for reviewing individual applications that would give manufacturers a time frame within which to submit supplemental data necessary for the FDA's review.

Recommendation 6-6. Conduct a full review of currently marketed/approved opioids. To consistently carry out its public health mission with respect to opioid approval and monitoring, the U.S. Food and Drug Administration should develop a process for reviewing, and com-

plete a review of, the safety and effectiveness of all approved opioids, utilizing the systems approach described in Recommendation 6-1.

Finally, the process for initial DEA scheduling of drugs could benefit from the explicit incorporation of the public health considerations discussed in this report. The FDA and the DEA are already required to take "risk to public health" into account in making drug scheduling decisions, but the considerations included under this heading have not been enumerated in detail, and the two agencies may differ in prioritizing certain benefits or risks. Moreover, the ultimate impact on health outcomes related to these decisions remains largely unknown.

Recommendation 6-7. Apply public health considerations to opioid scheduling decisions. To ensure appropriate management of approved opioids, the U.S. Food and Drug Administration and the U.S. Drug Enforcement Administration should apply the same public health considerations outlined in Recommendation 6-1 for approval decisions to scheduling and rescheduling decisions, and study empirically the outcomes of scheduling determinations at the patient and population health levels.

REFERENCES

Alford, D.P., L. Zisblatt, P. Ng, S.M. Hayes, S. Peloquin, I. Hardesty, and J.L. White. 2015. SCOPE of pain: An evaluation of an opioid risk evaluation and mitigation strategy continuing education program. *Pain Medicine* 17(1). http://onlinelibrary.wiley.com/doi/10.1111/pme.12878/pdf (accessed May 26, 2017).

Avorn, J., M. Chen, and R. Hartley. 1982. Scientific versus commercial sources of influence on the prescribing behavior of physicians. *American Journal of Medicine* 73(1):4-8.

Blanchette, C.M., A.P. Nunes, N.D. Lin, K.M. Mortimer, J. Noone, K. Tangirala, S. Johnston, and B. Gutierrez. 2015. Adherence to Risk Evaluation and Mitigation Strategies (REMS) requirements for monthly testing of liver function. *Drugs in Context* pii:212272.

Booz Allen Hamilton. 2006. *Independent evaluation of FDA's first cycle review performance—retrospective analysis final report*. https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm109759.pdf (accessed March 12, 2017).

Boudes, P.F. 2015. An analysis of U.S. Food and Drug Administration clinical hold orders for drugs and biologics: A prospective study between 2008 and 2014. *Pharmaceutical Medicine* 29(4):203-209.

Butler, S.F., S.H. Budman, A. Licari, T.A. Cassidy, K. Lioy, J. Dickinson, J.S. Brownstein, J.C. Benneyan, T.C. Green, and N. Katz. 2008. National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™): A real-time, product-specific, public health surveillance system for monitoring prescription drug abuse. *Pharmacoepidemiology and Drug Safety* 17(12):1142-1154.

Carpenter, D., E.J. Zucker, and J. Avorn. 2008. Drug review deadlines and safety problems. *New England Journal of Medicine* 358(13):1354-1361.

Carpenter, D., J. Chattopadhyay, S. Moffitt, and C. Nall. 2012. The complications of controlling agency time discretion: FDA review deadlines and postmarket drug safety. *American Journal of Political Science* 56(1):98-114.

Chumpitazi, C.E., C.A. Rees, E.A. Camp, and M.B. Bernhardt. 2016. Decreased opioid prescribing in a pediatric emergency department after the rescheduling of hydrocodone. *American Journal of Emergency Medicine* 52(4):547-553.

Cicero, T.J., J.A. Inciardi, and A. Muñoz. 2005. Trends in abuse of OxyContin® and other opioid analgesics in the United States: 2002–2004. *The Journal of Pain* 6(10):662-672.

Cicero, T.J., R.C. Dart, J.A. Inciardi, G.E. Woody, S. Schnoll, and A. Muñoz. 2007. The development of a comprehensive risk-management program for prescription opioid analgesics: Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS). *Pain Medicine* 8(2):157-170.

Ciociola, A.A., R.G. Karlstadt, D.J. Pambianco, K.L. Woods, and E.D. Ehrenpreis. 2014. The Food and Drug Administration advisory committees and panels: How they are applied to the drug regulatory process. *American Journal of Gastroenterology* 109(10):1508-1512.

Cortez, N. 2016. The statutory case against off-label promotion. *University of Chicago Law Review* 83:124-142.

Darrow, J.J., J. Avorn, and A.S. Kesselheim. 2014. New FDA breakthrough-drug category: Implications for patients. *New England Journal of Medicine* 370(13):1252-1258.

DEA (U.S. Drug Enforcement Administration). 2014. *Schedules of controlled substances: Placement of hydrocodone combination products into Schedule II. Background, data, and analysis: Eight factors determinative of control and findings pursuant to 21 U.S.C. 812(b).* http://ws.westernu.edu/WesternU-News/docs/DEAs-Eight-Factor-Analysis-HCP.pdf (accessed March 1, 2017).

DEA. 2017a. *Controlled substance schedules.* https://www.deadiversion.usdoj.gov/schedules (accessed March 10, 2017).

DEA. 2017b. *Pharmacist's manual—Section IX—Valid prescription requirements.* https://www.deadiversion.usdoj.gov/pubs/manuals/pharm2/pharm_content.htm (accessed March 10, 2017).

Dhalla, I.A., N. Persaud, and D.N. Juurlink. 2011. Facing up to the prescription opioid crisis. *British Medical Journal* 343:d5142.

Dineen, K.K. 2016. Addressing prescription opioid abuse concerns in context: Synchronizing policy solutions to multiple complex public health problems. *Law & Psychology Review* 40(1).

Dorsey, E.R., A. Rabbani, S.A. Gallagher, R.M. Conti, and G.C. Alexander. 2010. Impact of FDA black box advisory on antipsychotic medication use. *Archives of Internal Medicine* 170(1):96-103.

Downing, N.S., J.A. Aminawung, N.D. Shah, H.M. Krumholz, and J.S. Ross. 2014. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005–2012. *Journal of the American Medical Association* 311(4):368-377.

Dusetzina, S.B., A.S. Higashi, E.R. Dorsey, R. Conti, H.A. Huskamp, S. Zhu, C.F. Garfield, and G.C. Alexander. 2012. Impact of FDA drug risk communications on health care utilization and health behaviors: A systematic review. *Medical Care* 50(6):466-478.

Edlund, M.J., B.C. Martin, A. Devries, M.Y. Fan, J.B. Braden, and M.D. Sullivan. 2010. Trends in use of opioids for chronic non-cancer pain among individuals with mental health and substance use disorders: The TROUP study. *The Clinical Journal of Pain* 26(1):1-8.

Fain, K., M. Daubresse, and G.C. Alexander. 2013. The Food and Drug Administration Amendments Act and postmarketing commitments. *Journal of the American Medical Association* 310(2):202-204.

FDA (U.S. Food and Drug Administration). 1998. *Guidance for industry. Providing clinical evidence of effectiveness for human drug and biological products*. https://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf (accessed March 15, 2017).

FDA. 1999. *Guidance for industry—Applications covered by section 505(b)(2)*. https://www.fda.gov/downloads/Drugs/Guidances/ucm079345.pdf (accessed June 12, 2017).

FDA. 2003. *Guidance for industry.* #152. *Evaluating the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern*. http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf (accessed March 15, 2017).

FDA. 2009a. *Acetaminophen overdose and liver injury: Background and options for reducing injury.* https://www.fda.gov/downloads/AdvisoryCommittees/.../UCM164897.pdf (accessed March 15, 2017).

FDA. 2009b. *Testosterone gel safety concerns prompt FDA to require label changes, medication guide*. News Release. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149580.htm (accessed March 15, 2017).

FDA. 2010a. *FDA Transparency Initiative: Draft Proposals for Public Comment Regarding Disclosure Policies of the U.S. Food and Drug Administration*. https://www.fda.gov/downloads/aboutfda/transparency/publicdisclosure/glossaryofacronymsandabbreviations/ucm212110.pdf (accessed June 14, 2017).

FDA. 2010b. *Keeping watch over direct-to-consumer ads*. http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107170.htm (accessed February 14, 2017).

FDA. 2012. *Drug Safety and Risk Management Advisory Committee (DSaRM) Meeting—October 29–30, 2012: FDA briefing document*. https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/drugsafetyandriskmanagementadvisorycommittee/ucm325708.pdf (accessed March 15, 2017).

FDA. 2013. *Structured approach to benefit-risk assessment in drug regulatory decision-making: PDUFA V plan (FY 2013–2017)*. Silver Spring, MD: Center for Drug Evaluation and Research.

FDA. 2014a. *All manufacturers of prescription combination drug products with more than 325 mg of acetaminophen have discontinued marketing*. https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm390509.htm (accessed March 15, 2017).

FDA. 2014b. *Guidance for industry—Analgesic indications: Developing drug and biological products*. Silver Spring, MD: Center for Drug Evaluation and Research. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm384691.pdf (accessed January 22, 2017).

FDA. 2014c. *Guidance for industry—Expedited programs for serious conditions: Drugs and biologics*. Silver Spring, MD: Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf (accessed June 12, 2017).

FDA. 2014d. *The public's stake in adverse event reporting*. Silver Spring, MD: Center for Drug Evaluation and Research. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm179586.htm (accessed January 22, 2017).

FDA. 2014e. *Release from postmarketing requirement & new postmarketing requirement*. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM484415.pdf (accessed March 15, 2017).

FDA. 2015a. *FDA's Sentinel Initiative*. http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm (accessed March 15, 2017).

FDA. 2015b. *Prescription drug advertising: Questions and answers*. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm076768.htm#control_advertisements (accessed February 14, 2017).

FDA. 2015c. *Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS)*. http://www.accessdata.fda.gov/drugsatfda_docs/rems/TIRF_2015-12-21_REMS_DOCUMENT.pdf (accessed March 15, 2017).

FDA. 2016a. *Fact sheet—FDA opioids action plan*. https://www.fda.gov/newsevents/newsroom/factsheets/ucm484714.htm (accessed June 9, 2017).

FDA. 2016b. *New safety measures announced for immediate release (IR) opioids*. https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm491437.htm (accessed June 18, 2017)

FDA. 2016c. *New safety measures announced for opioid analgesics, prescription opioid cough products, and benzodiazepines*. https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm518110.htm (accessed June 18, 2017).

FDA. 2016d. *Summary minutes of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee joint meeting, May 3-4, 2016*. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM509895.pdf (accessed April 21, 2017).

FDA. 2017a. *Drugs @ FDA: Summary review of Nuplazid*. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=207318 (accessed March 15, 2017).

FDA. 2017b. *Drugs @ FDA: Summary review of Zohydro ER*. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=202880 (accessed March 15, 2017).

FDA. 2017c. *Drug safety communications*. https://www.fda.gov/Drugs/DrugSafety/ucm199082.htm (accessed March 15, 2017).

FDA. 2017d. *FDA requests removal of Opana ER for risks related to abuse*. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery (accessed June 9, 2017).

FDA. 2017e. *Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting Opioid Analgesics*. https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm (accessed June 4, 2017).

Findlay, S. 2015. Health policy brief: The FDA's Sentinel Initiative. *Health Affairs*. June 4. http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=139 (accessed March 15, 2017).

GAO (U.S. General Accounting Office). 2003. *Report to congressional requesters: Prescription drugs: OxyContin abuse and diversion and efforts to address the problem*. http://www.gao.gov/new.items/d04110.pdf (accessed February 15, 2017).

Henningfield, J.E., and C.R. Schuster. 2009. Risk management and post-marketing surveillance of CNS drugs. *Drug and Alcohol Dependence* 105(Suppl. 1):S56-S64.

HHS (U.S. Department of Health and Human Services) OIG (Office of Inspector General). 2013. *FDA lacks comprehensive data to determine whether Risk Evaluation and Mitigation Strategies improve drug safety*. https://oig.hhs.gov/oei/reports/oei-04-11-00510.pdf (accessed June 4, 2017).

IOM (Institute of Medicine). 2012. *Ethical and scientific issues in studying the safety of approved drugs*. Washington, DC: The National Academies Press.

Jones, C.M. 2013. Heroin use and heroin use risk behaviors among nonmedical users of prescription opioid pain relievers—United States, 2002–2004 and 2008–2010. *Drug and Alcohol Dependence* 132(1):95-100.

Jones, C.M., P.G. Lurie, and D.C. Throckmorton. 2016. Effect of U.S. Drug Enforcement Administration's rescheduling of hydrocodone combination analgesic products on opioid analgesic prescribing. *JAMA Internal Medicine* 176(3):399-402.

Kravitz, R.L., R.M. Epstein, M.D. Feldman, C.E. Franz, R. Azari, M.S. Wilkes, L. Hinton, and P. Franks. 2005. Influence of patients' requests for direct-to-consumer advertised antidepressants: A randomized controlled trial. *Journal of the American Medical Association* 293(16):1995-2002.

Lasser, K.E., D.L. Seger, D.T. Yu, A.S. Karson, J.M. Fiskio, A.C. Seger, N.R. Shah, T.K. Gandhi, J.M. Rothschild, and D.W. Bates. 2006. Adherence to black box warnings for prescription medications in outpatients. *Archives of Internal Medicine* 166(3):338-344.

Lexchin, J. 2012. New drugs and safety: What happened to new active substances approved in Canada between 1995 and 2010? *Archives of Internal Medicine* 172(21):1680-1681.

Manchanda, P., and E. Honka. 2005. The effects and role of direct-to-physician marketing in the pharmaceutical industry. An integrative review. *Yale Journal of Policy, Law, and Ethics* 5(2):785-822.

McKinlay, J.B., F. Trachtenberg, L.D. Marceau, J.N. Katz, and M.A. Fischer. 2014. Effects of patient medication requests on physician prescribing behavior: Results of a factorial experiment. *Medical Care* 52(4):294-299.

NAS (National Academy of Sciences). *The Drug Efficacy Study of the National Research Council's Division of Medical Sciences, 1966-1969*. http://www.nasonline.org/about-nas/history/archives/collections/des-1966-1969-1.html (accessed August 2, 2017).

Nelson, L.S., and J. Perrone. 2012. Curbing the opioid epidemic in the United States: The Risk Evaluation and Mitigation Strategy (REMS). *Journal of the American Medical Association* 308(5):457-458.

NIDA (National Institute on Drug Abuse). 2017. *How do opioids work?* https://teens.drugabuse.gov/teachers/mind-over-matter/opioids/how-do-opioids-work (accessed May 25, 2017).

Noah, L. 2003. Challenges in the federal regulation of pain management technologies. *The Journal of Law, Medicine, & Ethics* 55.

Nourjah, P., S.R. Ahmad, C. Karwoski, and M. Willy. 2006. Estimates of acetaminophen (paracetomal)-associated overdoses in the United States. *Pharmacoepidemiology and Drug Safety* 15(6):398-405.

OIG (Office of the Inspector General). 2016. *FDA is issuing more postmarketing requirements, but challenges with oversight persist.* OEI-01-14-00390. Washington, DC: Office of the Deputy Inspector General for Evaluation and Inspections.

Olson, M.K. 2008. The risk we bear: The effects of review speed and industry user fees on new drug safety. *Journal of Health Economics* 27(2):175-200.

Pew Charitable Trusts. 2013. *Persuading the prescribers: Pharmaceutical industry marketing and its influence on physicians and patients*. http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients (accessed February 15, 2017).

Radley, D.C., S.N. Finkelstein, and R.S. Stafford. 2006. Off-label prescribing among office-based physicians. *Archives of Internal Medicine* 166(9):1021-1026.

Reaves, N. 2009. *Drug approvals and drug safety: Preliminary results*. Presented at the Annual Conference of the Pennsylvania Economic Association, West Chester, PA, June 4-6.

Robertson, C., S. Rose, and A.S. Kesselheim. 2012. Effect of financial relationships on the behaviors of health care professionals: A review of the evidence. *The Journal of Law, Medicine & Ethics* 40(3):452-466.

Sarpatwari, A., J. Avorn, and A.S. Kesselheim. 2014. Using a drug-safety tool to prevent competition. *New England Journal of Medicine* 370:1476-1478.

Sarpatwari, A., J.M. Franklin, J. Avorn, J.S. Seeger, J.E. Landon, and A.S. Kesselheim. 2015. Are risk evaluation and mitigation strategies associated with less off-label use of medications? The case of immune thrombocytopenia. *Clinical Pharmacology and Therapeutics* 97(2):186-193.

Secora, A.M., C.M. Dormitzer, J.A. Staffa, and G.J. Dal Pan. 2014. Measures to quantify the abuse of prescription opioids: A review of data sources and metrics. *Pharmacoepidemiology and Drug Safety* 23(12):1227-1237.

Skeldon, S.C., K.B. Kozhimannil, S.R. Majumdar, and M.R. Law. 2015. The effect of competing direct-to-consumer advertising campaigns on the use of drugs for benign prostatic hyperplasia: Time series analysis. *Journal of General Internal Medicine* 30(4):514-520.

Spence, M.M., S.S. Teleki, T.C. Cheetham, S.O. Schweitzer, and M. Millares. 2005. Direct-to-consumer advertising of COX-2 inhibitors: Effect on appropriateness of prescribing. *Medical Care Research and Review* 62(5):544-559.

Spillane, J.F. 2004. Debating the Controlled Substances Act. *Drug and Alcohol Dependence* 76(1):17-29.

Swann, M.M., K.L. Baxter, H.I. Field, J.W. Howie, I.A.M. Lucas, E.L.M. Millar, J.C. Murdoch, J.H. Parsons, and E.G. White. 1969. *Report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine*. London, UK: HMSO.

Van Zee, A. 2009. The promotion and marketing of OxyContin: Commercial triumph, public health tragedy. *American Journal of Public Health* 99(2):221-227.

Zettler, P.J. 2015. Toward coherent federal oversight of medicine. *San Diego Law Review* 52:427-500.

ANNEX TABLE 6-1 Extended-Release (ER)/Long-Acting (LA) Opioid Post-Marketing Study Requirements

Main Study Objective	Research Schedule
Quantify the serious risks of misuse, abuse, and addiction associated with long-term use of opioid analgesics for management of chronic pain.	Final Protocol Submission: 11/2015 (completed) Study Completion: 10/2019 Final Report Submission: 03/2020
Measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records.	Final Protocol Submission: 11/2014 (completed) Study Completion: 04/2019 Final Report Submission: 09/2019
Assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ).	Final Protocol Submission: 04/2015 (completed) Study Completion: 10/2015 (completed) Final Report Submission: 01/2016 (completed)
Evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ).	Final Protocol Submission: 04/2015 (completed) Study Completion: 10/2016 Final Report Submission: 02/2017
Validate measures of prescription opioid substance use disorder and addiction in patients who have received or are receiving opioid analgesics for chronic pain.	Final Protocol Submission: 04/2015 (completed) Study Completion: 12/2016 Final Report Submission: 05/2017
Develop and validate an algorithm using coded medical terminologies and other electronic health care data to identify opioid-related overdose and death.	Final Protocol Submission: 11/2014 (completed) Study Completion: 09/2016 Final Report Submission: 12/2016

ANNEX TABLE 6-1 Continued

Main Study Objective	Research Schedule
Develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA opioid analgesic.	Final Protocol Submission: 11/2014 (completed) Study Completion: 10/2016 Final Report Submission: 01/2017
Define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction, using coded medical terminologies and other electronic health care data.	Final Protocol Submission: 03/2015 (completed) Study Completion: 10/2017 Final Report Submission: 01/2018
Evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse using a validated patient survey.	Final Protocol Submission: 03/2015 (completed) Study Completion: 09/2018 Final Report Submission: 12/2018
Evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse, and/or addiction using medical record review.	Final Protocol Submission: 03/2015 (completed) Study Completion: 03/2017 Final Report Submission: 06/2017
Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least 1 year to treat chronic pain. Include an assessment of risk relative to efficacy.	Final Protocol Submission: 11/2014 (completed) Trial Completion: 02/2019 Final Report Submission: 08/2019

SOURCE: FDA, 2014e.

APPENDIXES

Appendix A

Data Sources and Methods

DESCRIPTION OF THE STUDY COMMITTEE

The study committee consisted of 18 members with expertise in pain management, basic pain research, epidemiology, medical anthropology, substance use disorder, nursing, law, drug development, public health, health policy and policy modeling, and decision science. Two consultants with expertise in health care and food and drug law were appointed to contribute to the regulatory components of the report. See Appendix B for biographical sketches of the committee members. The committee convened for six 2-day meetings in July 2016, September 2016, November 2016, December 2016, January 2017, and March 2017.

LITERATURE REVIEW

Several strategies were used to identify literature relevant to the committee's charge. First, a search of bibliographic databases, including MEDLINE, Scopus, and Web of Science, was conducted to obtain articles from peer-reviewed journals. In addition, the Cochrane Database of Systematic Reviews was queried, as were relevant federal, state, and local agencies and organizations for guidelines or other grey literature. The LexisNexis database was also reviewed for relevant legal and policy literature. The searches focused on pain management, education, and research, as well as opioids, epidemiology, law, and policy. The keywords used included *best practices, pain management, evidence-based treatment, epidemiology, insurance/reimbursement (health coverage, health insurance, Medicaid, Medicare, payer reimbursement), non-pharmaceutical pain management*

(acupuncture, cognitive behavioral therapy, self-care, non-pharmacologic pain management, self-management, psychological pain management), pharmacologic pain management (pain relievers, pain medicine, pharmacological treatment, medical pain management), pain conditions (acute pain, analgesia, arthritis, back pain, burn pain, cancer, chronic pain, chronic diseases, end of life, fibromyalgia, hyperalgesia, joint pain, knee pain, mental health disorders, neck pain, neuropathic pain, osteoarthritis, palliative care, post-traumatic stress, shoulder pain), age (young adult, adult, geriatric, nursing home residents, pregnant women, neonatal, neonatal abstinence syndrome, neonatal opioid withdrawal syndrome, nursing mothers), law enforcement (policing, drug enforcement, prescription drug monitoring), public health, vulnerable populations, opioids, heroin, fentanyl, abuse/misuse, abuse-deterrent, addiction/dependence, illicit drugs, medication assisted treatment, naloxone, opioid diversion, overdose/death, prescribing practices, routes of administration, safe use/storage/disposal, synthetic opioids). In addition, committee members, meeting participants, and others from the public submitted articles and reports on these topics.

PUBLIC WORKSHOPS

The committee hosted a brief public session at its first meeting as well as two public workshops to obtain information on specific aspects of the study charge. These were held in conjunction with the committee's July, September, and November meetings. The committee determined the topics and speakers for the public workshops. The committee also held open forums at each public workshop at which members of the public were encouraged to provide testimony on any topics related to the study charge. The committee found these workshops to be highly informative for its deliberations. Agendas for the three meetings are presented in Boxes A-1 through A-3.

The brief public session at the committee's first meeting in July (see Box A-1) was attended by representatives from the U.S. Food and Drug Administration (FDA), the study sponsor, to review and discuss the charge to the committee. The first workshop, held in September, focused on the portion of the committee's task related to updating the state of the science of pain medicine and related education and research (see Box A-2). The workshop presentations and discussions are summarized in a Proceedings of a Workshop—in Brief titled *Pain Management and Prescription Opioid-Related Harms: Exploring the State of the Evidence*, which was released to the public on November 4, 2016.

The second workshop, held in November, focused on regulatory strategies that can be implemented by the FDA, as well as actions that can be taken by others, to address the opioid epidemic while taking into account the needs of pain patients (see Box A-3).

BOX A-1
Meeting 1 Open Session Agenda

July 6, 2016

Room 106
Keck Center
500 Fifth Street, NW
Washington, DC 20001

1:00 pm **Welcome and Introductions**
Richard Bonnie, L.L.B., Committee Chair

1:15 pm **Background on the Opioid Epidemic**
Christopher Jones, Pharm.D., M.P.H., Director, Division of Science Policy
Office of the Assistant Secretary for Planning and Evaluation,
U.S. Department of Health and Human Services

1:45 pm **Public Comment (as needed)**

2:00 pm **FDA Charge to the Committee: FDA Opioid Action Plan and Incorporating the Broader Public Health Impact into the Formal Risk-Benefit Assessment for Opioids**
Robert M. Califf, M.D.
Commissioner of Food and Drugs

2:20 pm **Discussion of Committee Statement of Task**

FDA Representatives:

Robert M. Califf, M.D.
Commissioner of Food and Drugs

Doug Throckmorton, M.D., Deputy Center Director for Regulatory Programs
Center for Drug Evaluation and Research, FDA

Sharon Hertz, M.D., Director, Division of Anesthesia, Analgesia, and Addiction Products

Joshua Lloyd, M.D., Clinical Team Leader, Division of Anesthesia, Analgesia, and Addiction Products

3:10 pm **Closing Remarks**
Richard Bonnie, L.L.B., Committee Chair

3:15 pm **Adjourn Open Session**

BOX A-2
Pain Management and Prescription Opioid-Related Harms: Exploring the State of the Evidence

A Workshop Hosted by the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse

September 22, 2016

Auditorium
National Academy of Sciences Building
2101 Constitution Avenue, NW
Washington, DC 20418

Agenda

The Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse is hosting two workshops as part of its information gathering. This first workshop will feature presentations on and discussion of topics relevant to the first four elements of the committee's statement of task:

- the state of the science of pain research, care, and education, including the evolving role of opioids in pain management;
- best practices regarding safe and effective pain management;
- the epidemiology of the prescription opioid epidemic and strategies to address it; and
- areas for future research to inform efforts by the U.S. Food and Drug Administration (FDA) to further develop a framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the public health consequences of opioids.

The second workshop, scheduled for November 4, 2016, in Washington, DC, will focus on the fifth element of the committee's statement of task: actions that the FDA and others can take now to address the opioid epidemic, including the FDA actions to be taken as part of development, review, and approval of pain medicines.

8:30 am **Welcome and Opening Remarks**
Richard Bonnie, L.L.B., Committee Chair

8:45 am **Session 1 – Perspectives on Progress and Future Directions in Clinical Pain Management and Provider Education**
Moderator: David Clark, M.D., Ph.D., Palo Alto Veterans Affairs Pain Clinic and Stanford University (Committee Member)

Pharmacological Pain Management, the Evolving Role of Opioids, and Improving Education of Health Care Providers
James P. Rathmell, M.D., Brigham and Women's Health Care and Harvard University (15 min)

Non-Pharmacological Pain Management
David Shurtleff, Ph.D., National Center for Complementary and Integrative Health, National Institutes of Health (15 min)

Research on Pain Management and Education at the National Institutes of Health: Response to the 2011 IOM Report Relieving Pain in America
David A. Thomas, Ph.D., Division of Epidemiology, Services and Prevention Research, National Institute on Drug Abuse; National Institutes of Health Pain Consortium (15 min)

DISCUSSION (20 min)

9:55 am **BREAK**

10:10 am **Session 2 – Perspectives on Progress and Future Directions in Basic Pain Research and the Development of New Analgesics**
Moderator: Jose Moron-Concepcion, Ph.D., Washington University (Committee Member)

Identification of Targets for New Analgesics
Clifford Woolf, M.D., Ph.D., Harvard University (15 min)

Barriers to and Facilitators of Discovery and Development of New Analgesics
William Schmidt, Ph.D., NorthStar Consulting, LLC (15 min)

Opioid Analgesia and Reward: Can They Be Separated?
Howard Fields, M.D., Ph.D., University of California, San Francisco (15 min)

DISCUSSION (20 min)

11:20 am **Public Comment/Continued Discussion of Morning Sessions**
Moderator: Richard Bonnie, L.L.B., University of Virginia (Committee Chair)

11:45 am **LUNCH**

12:30 pm **Session 3 – Trends in Harms and Consequences of Prescription Opioids**
Moderator: Lee Hoffer, Ph.D., Case Western Reserve University (Committee Member)

continued

BOX A-2 Continued

Intertwined Epidemics: Opioid- and Heroin-Related Overdoses
Daniel Ciccarone, M.D., M.P.H., University of California, San Francisco (15 min)

Prescription Drug Abuse in Rural Appalachia: Ushering in the Next Decade of the Epidemic
Jennifer Havens, Ph.D., M.P.H., University of Kentucky (15 min)

Harms and Consequences of Prescription Opioid Use Among Subpopulations
Linda B. Cottler, Ph.D., M.P.H., F.A.C.E., University of Florida (15 min)

DISCUSSION (20 min)

1:40 pm **Session 4 – Interventions to Reduce Opioid-Related Harms: Misuse, Abuse, Addiction, and Overdose**
Moderator: Traci Green, Ph.D., M.Sc., Boston University (Committee Member)

Prescription Drug Monitoring Programs and Other State-Level Strategies
Tamara M. Haegerich, Ph.D., Division of Unintentional Injury Prevention, Centers for Disease Control and Prevention (15 min)

Naloxone for Opioid Safety
Phillip Coffin, M.D., M.I.A., San Francisco Department of Public Health (15 min)

Opioid Analgesics with Abuse-Deterrent Properties: Current Data and Future Opportunities
Richard C. Dart, M.D., Ph.D., Rocky Mountain Poison and Drug Center (15 min)

Agonist Therapies for Treatment of Opioid Addiction
Yngvild Olsen, M.D., M.P.H., Institute for Behavioral Resources, Inc. (15 min)

DISCUSSION (20 min)

3:05 pm **BREAK**

3:20 pm **Session 5 – Reflections on the Day: Promising Ideas and Interventions and Remaining Critical Issues**
Moderator: Richard Bonnie, L.L.B., University of Virginia (Committee Chair)

Daniel Raymond, Policy Director, Harm Reduction Coalition (10 min)

Penney Cowan, Founder and CEO, American Chronic Pain Association (10 min)

Jonathan Goyer, Outreach Coordinator, Anchor Recovery Community Center (10 min)

Christin Veasley, Co-Founder and Director, Chronic Pain Research Alliance (10 min)

DISCUSSION (20 min)

4:25 pm **Closing Remarks**
Richard Bonnie, L.L.B., Committee Chair

4:30 pm **Adjourn**

BOX A-3
Regulatory Strategies to Address Prescription Opioid-Related Harms

A Workshop Hosted by the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse

November 4, 2016

Room 125
National Academy of Sciences Building
2101 Constitution Avenue, NW
Washington, DC 20418

Agenda

This second workshop hosted by the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse will include presentations on and discussion of topics relevant to the fifth element of the committee's statement of task: actions that based on available data the U.S. Food and Drug Administration (FDA) and others can take to address the opioid epidemic while taking into account the needs of pain patients, including FDA actions to be taken as part of development, review, and approval of pain medicines.

8:15 am **Welcome and Introductions**
Richard Bonnie, L.L.B., Committee Chair

8:25 am **Directions for Future Research to Support Regulatory Decision Making**
Nora D. Volkow, M.D., National Institute on Drug Abuse (30 min)

DISCUSSION (15 min)

9:10 am **FDA Perspectives on Balancing the Risks and Benefits of Opioid Analgesics**
Joshua Lloyd, M.D., Center for Drug Evaluation and Research, U.S. Food and Drug Administration (20 min)

Peter Lurie, M.D., M.P.H., Office of the Commissioner, U.S. Food and Drug Administration (20 min)

DISCUSSION (20 min)

10:10 am **BREAK**

10:25 am **Perspectives on How to Incorporate Public Health Considerations into an FDA Regulatory Evaluation Framework**
Moderator: Aaron Kesselheim, M.D., J.D., M.P.H., Harvard Medical School (Committee Member)

Bruce Psaty, M.D., Ph.D., M.P.H., University of Washington (15 min)

Wendy E. Parmet, J.D., Northeastern University (15 min)

G. Caleb Alexander, M.D., M.S., Johns Hopkins University (15 min)

Diana Zuckerman, Ph.D., National Center for Health Research (15 min)

DISCUSSION (20 min)

11:50 am **LUNCH**

12:30 pm **Accelerating the Development of Better Treatments for Pain: Notes from the Drug Development Battlefield**

Nathanial Katz, M.D., M.S., Analgesic Solutions (15 min)

DISCUSSION (10 min)

12:55 pm **Perspectives on Regulatory Opportunities for Improving the Communication of Drug Safety Information**
Moderator: Valerie Reyna, Ph.D., Cornell University (Committee Member)

Provider Education and Opioid Risk Evaluation and Mitigation Strategies
Daniel P. Alford, M.D., M.P.H., Boston University (15 min)

Safety Communications and Product Labeling
Lisa Schwartz, M.D., M.S., and Steven Woloshin, M.D., M.S., Dartmouth (20 min)

Product Labeling to Communicate Benefits and Risks of Treatment for Opioid Use Disorder in Pregnant Women
Hendrée Jones, Ph.D., University of North Carolina at Chapel Hill (15 min)

DISCUSSION (20 min)

2:10 pm **BREAK**

continued

BOX A-3 Continued

2:25 pm	**Post-Marketing Surveillance: Lessons Learned and Recommendations for the Future** *Theodore J. Cicero, Ph.D., Washington University (15 min)* **DISCUSSION (10 min)**
2:50 pm	**Prevalence, Correlates, and Regulatory Strategies Related to Pain, Opioid Misuse, and Overdose: The Experience in Vancouver, Canada** *Pauline Voon, R.N., Ph.D. (c), University of British Columbia (15 min)* **DISCUSSION (10 min)**
3:15 pm	**Public Comment/Continued Discussion of Day's Presentations** *Richard Bonnie, L.L.B.,* Committee Chair
3:55 pm	**Closing Remarks** *Richard Bonnie, L.L.B.*, Committee Chair
4:00 pm	**Adjourn**

Appendix B

Biographical Sketches of Committee Members and Consultants

COMMITTEE MEMBERS

Richard J. Bonnie, LL.B. (*Chair*), is the Harrison Foundation professor of medicine and law, professor of psychiatry and neurobehavioral sciences, professor of public policy, and director, Institute of Law, Psychiatry and Public Policy at the University of Virginia. He was elected to the National Academy of Medicine (NAM) in 1991. He teaches and writes about criminal justice, bioethics, and public policies relating to mental health, substance abuse, and public health. He was associate director of the National Commission on Marijuana and Drug Abuse (1971–1973), secretary of the first National Advisory Council on Drug Abuse (1975–1985), and chair of a Commission on Mental Health Law Reform (2006–2011) at the request of the chief justice of Virginia. He has also served on the MacArthur Foundation's research networks on Mental Health and the Law, Mandated Community Treatment, and Law and Neuroscience. Mr. Bonnie has chaired numerous consensus committees for the National Academies of Sciences, Engineering, and Medicine, including multiple studies on tobacco policy, underage drinking, elder mistreatment, injury prevention, juvenile justice, and the health and well-being of young adults. He received the Yarmolinsky Medal in 2002 for his contributions to the NAM and the National Academies. In 2007, Mr. Bonnie received the University of Virginia's highest honor, the Thomas Jefferson Award. He holds a B.A. from Johns Hopkins University and an LL.B. from the University of Virginia School of Law.

Hortensia de los Angeles Amaro, Ph.D., is associate vice provost for community research initiatives and dean's professor of social work and preventive medicine at the University of Southern California. Previously, she served as associate dean and distinguished professor of health sciences and of counseling psychology in the Bouve College of Health Sciences, and director of the Institute on Urban Health Research at Northeastern University. Prior to that, she served as professor in the Boston University School of Public Health and School of Medicine. Her research interests include alcohol and drug use and addiction among adolescents and adults, substance abuse and mental health treatment for Latinos and African Americans, and alcohol and drug use among college populations. She is a member of the National Academy of Medicine and has received numerous awards from professional, government, and community organizations and honorary degrees from Simmons College and the Massachusetts School of Professional Psychology. Additionally, she has served on review and advisory committees for the National Institutes of Health, including the National Institute on Drug Abuse, and for the U.S. Department of Health and Human Services, the Substance Abuse and Mental Health Services Administration, and the U.S. Centers for Disease Control and Prevention. Dr. Amaro founded five substance abuse treatment programs for women in Boston and served on the board of the Boston Public Health Commission for 14 years. She received her Ph.D. in psychology from the University of California, Los Angeles.

Linda Burnes Bolton, Dr.P.H., R.N., FAAN, is system chief nursing executive and vice president for nursing at Cedars-Sinai in Los Angeles. Her research, teaching, and clinical expertise include nursing and patient care outcomes, improving organization performance, quality care, and cultural diversity within the health professions. She is co-investigator of the regional Collaborative Alliance for Nursing Outcomes research team and has made significant contributions to the advancement of nurses and other clinical team members in decreasing patient harm. Dr. Burnes Bolton is a past president of the American Academy of Nursing, American Organization of Nurse Executives, and National Black Nurses Association. She has provided leadership for several state and national programs, including service as chair of the Robert Wood Johnson Foundation advisory committee on Transforming Care at the Bedside and the Veterans Affairs Commission on Nursing, and vice chair of the Robert Wood Johnson Foundation Initiative on the Future of Nursing at the Institute of Medicine. She is a trustee at Case Western Reserve University and a board member of the Robert Wood Johnson Foundation. She received the James R. Klinenberg, MD and Lynne Klinenberg-Linkin Endowed Chair in 2016. Dr. Burnes Bolton earned her B.S. degree in nursing from Arizona State University. She received her M.S.

degree in nursing as well as her M.P.H. and Dr.P.H. from the University of California, Los Angeles. She was elected to the National Academy of Medicine in 2015.

Jonathan P. Caulkins, Ph.D., is university professor of operations research and public policy in the Heinz College of Carnegie Mellon University. His research interests include modeling the effectiveness of interventions related to drugs, crime, violence, delinquency, and prevention. He has been on the Heinz College faculty since 1990, with leaves of absence to be co-director of RAND's Drug Policy Research Center in Santa Monica (1994–1996), to found RAND's Pittsburgh Office (1999–2001), and to teach at Carnegie Mellon's campus in Doha, Qatar (2005–2011). He has published on such topics as epidemiological models for examining marijuana use over the life course and evidence of the effectiveness of drug policy interventions. Dr. Caulkins serves or has served on the editorial board of *Management Science*, *Operations Research*, *Mathematical and Computer Modelling*, *Journal of Drug Issues*, *Socio-Economic Planning Sciences*, and *I/S: A Journal of Law and Policy for the Information Society*, and has refereed for more than 85 different journals. He completed his undergraduate work in engineering and computer science at Washington University in St. Louis. He holds master's degrees in systems science and mathematics (Washington University, 1987) and electrical engineering and computer science (Massachusetts Institute of Technology, 1989) and a Ph.D. in operations research (Massachusetts Institute of Technology, 1990).

David Clark, M.D., Ph.D., is professor of anesthesia, perioperative medicine and pain at Stanford University and director of the Palo Alto Veterans Affairs Pain Clinic, and as such comes into contact with pain and its consequences in many settings. Commonly encountered pain consultations include patients with very difficult-to-manage postoperative pain, patients with chronic pain after surgical procedures, and patients with chronic pain syndromes related to war injuries. Referral to his pain management clinic due to difficulties with opioid management is extremely common. His laboratory has been dedicated for more than a decade to identifying mechanisms supporting chronic pain as well as maladaptations to opioids. Much of this work has focused on genetic mechanisms and approaches, including the use of laboratory animals and humans. Some of his laboratory's findings have resulted in translational studies and clinical trials. Current projects include efforts to understand immunological contributions to chronic pain after limb injury, pain mechanisms after traumatic brain injury, and maladaptations to the long-term use of opioids. Dr. Clark received both his Ph.D. in pharmacology and his M.D. from Vanderbilt University.

Eli Eliav, D.M.D., Ph.D., is a professor and the director of the Eastman Institute for Oral Health at the University of Rochester and the vice dean for oral health within the School of Medicine and Dentistry at the University of Rochester Medical Center. Dr. Eliav joined the University of Rochester Medical Center in 2013. Previously, he served as the chair of the Department of Diagnostic Sciences, the director of the Center for Temporomandibular Disorders and Orofacial Pain, and Carmel Endowed Chair in Algesiology at Rutgers School of Dental Medicine, part of Rutgers University. He earned his D.M.D. and Ph.D. from the Hebrew University in Jerusalem, specialized in oral medicine in Hadassah Medical Center in Jerusalem, and trained in the National Institute for Dental and Craniofacial Research. He is a member of several professional organizations, including the American Pain Society and International Association for the Study of Pain. Dr. Eliav's current research projects involve orofacial pain, quantitative sensory testing, neuropathic pain, pain modulation, and the role of inflammation in neuropathic pain.

Garret FitzGerald, M.D., F.R.S., professor of medicine and pharmacology, is the McNeil professor in translational medicine and therapeutics at the Perelman School of Medicine at the University of Pennsylvania, where he chairs the Department of Systems Pharmacology and Translational Therapeutics and directs the Institute for Translational Medicine and Therapeutics. Dr. FitzGerald's research has been characterized by an integrative approach to elucidating the mechanisms of drug action, drawing on work in cells, model organisms, and humans. His work contributed fundamentally to the development of low-dose aspirin for cardioprotection. Dr. FitzGerald's group was the first to predict and then mechanistically explain the cardiovascular hazard from nonsteroidal anti-inflammatory drugs (NSAIDs). He has also discovered many products of lipid peroxidation and established their utility as indices of oxidant stress in vivo. Dr. FitzGerald's laboratory was the first to discover a molecular clock in the cardiovascular system and has studied the importance of peripheral clocks in the regulation of cardiovascular and metabolic function. Dr. FitzGerald has received the Boyle, Coakley, Harvey, and St. Patrick's Day medals; the Lucian, Scheele, and Hunter Awards; and the Cameron, Taylor, Herz, Lefoulon-Delalande, and Schottstein Prizes. He is a member of the National Academy of Medicine, a fellow of the American Academy of the Arts and Sciences and of The Royal Society, and an honorary member of the Royal Irish Academy.

Traci C. Green, Ph.D., M.Sc., is an epidemiologist whose research focuses on opioid use, addiction, and injury. Specifically, the areas in which she is most interested and to which she has contributed include the intersecting

worlds of HIV infection and drug abuse, nonmedical use of prescription drugs, corrections health, drug policy, and opioid overdose prevention and intervention. By consequence, this work addresses issues of health disparities, gender, and place effects on health. She earned a master of science degree in epidemiology and biostatistics from McGill University and a Ph.D. in epidemiology from Yale University. Dr. Green helped design the ASI-MV®, a real-time illicit and prescription drug abuse surveillance system developed by Inflexxion, Inc. Currently, she is deputy director of the Boston Medical Center Injury Prevention Center and associate professor of emergency medicine and epidemiology at the Warren Alpert School of Medicine at Brown University. Dr. Green chairs the Drug Overdose Prevention and Rescue Coalition for the Rhode Island Department of Health and advises the Rhode Island governor on addiction and overdose. She is a past recipient of salary support (<$3,000) from Purdue Pharmaceuticals for development of an educational brochure on overdose prevention for drug users injecting illicit pharmaceutical opioids. She is a member of the Board of Scientific Counselors for the National Center for Injury Prevention and Control and served on a workgroup to critically review the 2016 U.S. Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain. Her research is supported by the CDC, the National Institute on Drug Abuse, the Agency for Healthcare Research and Quality, the Patient-Centered Outcomes Research Institute, and the U.S. Department of Justice.

Miguel Hernán, M.D., Dr.P.H., studies causal inference methods and implements them to evaluate strategies for the treatment and prevention of disease. Together with collaborators in several countries, he designs analyses of health care databases, epidemiologic studies, and randomized trials. Dr. Hernán teaches clinical data science at the Harvard Medical School, clinical epidemiology at the Harvard-Massachusetts Institute of Technology Division of Health Sciences and Technology, and causal inference methodology at the Harvard T.H. Chan School of Public Health, where he is the Kolokotrones professor of biostatistics and epidemiology and where he has mentored dozens of doctoral students and postdoctoral fellows. His book *Causal Inference*, co-authored with James Robins and freely available online, is used in graduate programs throughout the world. Dr. Hernán is a fellow of the American Association for the Advancement of Science, past chair of the American Statistical Association Section on Statistics in Epidemiology, past associate editor of the *Journal of the American Statistical Association* and of *Biometrics*, associate editor of the *American Journal of Epidemiology*, and an editor of *Epidemiology*. He has served on several committees of the National Academies of Sciences, Engineering, and Medicine.

Lee D. Hoffer, Ph.D., is an associate professor of anthropology at Case Western Reserve University. His research focuses on understanding the political, social, economic, and cultural contexts related to illicit drug use. His ongoing research involves synthesizing computational modeling techniques and ethnographic research to develop new tools for policy makers and researchers. Borrowing from theories of complexity systems, these projects seek to connect the rich descriptive detail offered by anthropology with the epidemiology of drug abuse. Dr. Hoffer's research has informed a range of topics, including HIV risk behaviors, diagnostic nosology for substance use disorders, and understanding trends in drug use, as well as drug policy and intervention studies. More recently, his research examines how illicit drug markets and the acquisition of drugs influence behaviors and negative health outcomes. His fieldwork focuses on customer transactions, the interactions between addiction and drug acquisition, and the social and economic exchange relationships between users and their dealers. His book *Junkie Business: The Evolution and Operation of a Heroin Dealing Networ*k (2006), details much of this work. His research is supported by grants from the National Institutes of Health, National Institute on Drug Abuse (NIDA), as well as the National Science Foundation (Cultural Anthropology & Methods, Measurement, and Statistics program). From 1997 to 1999 he was Colorado's representative to the NIDA Community Epidemiology Workgroup. He was also active in the Colorado Department of Public Health and Environment and the Centers for Disease Control and Prevention HIV community planning efforts. From 2002 to 2005 he trained as a (T32) NIDA postdoctoral fellow in psychiatric epidemiology at Washington University School of Medicine, Epidemiology and Prevention Research Group. From 2013 to 2014 he served on the National Research Council Committee on the Context of Military Environments: Social and Organizational Factors. He holds an M.A. in anthropology and a Ph.D. in health and behavioral sciences from the University of Colorado Denver and an M.P.E. (master of psychiatric epidemiology) from the Washington University School of Medicine in St. Louis.

Paul E. Jarris, M.D., M.B.A., is senior vice president, Maternal and Child Health Program Impact, and deputy medical officer at the March of Dimes. He leads the March of Dimes' Maternal and Child Health Program Impact department, with overall responsibility for the March of Dimes Prematurity Campaign, which seeks to reduce the rate of preterm birth, the number one cause of death among babies in the United States. Dr. Jarris, a nationally known expert in national health care policy, clinical quality initiatives, and disease prevention and wellness, among other areas, previously served as executive director of the Association of State and Territorial Health Officials (ASTHO). One of his many achievements at ASTHO was part-

nering with the March of Dimes to challenge all 50 states, the District of Columbia, and Puerto Rico to lower their preterm birth rates. Dr. Jarris has had a distinguished career spanning 20 years leading policy and care initiatives to improve public health at the local, state, and national levels. Prior to his role at ASTHO, he served as commissioner of health for the State of Vermont, where he led health care policy matters and championed new public health initiatives, addressing access to care, prevention, and the factors that impact population health. In addition, he has held a number of health insurance executive-level positions, including president and CEO of Vermont Permanente Medical Group. Throughout his career, Dr. Jarris has received numerous prestigious awards and honors, and has served as a member of many health-related boards and committees. He received his B.A. from the University of Vermont, his M.D. at the University of Pennsylvania School of Medicine, and an M.B.A. from the University of Washington.

Karol Kaltenbach, Ph.D., is emeritus professor of pediatrics at the Sidney Kimmel Medical College of Thomas Jefferson University and professor of psychiatry and human behavior (retired). She is the former director of Maternal Addiction Treatment, Education and Research (MATER), a division of the Department of Pediatrics, Sidney Kimmel Medical College of Thomas Jefferson University. MATER includes Family Center, a comprehensive intensive outpatient treatment program for pregnant and parenting opioid-dependent women; My Sister's Place, a long-term residential treatment program for women and children; and a research component. Family Center has provided the prototype both nationally and internationally for the management of opioid use disorders during pregnancy and the treatment of neonatal abstinence. Dr. Kaltenbach is a member of the College on Problems of Drug Dependence and has been the principal investigator of grants from the National Institute on Drug Abuse (NIDA) and the Center for Substance Abuse Treatment. She was the principal investigator at the Jefferson site for the NIDA MOTHER clinical trial comparing the use of buprenorphine and methadone in the treatment of opioid dependence during pregnancy and was the lead principal investigator of the MOTHER developmental follow-up study. She is a co-investigator of a NIDA-funded clinical trial investigating the use of buprenorphine in the treatment of neonatal abstinence syndrome (NAS) and co-investigator of a U.S. Department of Health and Human Services' Children's Bureau–funded intervention project investigating whether the use of a mindfulness-based parenting intervention for mothers with opioid use disorders can improve parenting outcomes. Dr. Kaltenbach is an internationally recognized expert in the field of maternal addiction and has published extensively on the management of opioid use disorders during pregnancy and NAS, trauma-informed treatment for pregnant and parenting women with substance use disorders,

and the effect of prenatal drug exposure on the perinatal and developmental outcomes of children. She has lectured throughout the world and has participated in the development of national guidelines for the management of opioid-dependent pregnant women and their neonates in Australia and Norway.

Aaron S. Kesselheim, M.D., J.D., M.P.H., is an associate professor of medicine at Harvard Medical School and a faculty member in the Division of Pharmacoepidemiology and Pharmacoeconomics in the Department of Medicine at Brigham and Women's Hospital. Within the Division, Dr. Kesselheim leads the Program On Regulation, Therapeutics, And Law (PORTAL), an interdisciplinary research center addressing intersections among prescription drugs and medical devices, patient health outcomes, and regulatory practices and the law. Current areas of focus include the research and development process; U.S. Food and Drug Administration (FDA) approval; and the costs, availability, and evidence-based use of these products. In 2013, Dr. Kesselheim was named a Greenwall faculty scholar in bioethics by the Greenwall Foundation, which supports innovative empirical research in bioethics. Dr. Kesselheim's work is also currently funded by the FDA, the Robert Wood Johnson Foundation Public Health Law Research Program, and the Laura and John Arnold Foundation. He has testified before Congress on pharmaceutical policy, medical device regulation, generic drugs, and modernizing clinical trials, and served as a consultant for the National Institutes of Health, FDA, U.S. Patent and Trademark Office, and numerous state government offices. Dr. Kesselheim also serves as a supervisor for the Petrie-Flom Center for Health Law Policy, Biotechnology, and Bioethics at Harvard Law School; a core faculty member of the Harvard Medical School Center for Bioethics; and a visiting associate professor of law at Yale Law School, where he teaches FDA law. He graduated from Harvard College and received his postgraduate training at the University of Pennsylvania School of Medicine and Law School, and most recently at the Harvard School of Public Health. He is board certified in internal medicine and serves as a primary care physician.

Anne Marie McKenzie-Brown, M.D., is an associate professor in the Department of Anesthesiology at Emory University, where she is the director of the Division of Pain Management and director of the Emory Pain Center. Her clinical expertise includes the diagnosis and treatment of cervical and lumbar spinal pain syndromes and sacroiliac joint pain, complex regional pain syndrome, other neuropathic pain syndromes, and cervicogenic headaches. She attended medical school at the Johns Hopkins University School of Medicine and completed her residency in anesthesiology at the Emory Department of Anesthesiology. She is a member of several professional

organizations, including the American Pain Society, the American Society of Anesthesiology, the American Society of Interventional Pain Physicians, and the North American Spine Society.

Jose Moron-Concepcion, Ph.D., is an associate professor in the Departments of Anesthesiology and Neuroscience at Washington University in St Louis. Dr. Moron-Concepcion is a world leader in the study of the nervous system's adaptive responses to chronic opioid exposure. Research in his laboratory is focused on understanding the mechanisms underlying opioid addiction and the intersection with pain. In addition, his lab is interested in elucidating mechanisms underlying pain in the central nervous system and in the periphery. After completing his Ph.D. in biochemistry at the University of Barcelona (Spain), Dr. Moron-Concepcion was awarded a fellowship to join the intramural program at the National Institute on Drug Abuse to work in the laboratory of Dr. Toni Shippenberg, a pioneer in the field of opioid pharmacology. Then, he continued his postdoctoral training in the laboratory of Dr. Lakshmi Devi at Mount Sinai, where he continued his studies on the mechanisms of opioid dependence. After completing his training, he was recruited as a faculty member in the Department of Pharmacology at The University of Texas Medical Branch. He then moved to Columbia University in New York, where he was on the faculty of the Department of Anesthesiology for 6 years. Dr. Moron-Concepcion joined the faculty of Washington University on October 1, 2015.

A. David Paltiel, Ph.D., M.B.A., is professor of health policy and management at both the Yale School of Public Health and the Yale School of Management. He employs the methods of operations research to address issues of resource allocation and decision making in health and medicine. He has conducted numerous model-based cost-effectiveness analyses of prevention, screening, and treatment interventions, including several widely cited studies of expanded HIV screening in the United States and abroad. He has served on guideline review and advisory committees for the National Institutes of Health, the U.S. Centers for Disease Control and Prevention (CDC), the U.S. Preventive Services Task Force, the Institut de Veille Sanitaire (French national equivalent of the CDC), and the French National Agency for AIDS Research (ANRS). He has served on five previous project committees for the National Academies of Sciences, Engineering, and Medicine, including panels that produced the 2004 report on the Ryan White CARE Act, the 2007 Evaluation of the President's Emergency Plan for AIDS Relief, and the 2009 Review of Priorities in the National Vaccine Plan. Dr. Paltiel holds a B.A. from McGill University and received both an M.B.A. and a Ph.D. in operations research from Yale.

Valerie Reyna, Ph.D., is the Lois and Melvin Tukman professor of human development, director of the Human Neuroscience Institute, director of the Cornell University Magnetic Resonance Imaging Facility, and co-director of the Center for Behavioral Economics and Decision Research. Her research integrates brain and behavioral approaches to understand and improve judgment, decision making, and memory across the life span. Her recent work has focused on the neuroscience of risky decision making and its implications for health and well-being, especially in adolescents; applications of cognitive models and artificial intelligence to improving understanding of genetics (e.g., in breast cancer); and medical and legal decision making (e.g., about jury awards, medication decisions, and adolescent culpability). She currently has an unrestricted research grant from the Xerox Corporation and has studied treatment adherence in diabetes patients among other topics. She is a developer of fuzzy-trace theory, a model of the relation between mental representations and decision making that has been widely applied in law, medicine, and public health. Dr. Reyna has been elected to the National Academy of Medicine and is a fellow of the Society of Experimental Psychologists, the oldest and most prestigious honorary society in experimental psychology. She is also a fellow of the American Association for the Advancement of Science; the Divisions of Experimental Psychology, Developmental Psychology, Educational Psychology, and Health Psychology of the American Psychological Association; and the Association for Psychological Science. Dr. Reyna has been a visiting professor at the Mayo Clinic; a permanent member of study sections of the National Institutes of Health; and a member of advisory panels for the National Science Foundation, the MacArthur Foundation, and the National Academies of Sciences, Engineering, and Medicine. For example, she is on the Advisory Committee of the National Academies' Division of Behavioral and Social Sciences and Education, which oversees 10 boards and standing committees, and serves as the chief scientific liaison and representative to the Federation of Associations in Behavioral and Brain Sciences of the Psychonomic Society. Dr. Reyna is the editor of *Psychological Science in the Public Interest* and sits on the editorial board of such journals as *Decision* and *Journal of Experimental Psychology: Learning, Memory, and Cognition*, leading journals in psychology. She has received many years of research support from private foundations and U.S. government agencies, and currently serves as principal investigator of several grants and awards (e.g., from the National Science Foundation and the National Institutes of Health).

Mark Schumacher, Ph.D., M.D., is a professor of anesthesiology at the University of California, San Francisco (UCSF), with a clinical, research, and educational focus on pain management. He is currently division chief of pain medicine in the Department of Anesthesia and Perioperative Care. Dr.

Schumacher was the principal investigator for National Institutes of Health/National Institute on Drug Abuse awards in 2012 and 2015 to establish a Center of Excellence in Pain Education at UCSF. He has expertise in opioid and nonopioid strategies in pain control and has worked successfully to introduce multidisciplinary pain care and nonopioid analgesic strategies at UCSF Medical Center. His scientific achievements include being part of the team that isolated the Capsaicin Receptor–TRPV1, a major target in the development of nonopioid analgesic therapies. He is a member of several professional societies, including the International Anesthesia Research Society, the International Association for the Study of Pain, the American Pain Society, and the Association of University Anesthesiologists. Dr. Schumacher received his Ph.D. in physiology and pharmacology as well as his M.D. from the University of California, San Diego.

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Margaret (Mimi) Foster Riley, J.D., is a professor at the University of Virginia's (UVA's) Law School, has a secondary appointment at the medical school, and has an affiliation with the Batten School of Public Policy. Ms. Riley has written and presented extensively about health care law, bioethics, and food and drug law. She serves as chair of UVA's Embryonic Stem Cell Research Oversight Committee and as legal advisor to the Health Sciences Institutional Review Board. She was a member of the National Research Council Committee Assessing Toxicologic Risks to Human Subjects Used in Controlled Exposure Studies of Environmental Pollutants and served on the National Research Council Committee on Revisions to the Common Rule for the Protection of Human Subjects. She has advised numerous committees of the Institute of Medicine, the National Institutes of Health, the National Science Foundation, and the Virginia Bar. Ms. Riley received her bachelor's degree from Duke University and her law degree from Columbia University.

Patricia J. Zettler, J.D., is an associate professor of law and a faculty member of the Center for Law, Health & Society at the Georgia State University College of Law. She writes and teaches about food and drug law, health law and policy, and torts. Before joining Georgia State in 2015, she was a fellow at the Center for Law and the Biosciences at Stanford Law School. Prior to her fellowship, she served as an associate chief counsel in the U.S. Food and Drug Administration's (FDA's) Office of the Chief Counsel, where she advised the FDA and the U.S. Department of Health and Human Services on various issues, including drug safety, human subjects protection, expanded access to investigational drugs, over-the-counter drugs, dietary supplements, prescription drug advertising and promotion, incentives for

developing antibiotics, and advisory committees. In addition to her legal background, Ms. Zettler has bioethics experience through work at the Program in Medical Ethics at the University of California, San Francisco, and at the Department of Bioethics at the National Institutes of Health. Ms. Zettler received her undergraduate and law degrees from Stanford University, both with distinction.

Appendix C

Existing Data Sources on Opioid Use, Misuse, Overdose, and Other Harms

Data	Source	Numerators	Description
National Forensic Laboratory Information System (NFLIS)	U.S. Drug Enforcement Administration (DEA)	Drug cases investigated by the DEA at compound level (diversion)	Chemistry on drugs seized by law enforcement is analyzed by state, county, and volunteer forensic labs. Available for states, participating localities, and nationally.
Poison control calls	State poison control centers, National Poison Data System (NPDS)	Poison control calls related to "intentional exposures" (includes abuse, misuse, and suspected suicidal) or "intentional abuse exposures"	Number of exposure calls by drug/substance at state and national levels.
Drug treatment admissions (e.g., Treatment Episode Data Set [TEDS])	State and local drug treatment agencies	Lifetime nonmedical opioid, heroin users; past-year and past-month heroin use, any nonmedical opioid use (not product-specific)	Admissions to publicly funded treatment programs and opioid substitution programs by primary, secondary, and tertiary drug, route of administration, demographics. Available at local, state, and national levels.
Arrestee Drug Abuse Monitoring (ADAM) Program	Office of National Drug Control Policy	Survey/urine screen of recently arrested individuals (diversion)	Urinalysis results (marijuana, cocaine, opiates, methamphetamine) and self-reported drug use.
System to Retrieve Information from Drug Evidence (STRIDE)	DEA	Street drug price by geographic area; street drug purity by geographic area	Drug exhibits sent to the DEA laboratories. Provides national data on purity and weight of each sample by month seized. Totals annual seizure weights by drug.

	Timing	Strengths	Limitations
	Monthly	Uniform data collection across sites and over time. Detects new/emerging drugs.	Captures only mentions, not quantity seized. Not an appropriate surrogate for misuse. Decisions regarding enforcement and prosecution may influence which drugs are seized/tested. Significant lag in identifying new synthetic drugs because reference standards may not exist.
	Monthly	Ability to detect new/emerging drugs in real time. Product- and drug-specific information.	NPDS analyses must be requested and purchased; available 12 months after year ends; specific poison center data may be available in real time (depends on center). Possible misclassification of drug involved and reason for exposure. May underrepresent most severe cases of misuse.
	Annual, semiannual, or monthly depending on source	Data collection is relatively uniform across states.	May be influenced by funding streams and referral sources (e.g., criminal justice diversion or emphasis on certain drugs). Publicly available TEDS data lag 1–2 years. Limited differentiation of opioid products. Not nationally representative.
	Annual	Uniform data collection across sites; sample includes individuals generally not captured in other datasets (e.g., drug treatment).	Male arrestees only, limited to five sites in 2012. No longer fully operational. Not an appropriate surrogate for misuse.
	Annual	Only source of data on illicit drug purity and price. Complete datasets can be obtained via Freedom of Information Act (FOIA) request and analyzed.	Strongly influenced by enforcement activities; not representative.

continued

Data	Source	Numerators	Description
Uniform Crime Report (UCR)	Federal Bureau of Investigation	Arrests due to possession or trafficking of heroin and other opiates	UCR Part II contains annual summary of drug-related arrests (possession, sale). Reported by each law enforcement unit at the local level.
National Survey on Drug Use and Health (NSDUH)	Substance Abuse and Mental Health Services Administration (SAMHSA)	Lifetime nonmedical opioid, heroin users; first-time nonmedical opioid use, heroin initiates; past-year and past-month heroin use, nonmedical opioid use by therapeutic drug class; *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, diagnosed abuse or dependence	Self-reported drug use and abuse/dependence among respondents aged ≥12. Results available at national level and for some metropolitan statistical areas (MSAs) and substate areas.
Youth Risk Behavior Surveillance System (YRBSS)	U.S. Centers for Disease Control and Prevention (CDC)	Youth rates of nonmedical use of prescription opioids	National school-based survey of self-reported drug use. Includes results at state (n = 47) and local (n = 22) levels.
Monitoring the Future (MTF)	University of Michigan	Misuse rates among middle school, high school, college students and young adults	Nationally representative survey of self-reported drug use among 8th, 10th, 12th graders.
Automation of Reports and Consolidated Orders System (ARCOS)	DEA	Amount of manufactured controlled substance circulating through legal means, by compound	Measure of prescription drug supply based on mandatory reporting for Schedule I and II controlled substances and selected Schedule III and IV substances from manufacture to sale. Data for each substance reported by quantity (e.g., mg, dosage unit) and 3-digit zip code.

	Timing	Strengths	Limitations
	Annual	System has been in operation more than 30 years; is being updated to allow online analysis.	Strongly influenced by enforcement priorities. Only four categories of drugs. No ability to do any data analysis other than summaries.
	Annual	Longitudinal data collection supports analysis of changes over time. Data can be analyzed online.	Household survey excludes institutionalized and unhoused individuals.
	Every 2 years	Representative/weighted sample for United States and some states/localities. Longitudinal data collection supports analysis of changes over time.	Limited to youth attending school.
	Annual	Longitudinal data collection supports analysis of changes over time.	Limited to youth attending school. Not site-specific. Asks about only two prescription opioid products; the rest are considered "narcotics other than heroin."
	Annual	Comprehensive inventory of all legal drug sources. Can be analyzed longitudinally down to zip code level by individual substance, formula (e.g., extended-release).	Cannot discern between licit and illicit drug use. Data must be procured through FOIA request.

continued

Data	Source	Numerators	Description
Drug mortality	Local medical examiners/coroners, state vital records, National Center for Health Statistics nationwide data; SAMHSA's Drug Abuse Warning Network (DAWN-ME) (ended 2011)	Counts of drug-related mortality by compound, some by *International Classification of Diseases* (ICD) code; for DAWN-ME: mortality data (only for 13 states)	Cause of death and toxicology, drug poisoning deaths, and drug-induced deaths. DAWN-ME captured agent-level data.
Emergency department (ED) visits and/or hospital discharges for drug-related causes	CDC (SAMHSA's Drug Abuse Warning Network [DAWN-ED] ended 2011; also the Nationwide Emergency Department Sample [NEDS], which conducted a 20 percent sample of EDs, was discontinued)	Unclear, but documentation suggests these will be ICD code–defined ED visits (e.g., unintentional poisoning); for DAWN-ED: misuse/abuse-related ED visits	National Hospital Care Survey is a new survey that will provide data on health care delivery in inpatient, outpatient, and EDs, as well as other ambulatory settings. Will include data on drug-related care episodes. Previously, DAWN-ED collected data using retrospective records review at EDs selected through longitudinal probability sampling. DAWN-ED captured agent-level data on exposures and clinical drug-involved consequences.
HIV/hepatitis C virus (HCV) data	State and local health departments	New cases of HIV related to injection drug use (IDU); new cases of HCV related to IDU	New infections attributed to IDU, IDU by men who have sex with men (MSM), and heterosexual modes of transmission.
Trends in trafficking reports	DEA Field Divisions	Street price of drugs; availability and sources of drug	Each Field Division reports price data, availability, sources, and trafficking by drug.

	Timing	Strengths	Limitations
	Annual, although preliminary reports are available at local level sooner	Data can be analyzed online through CDC WONDER. Data available by state.	Local medical examiner data may not include deaths where private physician was in attendance. Drug use may or may not be based on autopsy reports—depends on state law. State data have 1–2 year time lag; national NCHS is complete in 2–3 years. Cause of death determined by ICD category.
	New system is not functional	One of few measures of drug-related morbidity. Unclear at what level of geographic specificity these data will be reported.	New system is not yet operational. Longitudinal data from DAWN will not be compatible with new system. Unclear if agent-level data will be available, as this is a function of hospital toxicological testing procedures.
	HIV reports usually annual, sometime semiannual or monthly; HCV reports less frequent	Comprehensive record of individuals who test positive for HIV and risk factors. Reported at county, state, and national levels.	Risk group (e.g., IDU, MSM-IDU, heterosexual) is self-reported. Levels of HIV—and especially HCV—testing vary across sites.
	Semiannual	Extensive data on supply side. Unclear geographic specificity. Unclear whether product- and/or compound-specific.	DEA redacts sensitive data prior to release. Possible sampling biases, possible selection biases.

continued

Data	Source	Numerators	Description
Proprietary surveillance system	Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS)	Lifetime nonmedical opioid, heroin use; first-time nonmedical opioid use, heroin initiates; past-year and past-month heroin use, nonmedical opioid use by product; measures of diversion; street price of opioid products	Drug diversion, poison center, opioid treatment, impaired health care worker, Survey of Key Informants, college survey, StreetRx (streetrx.com for street drug price) programs.
Proprietary surveillance system	National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO)	Lifetime nonmedical opioid, heroin use; first-time nonmedical opioid use, heroin initiates; past-year and past-month heroin use; nonmedical opioid use by product; route of administration; lifetime and past-year nonfatal opioid overdose; source of opioids	Addiction Severity Index-Multimedia Version (ASI-MV) Connect includes assessments of adults on drug use and for treatment need (intake, criminal justice, drug courts, Temporary Assistance for Needy Families) at 3-digit zip code level. Web Informed Services (WIS) quantifies endorsement of drugs among drug-use forums and discussion boards. Comprehensive Health Assessment for Teens assesses teenagers and young adults on drug use and for treatment need at 3-digit zip code level.

Timing	Strengths	Limitations
Near real time	Product and substance with composition- and formulation-specific differentiation. Exposure among certain high-risk groups can be identified (e.g., impaired health care workers). Multifaceted data collection effort. Geographically identified data.	Must be requested and purchased. Possible sampling biases, possible information biases. Not nationally representative.
Near real time	Product and substance with composition- and formulation-specific differentiation. Multifaceted data collection effort. Geographically identified data. Exposure among important high-risk groups can be identified (e.g., pregnant women, sexual minorities). Geographically identified data.	Must be requested and purchased. Sampling bias possible; not a probability sample. Recall bias possible. Not nationally representative.