Using National Data and Expert Guidelines to Inform Opioid Prescribing in Normal Spontaneous Vaginal Delivery

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DISSERTATION

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DEDICATION

This work is dedicated to God for giving me the desire and ability to learn,
to my parents, Jim and Sylvia, for teaching me tenacity,
to my children, Kate and Josh, for inspiring me,
and to my generous husband, David Mills, for believing when I didn't.

I also dedicate this research to those who are suffering from opioid and substance use disorder.
You are not forgotten.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
AHA	American Hospital Association
AMA	American Medical Association
APHA	American Public Health Association
ASAM	American Society of Addiction Medicine
CDC	Centers for Disease Control and Prevention
CMS	Centers for Medicare and Medicaid Services
FDA	Food and Drug Administration
GLMM	Generalized Linear Method Model
HIPAA	Healthcare Information Portability and Protection Act
HHS	United States Department of Health and Human Services
IHI	Institute for Healthcare Improvement
IOM	Institute of Medicine
IQR	Interquartile range
IRB	Institutional Review Board
MCH	Maternal Child Health
MMWR	Morbidity and Mortality Weekly Report
NAS	National Academy of Sciences
NHDS	National Hospital Discharge Survey
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NSAID	Nonsteroidal Anti-inflammatory Drug
NSVD	Normal Spontaneous Vaginal Delivery
OBGYN	Obstetrics/Gynecology
OWH	Office for Women's Health
PDMP or PMP	Prescription Drug Monitoring Program/Prescription Monitoring Program
PHD	Premier Healthcare Database
PI	Principal Investigator
SAMHSA	Substance Abuse and Mental Health Services Administration
SAP	Statistical Analysis Plan
SME	Subject Matter Expert
SPH	School of Public Health
TJC	The Joint Commission
UIC	University of Illinois, Chicago
VBP	Value Based Purchasing
VIF	Variance Inflation Factors
WONDER	Wide-ranging OnLine Data for Epidemiologic Research

SUMMARY

There is a prescription opioid overdose epidemic in the United States (U.S.) and drug overdose deaths are the leading cause of injury death in the U.S. (CDC, 2015). Local, state and federal agencies are looking for opportunities to employ primary, secondary, and tertiary prevention strategies. In 2012, there were 259 million opioid prescriptions written, enough for every adult in the U.S. to have their own script. Alarmingly, prescription opioids are involved in almost half of opioid overdose deaths (Paulozzi et al., 2014; CDC, 2014a). According to the U.S. Centers for Disease Control and Prevention (CDC):

- "Women are more likely to have chronic pain, be prescribed prescription painkillers, be given higher doses, and use them for longer time periods than men.
- Women may become dependent on prescription painkillers more quickly than men.
- Women may be more likely than men to engage in 'doctor shopping' (obtaining prescriptions from multiple prescribers).
- Abuse of prescription painkillers by pregnant women can put an infant at risk. Cases of neonatal abstinence syndrome (NAS)—which is a group of problems that can occur in newborns exposed to prescription painkillers or other drugs while in the womb—grew by almost 300% in the United States between 2000 and 2009" (CDC, 2013).

There are data on opioid prescriptions for women during the reproductive years, pregnancy and postpartum. There are no such data for opioid prescriptions during labor and delivery or on the day of discharge, although labor and delivery is the number one reason for hospitalization in the United States (McDermott et al., 2017), and an especially vulnerable time for women. As government agencies including the CDC and organizations such as the American College of Obstetricians and Gynecologists continue to look for ways to prevent unnecessary

opioid use, the maternal population in labor and delivery presents a relevant and important population to consider. A descriptive epidemiological study was employed to illuminate possible patterns of aberrant prescribing behavior. This data analysis in conjunction with recommendations from subject matter experts in the obstetric community may serve as a foundation for clinical and administrative leadership to develop guidelines for opioid prescribing for maternal populations undergoing normal spontaneous vaginal delivery in the United States.

I. BACKGROUND AND PROBLEM STATEMENT

a. Study Objectives

This research had two distinct but interrelated parts. Part I served as the foundation to the overall study and Part II is the actionable part of the research that leaders and stakeholders may use in their communities and arenas of influence.

Part I: The first part of the research sought to analyze and describe opioid utilization patterns in a low-risk procedure: normal, spontaneous, vaginal delivery (NSVD) using national data from January 1, 2014 through December 31, 2016. Part II: The purpose of Part II was to assimilate subject matter expert (SME) input through an e-Delphi process to develop opioid prescribing guidelines for NSVD patients. To assist the panel in the formation of their recommendations, the analysis from Part I was summarized and presented to the SMEs involved with the Delphi panel.

b. Background and Context

Drug overdose deaths are the leading cause of injury death in the United States. The number of prescriptions written for opioids in the U.S. has quadrupled from 1999-2014 and almost half of all deaths due to an opioid overdose involve a prescription opioid (CDC, 2011; Rudd et al., 2016). The Senior Advisor and Chief Medical Officer for the Division of Unintentional Injury Prevention at the CDC states, “Patients’ predisposition to overdose could not have changed substantially in that time; what has changed substantially is their exposure to opioids” (Dowell et al., 2013). Typically, prescribing behavior relates to disease and injury incidence and prevalence, but this is not what the CDC is seeing in its surveillance data with regard to opioid prescribing.

Attention has largely been placed on the outpatient arena regarding opioid prescriptions for chronic pain. The inpatient arena typically requires more aggressive pain management therapy, so there have been fewer data published on inpatient-initiated opioid prescribing practices, and data relative to inpatient low-risk procedures are sparse (Herzig et al., 2014). Since delivery is the number one reason for hospitalization, it represents an important opportunity where reproductive health, pain management, and substance prescribing collide and where multiple interventions can take place, including strategies to prevent neonatal abstinence syndrome (NAS) (Ko et al., 2017). As agencies such as the Office for Women's Health (OWH) and professional organizations such as the American College of Obstetricians and Gynecologists (ACOG) continue to look for ways to prevent unnecessary opioid prescribing and exposure, the maternal population undergoing labor and delivery presents a relevant and important population to consider.

To create opioid prescribing recommendations in the labor and delivery population, it is critical to garner an understanding of where orders are being written and by whom and to characterize opioid utilization patterns and trends. In the outpatient setting, this work is being accomplished to varying levels of success through monitoring programs. As of November 2017, when Missouri became the final state to adopt this kind of program, all 50 states have implemented a prescription drug monitoring program known as a PDMP or PMP. The frequency of reporting ranges from real time to weekly; in most states, the responsibility for reporting belongs to the health departments, Boards of Pharmacy, or single state authorities. These databases report on outpatient prescriptions of controlled substances, including opioids prescribed and filled by licensed providers. The purpose of such reporting mandates is to enable the identification of diversion and abuse related to controlled substances, such as opioids.

There is significant variation in opioid prescribing patterns across the United States. "Wide geographic variation that does not reflect differences in the prevalence of injuries, surgeries or conditions requiring analgesics raises questions about opioid prescribing practices" (McDonald et al., 2012). Further, the CDC published a fact sheet entitled, Opioid Painkiller Prescribing-Where You Live Makes a Difference. The document reported that "health care providers in the highest-prescribing state wrote almost 3 times as many opioid painkiller prescriptions per person as those in the lowest prescribing state in the U.S.…there are twice as many painkiller prescriptions per person in the U.S. as in Canada" (CDC, 2014a). In Chapters 4 and 5 this is discussed further in a finite population, again showing significant geographical variation in opioid administration. Data from the CDC have shown that a small percentage of prescribers are responsible for prescribing the majority of opioids and that pain specialists represent only a fraction of such high-volume prescribers. Prescribers may, without intent, be contributing to the problem because of a lack of awareness regarding their own habits relative to those of their peers in the medical community and nationally.

In response to the opioid epidemic, in early 2016, the CDC continued its opioid-related work by publishing guidelines for opioid prescribing for chronic pain patients who are not undergoing cancer treatment or end of life care (Dowell et al., 2016). Shortly after the publication of the chronic pain guidelines, Dr. Frieden, the CDC Director, published an editorial in the New England Journal of Medicine acknowledging that, "Although the guideline addresses chronic pain, many patients become addicted to opioids after being treated for acute pain" (Frieden and Houry, 2016). Similarly, the recent Institute for Healthcare Improvement (IHI) report, "Addressing the Opioid Crisis in the United States," concluded that while a great deal of activity has focused on addressing opioid prescribing in the outpatient setting where the majority of chronic pain and palliative care is managed, a more comprehensive view would necessitate

looking at inpatient prescribing patterns as well (Martin et al., 2016). The IHI report findings showed that it is important to "avoid starting [patients on opioids], thus preventing opportunities of opioid use, misuse and abuse" (Martin et al., 2016). This sentiment has been reiterated by policy experts with an imperative to stakeholders to "engage and align all actors to create systems that can prevent new individuals from becoming dependent on opioids" (Martin and Laderman, 2016).

Hospitals are key actors on the prescribing stage because of their roles in ordering and dispensing controlled substances; thus, hospital settings of care are not exempt from the increased emphasis being placed on abstaining from opioid prescribing where possible. "Hospitals are under increased scrutiny from regulatory agencies over prescription drug abuse and the potential for drug diversion from medical institutions. For hospital leadership, it is a patient safety issue. It is an employee health issue. It is a clinical quality and readmissions issue. And it is a legal and compliance issue" (Umhoefer and Finnefrock, 2016). Even though the CDC has not yet provided guidance for the inpatient population, administrative and clinical leadership could reevaluate their mindset with regard to pain management and opioid exposures in their patient populations. This is especially important in populations where the U.S. is lagging in terms of quality of care such as the maternal population.

In U.S. hospitals today, maternity care is the most common reason for hospitalization (McDermott et al., 2017). There are multiple data sources describing the incidence of opioid prescribing during the reproductive years, pregnancy, and after discharge from delivery. Very little has been published to describe patterns of opioid prescribing in labor and delivery or on the day of discharge. Importantly, there is no national, all-payer, inpatient descriptive epidemiological study on opioid initiation during labor and delivery. This is a concerning data gap given the size and vulnerability of this population. Healthcare leaders cannot fully assess the

extent of appropriate opioid use during labor and delivery, nor effectively address potential misuse at their own hospitals, without these data. Further, national stakeholders have called for more data to describe opioid prescribing in the inpatient setting. The labor and delivery cohort present a significant and relevant population as clinical leaders consider the risk/benefit of opioid exposure. In this population, the exposure introduces risk both to the mother and the newborn.

c. Problem Statement and Study Questions

The U.S. Department of Health and Human Services' Office of Women's Health (OWH) has called for exploring and evaluating the opioid epidemic through the "lens of the specific needs of women." As a part of this mission, OWH aims to "foster a national conversation on best practices to prevent, diagnose and treat opioid-related hazards and death among women" (OWH, 2016). However, sub-optimal opioid prescribing patterns, such as prescribing opioids when non-addictive substances could be utilized instead, are difficult to assess in acute care environments where healthcare providers are often forced to make pain management decisions based on their own judgment. These decisions are influenced by several factors, some of which are outside the prescriber's control, such as hospital pain management protocols, formulary restrictions, and hospital culture and attitudes about pain management. These factors also include the perception of pain by the patient. As such, effectively assessing proper and improper prescribing habits requires the evaluator to consider many facets of the prescribing and dispensing dilemma for the provider as well as the patient and larger community. This dilemma has created a significant challenge as providers seek to control pain but not add to the overprescribing of opioids. Utilizing a "multifaceted public health approach" would include all three levels of prevention (Kolodny et al., 2015). Practitioners and leaders who are committed to primary prevention will be motivated to avoid exposing their patients to opioids when safer alternatives are available.

This consideration would include viewing such prevention through the perspective of women undergoing labor and delivery and newborns.

Labor and delivery is a time of acute pain, and while some opioid use may be appropriate, other pharmacologic approaches would be expected in low risk, straightforward procedures such as normal, spontaneous, vaginal delivery (NSVD). The CDC, along with local, state and other federal stakeholders have emphasized that responsible pain management includes avoiding writing a prescription for opioids when less risky modalities are available and efficacious. The American College of Obstetricians and Gynecologists (ACOG) has stated that pain management at delivery is appropriate, and prescribers should consider both pharmacologic and non-pharmacologic interventions. However, there has been no direct national guidance regarding prescribing opioids to this population, nor is there any national data for benchmarking inpatient opioid orders in this population. The closest provider-specific guidance available comes from a 2017 ACOG committee opinion based on fourteen-year-old data, which states that "in the hospital setting, pharmacologic analgesia should be available for all women in labor who desire medication" (ACOG, 2017). ACOG's most recent recommendations and guidance related to NSVD are general in nature, allowing for divergent opinions in pain management. In light of the U.S. opioid epidemic and the escalating numbers of women who have overdosed or died, this is a critical time to reevaluate pain management guidance in the most straightforward of labor and delivery procedures, NSVD without complications. Data exists regarding opioid prescribing practices before and after delivery, and recent data regarding opioid prescribing post-cesarean section (C-section) reported that most patients "are prescribed in excess of the amount needed" (Osmundson, et al., 2017). However, to date, there are no national descriptive epidemiological data to illuminate prescribing patterns during normal spontaneous vaginal delivery. Expert

opinion based on experience and epidemiological data could help form this guidance and possibly reduce unnecessary opioid exposure in the maternal population.

On account of the opioid epidemic, it is incumbent on clinicians, along with administrative and policy leadership, to reconsider their respective formulary, protocol and prescribing responsibilities concerning opioids. The CDC reported approximately 2.7 million vaginal deliveries in the final birth data for the U.S. in 2015 (Martin, 2017). The very size of this population warrants consideration as to how narcotics are deployed, but an additional and important factor is that this population will be discharged to care for an infant. “While actions to address prescription opioid abuse must target both prescribers and high-risk patients, prescribers are the gatekeepers for preventing inappropriate access and providing appropriate pain treatment” (US DHHS, 2015). Taking the lead from the U.S. Department of Health and Human Services, leaders must rethink why and how opioids are administered in their own systems of care. With new opioid abuse data, have leaders rethought how to deploy risk/benefit tools to evaluate protocols for pain management? Have they adapted their pain management philosophies based on the newest CDC census data highlighting the impact of prescription opioids on their communities? How might leaders use their own data and national data to assist them in viewing the opioid epidemic from the balcony—seeing the big picture and then drilling down to their own settings of care to investigate the factors related to opioid prescribing?

Leaders in maternal and child healthcare can benefit from understanding the overall patterns of opioid prescribing, which can elucidate variations by hospital factors (e.g., geography and academic status) and by patient factors (e.g., payer, documented substance abuse). A characterization of opioid utilization administered during hospitalization and on the day of discharge provides information which can then be used to set benchmarks for healthcare professionals to use in the future. Part I of this research entailed conducting a descriptive

epidemiological study to better understand the factors associated with opioid utilization practices in NSVD, which may serve as a foundation for providing recommendations to improve opioid prescribing patterns in maternal health in the United States. These data were then deployed to Obstetrics/Gynecology (OBGYN) experts to help complete Part II of the research by providing expert opinion for initial recommendations for opioid prescribing during NSVD and on the day of discharge. The results of both Part 1 and Part 2 of the research can be found in Chapter 4. In Chapter 5, an in-depth discussion on the implications of leadership and systems thinking will help leaders in maternal/child health (MCH) to adopt and implement guidelines to improve the care of mothers and newborns.

d. Leadership Implications and Relevance

Healthcare and public health leaders have an obligation to pay close attention to the health of the maternal/child population. “Improving the well-being of mothers, infants, and children is an important public health goal for the United States. Their well-being determines the health of the next generation and can help predict future public health challenges for families, communities, and the health care system” (healthypeople.gov). Healthcare systems may be responsible for implementing and operationalizing change to improve maternal health, but adaptive leaders are needed to spearhead the initiative if it is to be successful. Leaders who operate with an adaptive lens can identify the gap between the organization’s stated values and the organization’s performance and then provide guidance to clinicians and staff for navigating these complex challenges (Kouzes, 2007). The need for leaders in the MCH population to operationalize change with regard to opioid prescribing is paramount, not only for the MCH population, but for the communities in which they live.

Inpatient and outpatient populations are not only managed differently because of their respective settings of care, but also due to the severity of illness and injury. The CDC has issued

guidelines that leaders can use to initiate changes in opioid prescribing for the chronic pain population, which is primarily treated in the outpatient setting (Dowell et al., 2016). Similar work has not been performed for the inpatient population, because the inpatient population is heterogeneous and complex. This population comprises medical, surgical and urgent care populations with a wide variety of diagnoses and associated comorbidities and complications. Rising to this challenge is important because work being done in the outpatient population must eventually be married with prescribing in the inpatient population or the progress made in appropriate opioid prescribing will be limited. “The most important risk factor for opioid analgesic associated dependence or overdose is not a feature of any individual patient but instead simply involves receiving a prescription for opioids. For example, newly prescribed opioids after short-stay surgery are associated with a 44% increase in risk of becoming a long-term opioid user within 1 year” (Dowell et al., 2013). Both inpatient and outpatient populations need to be addressed appropriately. The CDC specifically points out in its recommendations for chronic pain that even in the acute care setting, there are situations where pain can be managed without opioids (Dowell et al., 2016). As will be discussed in Chapter 5, leaders can take best practices for opioid prescribing learned in the outpatient environment and then appropriately modify these practices for the inpatient setting.

A key tenet of successful leadership requires that leaders help their organizations adapt to change, and this work includes exploration and identification of the areas in which change is needed. In considering inpatient populations that could be targeted for more systematic discipline with regard to opioid prescribing, the labor and delivery population surfaces as a strong contender for several reasons. First, this is the most common reason for hospitalization. Second, upon discharge, this population is likely caring for an infant. Third, a subset of this population, NSVD patients without complications, are more homogenous in their presentation and treatment

relative to other patients. Fourth, maternal and child health is an important improvement goal in U.S. public health. Utilizing subject matter expert (SME) input and epidemiological data to inform opioid prescribing recommendations in the NSVD patient population would benefit multiple stakeholders as depicted in TABLE I.

TABLE I: RELEVANCE AND IMPACT OF PROPOSAL TO LEADERSHIP STAKEHOLDERS

Stakeholder Group	Relevance of Research Proposal	Short Term Impact	Implications
Public Health	Addresses the lack of data in labor and delivery (there are data on pregnancy and post-partum opioid prescribing but there are no data on labor and delivery). Directly impacts 4 of the 10 essential public health services.	Assists community leaders in using data to conduct a deeper dive in their own opioid prescribing to the inpatient maternal population.	Public health leaders can use regional data to inform assessment opportunities and community discussions regarding inpatient prescribing. SME recommendations can be used as springboard for other populations of interest where opioid prescribing practices need reformation.
Clinician and Hospital Leadership focused on Performance Improvement	Clinician and hospital leaders may employ a similar algorithm to run the data in their own hospitals to determine prescribing patterns relative to peer systems locally, in their respective census region, and in the nation.	Currently, there are no national or regional data to benchmark inpatient prescribing and compare prescribing patterns relative to patient and system characteristics. These data and the SME recommendations will provide clinicians with information by which to measure their own performance.	Clinicians and hospital leaders can use the findings of this analysis and the recommendations to assess collective system performance as well as to evaluate individual prescribers relative to peers and that national and regional provider communities.
Society Leaders, e.g., ACOG & American Society of Addiction Medicine (ASAM)	This research will provide national data and analysis that could help establish a baseline. The analysis and recommendations can be used to inform a policy white paper calling for guidelines to be used for opioid prescribing in the NSVD population.	Currently, ACOG does not provide specific guidelines in part because no data exist to inform a discussion regarding appropriate or "average" prescribing in a homogenous population such as NSVD.	ACOG and other organizations could use these data as an impetus for discussing opioid and narcotics prescribing in the NSVD population.
Policy Leaders (CDC, OWH)	The CDC has published guidelines for the outpatient sector where most opioid prescribing occurs. These data would begin to set a benchmark for further investigation into inpatient prescribing patterns. The OWH has called for greater attention on opioid prescribing to women. This data targets one of the largest hospital populations in the U.S.	Would add to the research performed by Herzig et al. in 2014 (inpatient study of non-surgical patients).	CDC will have baseline data to compare to outpatient data and trends over time. With further partnerships (for example with the OWH) they can use these and future data to inform guidelines for inpatient prescribing. The SME guidance could inform further guidelines coming from federal offices.

For practitioners closest to the patient, guidance is needed from clinician leaders who are willing to help the provider workforce with the complex challenges associated with the opioid prescribing environment. Each healthcare organization has its own system and culture driving the decisions and actions that are made by providers, administrators, and managers regarding patient care and pain management. Leaders who can influence others to make changes as "they discover their role in exacerbating the problems they want to solve" will more likely evolve their organization's approach in areas such as responsible prescribing (Stroh, 2015). It is not well understood when and how opioids are deployed during labor and delivery, and how such prescribing may vary across providers and populations. To evaluate progress in conscientious pain management, those seeking to improve maternal health must understand the care patterns in their hospitals, establish expected practice guidelines, and hold healthcare providers accountable for their actions in ordering highly addictive substances and/or issuing orders that can be potentially life threatening, such as concomitant orders of benzodiazepines and opioids.

Leaders must be willing to take a systems diagnostic approach to solve prescribing challenges in their own system. Ronald Heifetz, a renowned author and teacher in the adaptive leadership approach, is very directive in his recommendations for leaders seeking to solve complex challenges such as this. He emphasizes the importance of the separate but collective work of diagnosing the problem and then identifying the action that needs to take place to address and correct the problem (Heifetz et al., 2009; Heifetz et al., 2002). In assessing prescribing behavior in acute care, leaders will need data to evaluate their own organizations. For example, Larochelle and colleagues reported that for 91% of patients who suffered a non-fatal overdose, physicians continued prescribing opioids, and within two years up to 17% of the same patients overdosed again (Larochelle et al., 2015). This is a good example of stakeholders needing to understand their role in contributing to the very problem they are trying to solve.

Health system leaders need data to illustrate prescribing trends by provider, and over time, to assess performance improvement in opioid prescribing behavior. Organizationally, leaders will want to assess prescribers' behavior relative to the organization's values and goals in this arena. This is more easily attended to when the providers are employed by the system in which they practice because they have financial levers they can tie to specific practice goals. Beyond assessing individual prescribers, it would also be beneficial for leaders to do a comparative analysis and evaluate their system's aggregate provider prescriber behavior relative to other systems which have similar patient and hospital characteristics. Once that data is available, the leader must diagnose the problem. What is going on? Does the organization have prescriber outliers in their NSVD population? If so, is it a systemic problem or can it be characterized by practitioner, or in a particular hospital within the system? Is this a problem the leaders recognize in peer organizations and if so, are there collective learning opportunities for the leaders and stakeholders in each system? Adaptive leadership in any setting requires that stakeholders commit to an approach of inquiry, diagnosis, and treatment that ties back to the overarching goal of closing the gap between where the organization is relative to its values and goals and where it wants to be.

When leaders discover whether and to the extent there is a prescribing problem, they must identify the action required to address the problem or as Heifetz et al., refer to it, they must mobilize the system (Heifetz et al., 2009). The SME recommendations in Part II of the research can help inform leaders on how to initiate action in their own organizations. Although baseline data will be important to diagnose the problem and assess prescribing changes and aberrant prescribing behavior, action is needed to deploy sustainable change. Healthcare leaders understand the concept of diagnosis and treatment relative to patients, but in this scenario, they must understand it relative to their own system. Providing leaders with guidance from subject

matter experts can help mobilize them to create an intervention strategy. Once in place this can be used to “mobilize people to tackle an adaptive challenge” (Heifetz et al., 2009). This will be discussed in more detail in Chapter 5 as it relates to expert recommendations regarding the risk/benefit of opioid administration during labor and delivery and possible interventions.

From a public health perspective, decreasing opioid prescribing reduces the availability of opioids in the community and reduces the opportunity for abuse and addiction. Further, both the epidemiological data and the SME recommendations can help guide the development of oversight programs which are an important component of public health prevention efforts.

For hospital-owned alliances and integrated delivery networks, these data can inform performance measurement for quality improvement. This will become even more relevant as hospital systems review their respective pain management programs for the purposes of quality improvement and patient safety. More broadly, this research can better inform policy stakeholders and medical society leaders regarding practice patterns in the U.S. related to opioid administration in the maternal population. Characterizing prevalence, patient characteristics and hospital characteristics may help inform how and where leaders prioritize evaluating and changing opioid prescribing to improve the quality of care their organizations are providing to their communities.

II. CONCEPTUAL AND ANALYTICAL FRAMEWORK

a. Literature Review

Opioid Related Death, Overdose and Dependence: A Call to Action

The CDC estimates that 25% of Americans who receive a prescription opioid (PO) for chronic pain struggle with addiction (CDC, 2017a). Just as concerning are the almost two million Americans who have abused or are dependent on opioid medication (SAMHSA, 2017). With over 259 million prescriptions written each year for opioids, there are enough scripts for every adult American, although there has been no reported increase in pain to warrant such prescribing (Paulozzi et al., 2014). The mere availability of these drugs is problematic and the pharmaceutical industry is not without blame as many companies have presented a non-addictive safety profile for opioids.

Overdose and death related to both illicit and prescribed use of opioids is well documented in the U.S. and such data are readily available through the CDC and other federal agencies. It is also well understood and undisputed that the prescribing of opioids is fueling the tragedy. “Opioids, primarily prescription pain relievers and heroin, are the main drugs associated with overdose deaths. In 2014, opioids were involved in 28,647 deaths, or 61% of all drug overdose deaths; the rate of opioid overdoses has tripled since 2000” (Rudd et al., 2016). There is no sign that the crisis is abating and in fact, it is worsening. The White House declared the opioid epidemic a national emergency in late 2017 and has committed resources to continue to battle the crisis. Federal and state agencies have called explicit attention to the magnitude of the opioid epidemic and have made inroads toward addressing prevention and treatment. A subset of this work is included in Table II.

TABLE II: EXAMPLES OF AGENCY ACTIVITY ADDRESSING OPIOID EPIDEMIC

Agency	Publication, Legislation or Documentation	Date Released	Intent/Activity
CDC	CDC Guideline for Prescribing Opioids for Chronic Pain (Dowell et al., 2016)	March 2016	Summarizes literature and includes 12 guidelines for stakeholders, practitioners and patients regarding opioid prescribing and the risks and evidence.
	Chronic Pain & CDC Women's Health and Opioids (CDC, 2017b)	January 2017	Symposium related to women's health issues and addiction.
	Annual Surveillance Report of Drug-Related Risks and Outcomes: Surveillance Special Report 1. (CDC, 2017c)	August 2017	Data collected from multiple sources with CDC commentary regarding the U.S. epidemic of drug overdoses, deaths with extensive discourse on the role of prescription opioids in the epidemic.
Department of Health and Human Services (HHS)	Report by Behavioral Health Coordinating Committee Prescription Drug Abuse Subcommittee: Addressing Prescription Drug Abuse in the U.S. Current Activities and Future Opportunities (US DHHS, 2013)	2013	To improve the understanding of a variety of drug abuse activities and a review of opportunities for safe prescribing, treatment of dependence, and strengthening of programs and policies.
Executive Office of the President of the United States, Obama Administration	National Drug Control Strategy and Prescription Drug Abuse Prevention Plan (Executive Office of the President of the United States, 2016a)	2016	Reporting mixed results on strategy put into place in 2010 including as the first strategy "prevention."
Executive Office of the President of the United States, Trump Administration	The President's Commission on Combating Drug Addiction and the Opioid Crisis (Executive Office of the President of the United States, 2017)	November 2017	Final report encompassed more than 50 recommendations including establishing a national drug court system, easier access to opioid alternatives to treat pain, prescriber education, expanded use of PDMP systems in clinical practice, changes to approaches to setting reimbursement rates.
National Institute on Drug Abuse	America's Addiction to Opioids: Heroin and Prescription Drug Abuse (NIDA, 2014)	May 2014	Testimony by Dr. Nora Volkow to U.S. Senate Caucus on International Narcotics Control.
	Misuse of Prescription Drugs (NIDA, 2018)	August 2016; updated January 2018	Publication addressing scope of misuse, use in pregnancy, prevention and treatment.
Office of the Surgeon	Facing Addiction in America: Surgeon General's Report on	November 2016	First report of its kind from the Surgeon General's Office. Very detailed report

General	Alcohol, Drugs, and Health (U.S. Office of the Surgeon General, 2016)		covering neurobiology, prevention, early intervention, health systems and Substance Use Disorder (SUD), and public health vision.
Agency	Publication, Legislation or Documentation	Date Released	Intent/Activity
OWH	White Paper: Opioid Use, Misuse, and Overdose in Women (OWH, 2016)	December 2016	To examine prevention, treatment and recovery for women related to opioid use, misuse and overdose.
State of Pennsylvania	Obstetrics and Gynecology Pain Treatment (Pennsylvania Dept. of Health, 2016)	January 2016	Only current guidelines available in the U.S. on opioid prescribing with specific direction for pregnancy, labor, and post-partum opioid prescribing. These are only state guidelines. No federal adoption has transpired.
Substance Abuse and Mental Health Services Administration (SAMHSA)	Preventing Prescription Drug Misuse: Overview of Factors and Strategies (SAMHSA, 2016a) Preventing Prescription Drug Misuse: Who is at Risk (SAMHSA, 2016b)	May 2016	These sister publications provide background, context, and actionable information for prevention strategies, albeit primarily in the outpatient setting.
U.S. Food and Drug Administration (FDA)	NEJM: A Proactive Response to Prescription Opioid Abuse (Califf et al., 2016)	April 2016	A special report which addresses the main issues concerning opioid prescription abuse and actions the FDA will take while balancing individual pain control in the context of broader public health consequences.

Proponents on both sides of the U.S. political divide have strongly supported legislation that allocates one billion dollars to states over a two-year period to fight the opioid epidemic, and in December 2016, the 21st Century Cures Act was signed into law (Public Law, 2016). This law has been lauded as the first of its kind in over one half of a century to address mental health. In addition to federal agencies, there has been a considerable amount of work published by advocacy groups and associations demonstrating the need for evidence-based interventions at multiple levels including federal, state, and local provider and patient levels. The contributions vary in form, including recommended evidence-based practices, tools, policy statements on direction and resource allocation, as well as resource centers to help prescribers. Many organizations have multiple contributions addressing prevention and treatment. Selected examples are notated in TABLE III.

TABLE III: ORGANIZATIONAL RECOMMENDATIONS, PUBLICATIONS AND TOOLS

Organization	Publication, Legislation, Tools, Best Practice Recommendation	Date Released	Intent/Purpose
Academic Medical Centers	Federal Announcement from Office of the President of the United States (Executive Office of the President of the United States, 2016b)	March 2016	Sixty medical schools require students to take prescriber education to graduate. Education to be based on CDC recommendation for prescribing opioids for chronic pain.
American Medical Association (AMA)	Guidelines authored by AMA Taskforce (AMA, 2017)	June 2017	Taskforce identified six goals (which are included in other recommendations by other entities as well), including physician use of PDMPs; educate on prescribing; promote assessment and treatment; reduce stigma patients may feel related to opioid use disorder; collaborate to improve naloxone access; and safe storage and disposal of opioid medications.
American Pain Society and American Academy of Pain Medicine	The organizations combined efforts to produce guidelines for chronic opioid therapy (Chou et al., 2009).	2009	These guidelines purpose to provide practitioners guidance for chronic pain patients but will likely be displaced by the CDC guidelines.
American Pharmacists Association (APhA)	Online resource center focused on pharmacy community (APhA, 2018)	Current	Tools and guidelines focused on addressing appropriate opioid prescribing and use and misuse resources
American Public Health Association (APHA)	Policy Statement: Prevention and Intervention Strategies to Decrease Misuse of Prescription Pain Medication (APHA, 2015)	November 2015	Promote the inclusion of systems of accountability for doctors and prescribers; establish standards for safe and effective prescribing.
ASAM	National Practice Guidelines for the use of Medications in the Treatment of Addiction Involving Opioid Use (Kampman and Jarvis, 2015)	June 2015	Treatment guidelines for opioid use disorder (OUD), including those for special populations such as pregnant women and lactating women.
Institute for Healthcare Improvement (IHI)	Innovation Report: Addressing the Opioid Crisis in the United States (Martin et al., 2016)	April 2016	A 90-day scan to develop a gap analysis and recommended approaches for dealing with the prescription opioid epidemic.
Institute of Medicine (IOM)	Report: Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research (IOM, 2011)	2011	At the request of the Department of Health and Human Services and National Institutes of Health, the IOM provided an analysis based on expert judgment and evidence of the public health and clinical issues involving pain management in the outpatient setting.
Johns Hopkins Bloomberg School of Public Health	The Prescription Opioid Epidemic: An Evidence-Based Approach (Johns Hopkins, 2015)	2015	Expert panel convened and reported evidence-based recommendations and intervention strategies for reversing OD and injury related to opioids.

TABLE III: ORGANIZATIONAL RECOMMENDATIONS, PUBLICATIONS AND TOOLS

Organization	Publication, Legislation, Tools, Best Practice Recommendation	Date Released	Intent/Purpose
National Academies of Sciences, Engineering and Medicine	Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse (In progress) (NAS, 2018)	Ongoing meetings until study is complete	Study is currently underway and will inform the FDA on the state of the science specifically related to prescription opioid abuse. This study will update the 2011 IOM report (see above).
Physicians for Responsible Opioid Prescribing (PROP)	Letter to Dr. Mark Chassin, Chief Executive Officer and President of The Joint Commission (PROP, 2016a) and a letter to acting Administrator of the Centers for Medicare and Medicaid Services (CMS), Andy Slavitt (PROP, 2016b)	April 2016	Major lobbying activity to the Joint Commission and CMS to remove pain from the patient satisfaction survey used in hospitals for reimbursement related to value-based purchasing. These efforts were successful. Changes took effect in October 2017.
Society of Hospital Medicine	Publication: Implementation Guide for Pain Management (SHM, 2015)	2015	Pain management guide for hospitalists.
The Joint Commission	Sentinel Event Alert # 49 (TJC, 2012)	Aug. 2012	Sentinel Event Alert sent to the 21, 000 orgs TJC accredits to highlight Adverse Drug Events associated with opioid prescribing. Data came from TJC Sentinel Event database (2004-2011).
Trust for America's Health	Issue Report and Recommendations (TAH, 2013)	Oct. 2013	Similar observations and recommendations as seen in other reports with the inclusion of more specific graphics and information on state data included in report.

Opioid Prescribing Patterns in the Inpatient Setting and at Hospital Discharge

Until 2014, the literature showed no examination of inpatient opioid prescribing data. Herzig et al. reported on opioid prescribing in medical (non-surgical) patients in a representative sample of U.S. hospitals and the data in these 286 hospitals illustrated wide variance in opioid prescribing practices by U.S. region, even after adjusting for patient risk factors (Herzig et al., 2014). The authors concluded that more research was necessary to understand the variations in prescribing and pointed out that "reigning in inpatient prescribing may be a crucial step in curbing the opioid epidemic as a whole." Further, the authors called for prescribing guidelines in the hospital setting to promote standardized and safer practices and to provide support for clinical decision making (Herzig et al., 2014). The researchers' summation is supported by work previously published by the Institute for Healthcare Improvement (IHI) and others, noting that often the first prescription is ordered in the acute care setting.

The literature points to the significance of receiving an opioid as an inpatient and how that portends for continued prescribing post discharge. In opioid naïve patients (patients who have not been exposed to an opioid), opioid receipt at hospital discharge increases future chronic opioid use (Calcaterra et al., 2016). "Harms associated with prescription opioids are a major and increasing public health concern. Prescribing opioids for inpatients may contribute to the problem, especially if primary care practitioners continue opioid therapy that is initiated in the hospital" (Lail et al., 2014). Both the inpatient setting and the discharge disposition play a role in patients' exposure to opioids and subsequent risk for abuse, overdose, addiction and possible death.

There are groups that have released guidelines that are either very general or are specific to a non-labor and delivery population. Examples include The Society for Hospital Medicine

which issued guidelines to hospitalists for pain management in 2015 (SHM, 2015). These guidelines addressed the medical population as a whole and were not focused on labor and delivery or any surgical populations. The American Pain Society also released practice guidelines focused on post-surgical pain management (Chou et al., 2016). Guidance for general pain management was provided by The Joint Commission (TJC) Sentinel Alert 49, which addressed opioid related adverse drug events in the general hospital population. However, the focus of the TJC guidance was not on addiction as an adverse event, but adverse drug events in general, and especially respiratory depression (TJC, 2012). The State of Pennsylvania published non-discriminating pain management guidelines for the general labor and delivery population but these guidelines did not differentiate between uncomplicated and complicated delivery. This is discussed in more detail below. Specific guidelines for labor and delivery relative to NSVD and C-Section are needed.

Opioid Prescribing in the Maternal Population- Reproductive Years through Labor and Delivery

There are outpatient prescribing data for women during their reproductive years. Data were reported on women of reproductive age in the U.S. for the years 2008-2012 as well as in the state of New York for the years 2008-2013 (Ailes et al., 2015; Gallagher et al., 2016). There are also data on opioid prescribing during pregnancy. Pain is a common occurrence during pregnancy and pharmaceutical options including opioids are often employed to address pain despite the implications for the fetus (Yazdy et al., 2015). In an examination of claims data from one state's Medicaid program, approximately 30% of pregnant women filled a prescription for an opioid (Epstein et al., 2013). In another study analyzing a national Medicaid population of pregnant women, over 20% filled an opioid prescription (Desai et al., 2014). Although this is a smaller percentage than the single state analysis, it is concerning given the harms associated with opioid use during pregnancy, such as birth defects and impact on fetal development. In addition

to the Medicaid data, some of the earliest data for opioid prescribing in pregnancy are from a commercial insurer database which indicated that in over half a million pregnancies, 14% of women were prescribed opioids (Bateman et al., 2014). While there are outpatient study data describing patient characteristics and prevalence, examination of the problem in the maternal inpatient setting has been neglected.

Delivery Characteristics and Pain Management

There is an understanding in the medical community that C-Section and vaginal births should, in most cases, require a different pain management response. Vaginal births with complications such as lacerations, or those in which a clinician performed an episiotomy or employed forceps for delivery, are characterized differently than vaginal births without complications in regards to pain management. Regardless of delivery characteristics, there is no guidance for clinicians on opioid prescribing, despite the call for pain management and narcotic recommendations not only for C-Section patients, but specifically for vaginal delivery patients without complications (Jarlenski et al., 2017). It may be that no specific guidelines for uncomplicated deliveries have been provided because to date there have been no data describing the prevalence of opioid administration in this particular inpatient population.

In original research published in July of 2017, researchers found that for C-Section patients, opioids were overprescribed opioid upon hospital discharge. The study called for more research to assess whether inpatient opioid practice patterns can help "guide" discharge opioid prescribing practice (Osmundson et al., 2017). Other research has substantiated the call to reassess inpatient opioid administration. In surveys to six academic medical centers in the U.S. data revealed that post-cesarean delivery patients received significantly more opioids than what was needed to control pain, thereby creating leftover opioid medication and an opportunity for diversion (Bateman et al., 2017).

Although there are approximately four million births in the U.S. each year (Martin, 2017), there are no national data on opioid administration during labor and delivery and on day of discharge with the exception of data showing the prevalence of spinal and/or epidural analgesia administration and sixteen-year-old survey data from the previous two decades with erudition on the analgesic delivery route and size of hospital (Traynor et al., 2016; Marmor and Krol, 2002). There are also data for vaginal delivery patients post discharge revealing that approximately 10% of vaginal delivery patients filled a prescription for opioids upon discharge (Jarlenski et al., 2017). There are no national, all payer, descriptive data on opioid administration during hospitalization and on day of discharge for NSVD patients. The prevalence of opioid administration in this large patient population is unknown. Without this data, leaders cannot adequately ascertain whether opioid administration is prevalent, to what extent and in what patients or hospital settings and this lack of knowledge puts patients at risk for unnecessary opioid exposure.

The American College of Obstetricians and Gynecologists and Pain Management in Labor and Delivery

The American College of Obstetricians and Gynecologists Committee on Obstetric Practice, in conjunction with the American College of Nurse-Midwives (ACNM), published a Committee Opinion in February of 2017 entitled, "Approaches to Limit Intervention during Labor and Birth." The Committee performed an evidence review in part to "minimize the intervention for appropriate women who are in spontaneous labor at term. The desire to avoid unnecessary interventions during labor and birth is shared by health care providers and pregnant women" (ACOG, 2017). The Committee recommendations did not include specific information regarding opioid prescribing, stating, "the importance of avoiding pharmacologic analgesia or epidural anesthesia will vary with individual and patient values and medical circumstances. In

the hospital setting, pharmacologic analgesia should be available for all women in labor who desire medications" (ACOG, 2017). This recently published opinion supported previous statements from the ACNM. However, there are no explicit pain management guidelines for opioid prescribing during cesarean or normal, spontaneous, vaginal delivery (NSVD) procedures, apart from guidelines published in 2016 by the Commonwealth of Pennsylvania (Pennsylvania Dept. of Health, 2016). These guidelines did not distinguish between C-Section and NSVD pain management but did discourage pharmacologic therapies unless pain is unrelieved by other methods.

As the CDC has provided guidance in the outpatient sector, it is incumbent on leaders to take the initiative for the inpatient sector, especially in populations who are more characterized by their diagnosis homogeneity vs. heterogeneity. Stakeholder groups such as ACOG could use epidemiological data to evaluate the prevalence of opioid prescribing in discreet populations and use the findings to make appropriate recommendations for opioid administration. This guidance could help improve the quality of care in the MCH population by reducing opioid exposure for patients and by guiding clinicians in appropriate administration. This is discussed in more detail in both Chapters 4 and 5.

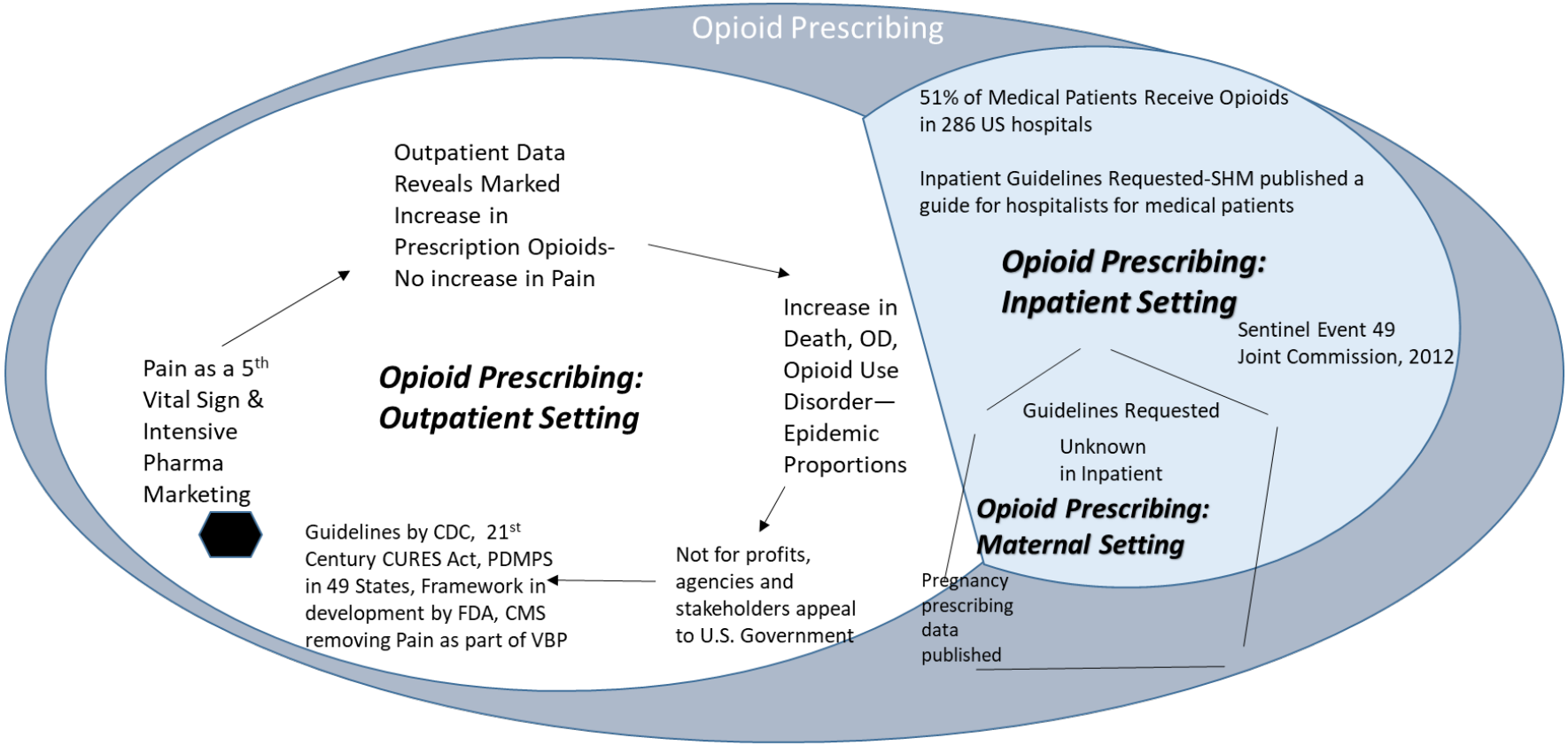
b. Conceptual Framework

The conceptual framework for this research is depicted in Figure 1. The literature is rich with data in the outpatient setting as previously outlined. The inpatient setting has less data and no national guidelines related to its largest patient population and the guidelines that are available are targeted at hospitalists performing pain management functions. Further, the maternal population presents as a viable population for reducing opioid exposure. There are data in pregnancy and during the reproductive years for this population, but no data for labor, birth and day of discharge. Data has recently been published on post discharge opioid administration

(Jarlenski et al., 2017). The availability of data on opioid prescribing and guidelines for this population has the potential to generate a sizeable impact on the overall opioid supply given the magnitude of the maternal population.

Outpatient data on opioid prescribing informed the guidelines released by the CDC in 2016. This same approach can be used for the inpatient setting, where data can inform recommendations and guidelines for opioid prescribing in discrete inpatient populations. In a first analysis of opioid administration in the NSVD population, the research in Part 1 of this study informs Part 2 of the study so that the resulting recommendations are based on data. Leaders will still need to think about the data and its relative application to their own system as their hospital and patient characteristics may be different in terms of what portends opioid administration nationally or regionally. This will require adaptive leadership skills in terms of assessing the situation, and then determining if there is a gap between where the organization strives to be and where it actually is relative to its values on narcotic administration. Chapter 5 discusses in more detail the principles of adaptive leadership relative to its application to this research. The conceptual framework below (Figure 1) highlights where the gaps are historically in the data and in opioid prescribing guidelines.

Figure 1. Conceptual Framework for Opioid Prescribing Activity, Data and Responses[1]



Outpatient Setting and select events and data leading to CDC guidelines
Inpatient Setting and limited data and lack of agency guidelines

1. Literature informing the Conceptual Framework included CDC, 2017a; CDC, 2017b; CDC, 2015; CDC, 2013; CDC, 2011; CMS, 2016; Dowell et al., 2016; Jarlenski et al., 2017; Morone and Weiner, 2013; Osmundson et al., 2017; PROP, 2016a; PROP, 2016b; Public Law, 2016; Sarpatwari et al., 2017; SHM, 2015; TJC, 2012; US FDA, 2017; and Yazdy et al., 2015.

III. STUDY DESIGN, DATA, AND METHODS

a. Analytical Approach

The aim of this study is to provide recommendations to clinical, administrative and policy leadership for opioid prescribing in the NSVD population through:

1. A retrospective, observational study;
2. Use of the CDC chronic pain guidelines for opioid prescribing to architect questions for a Delphi Panel; and
3. Delphi panel consensus recommendations for opioid prescribing in NSVD.

Data sources and collection methods for each part of the study can be found in Table IV.

TABLE IV: DATA SOURCES AND COLLECTION METHODS

Part	Research Questions	Data Source	Data Collection Method
I.	What are the patterns and possible predictors of opioid administration in NSVD patients during hospitalization? What are the patterns and possible predictors of opioid administration in NSVD patients on the day of discharge?	Secondary Data from Premier Healthcare Database (PHD)	Retrospective observational study with bivariate and Generalized Linear Mixed Model (GLMM) modeling
II.	How might clinicians in administrative and policy leadership roles contribute to opioid abuse prevention efforts by addressing opioid prescribing patterns in low-risk procedures such as NSVD patients?	Expert Recommendations for Opioid Prescribing Guidelines	Three rounds of surveying to e-Delphi participants in a single-blind design with predefined consensus parameters

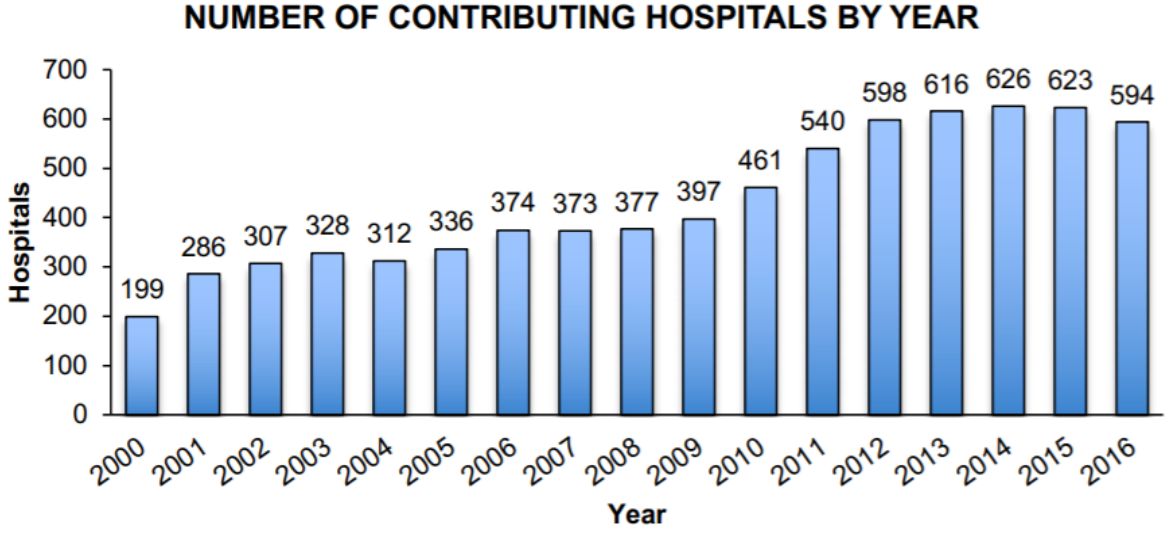
The two-part study design employed a mixed methods approach. The research questions necessitated a two-part approach given the need for epidemiologic data to support the subject matter expert consensus process. Part I comprised a retrospective, descriptive, observational study. Part II utilized a modified e-Delphi approach for consensus building toward recommendations for opioid prescribing for NSVD patients during labor and delivery and on day of discharge. The data from Part I informed the initial discussion guide for Part II. It is worth noting that there is strong precedent for including epidemiologic data related to opioid prescribing, use, abuse, overdose and death for the purposes of elucidating where corrective action or further exploration is warranted. Examples of this include the CDC's Morbidity and Mortality Weekly Report (MMWR) and the CDC's Wide-ranging Online Data for Epidemiologic Research (WONDER) data sets which are used extensively by local, state and federal agencies for these purposes.

b. Data Sources, Data Collection and Management

Part I consisted of a retrospective, descriptive, observational study which sought to analyze the demographic and clinical characteristics of NSVD patients administered opioid medications during hospitalization and on the day of discharge. The primary outcome of interest was whether a patient received an opioid during the hospitalization and/or on the day of discharge. The study purposed to describe hospital and patient level characteristics of patients who were prescribed opioids during the hospital stay and on discharge compared to those that did not receive opioids and to analyze opioid administration year over year. Finally, the study described normal practice for opioid prescribing during NSVD in the U.S. from January 1, 2014 through December 31, 2016.

The data source for Part I of the study is the Premier Healthcare Database (PHD). The PHD is the nation's largest hospital reported administrative database. Data are de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule per 45 CFR 164.506(d)(2)(ii)(B). The data set includes more than 768 million patient encounters (approximately 1 in 5 U.S. discharges) from an aggregate of 760 U.S. hospitals. See Figure 2. These data comprise inpatient and hospital-based outpatient encounters from all payers including Medicaid, and have been used for research purposes by academia, pharmaceutical companies, and federal agencies including CMS, FDA, the Agency for Healthcare Research and Quality and the National Institutes of Health (Premier, 2018).

Figure 2. Number of Premier Hospitals by Year Contributing Data

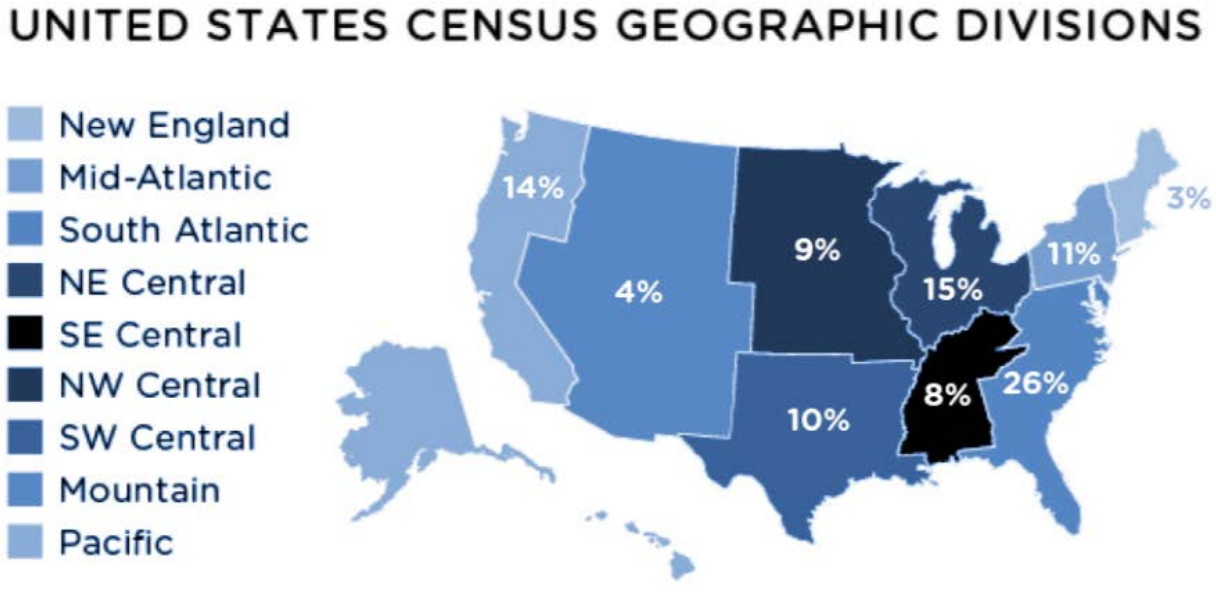


Source: Premier, 2018

"The Premier database contains data from standard hospital discharge files, including a patient's demographic and disease state, and information on billed services, including

medications, laboratory tests performed, diagnostics and therapeutic services in de-identified patient daily service records. In addition, information on hospital characteristics, including geographic location, bed size and teaching status, is also available" (Premier, 2018). The data are representative of the U.S. Census Geographic Divisions. See Figure 3.

Figure 3. Premier Data by Census Region



Source: Premier, 2018

c. Analysis Plan

Statistical integrity was ensured by an independent party. "Comparisons between patient and hospital characteristics for the hospitals that submit data to Premier and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) suggest that the patient populations are similar with regard to age, gender, length of

stay, mortality, primary discharge diagnosis and primary procedure groups" (Premier, 2018). Data were coded in a Statistical Analysis Software file format and all data are and will remain de-identified. Data coding, cleaning and formatting was conducted by an approved analyst from the Applied Sciences Division of Premier, Inc. The individuals working with the data were approved by the Chief Health Information Officer of Premier Applied Sciences with oversight from the Vice President of Premier Applied Sciences. A copy of the original data was converted into Excel files for extrapolation convenience. More detail on the data source is available in the statistical analysis plan (SAP) in Appendix A. Approval was obtained from the University of Chicago Illinois (UIC) Institutional Review Board and from Premier to designate Premier as a non-UIC study site (Appendix B).

An analytic dataset was created for Part I by utilizing de-identified patient data for inpatients aged 15-44 years hospitalized for NSVD for at least one service day as determined by the hospital charge master data during the years 2014-2016. The associated ICD-9 and ICD-10 codes for the study population can be found in Appendix A within the statistical analysis plan for Part I of the study. Exclusionary criteria included:

- Patients who have a contraindication to Nonsteroidal Anti-inflammatory Drugs (NSAIDs)
- Patients undergoing C-Section
- Patients with complicated deliveries (the SAP for specifics)
- Patients undergoing tubal ligation during the index hospitalization
- Death during the index hospitalization

The statistical analysis plan began by generating frequency tables for patient and hospital variables. Patient level variables included age group, marital status, race, ethnicity, payer type,

and length of stay. Hospital level variables included bed size, region, teaching status and urbanicity status, as defined by the U.S. Census.

Patient Characteristics for both Hospitalization and Day of Discharge

- Age Group
  - 15-18
  - 19-34
  - 35-44
- Marital Status
  - Married
  - Single
  - Other/Unknown
- Race
  - White
  - Black
  - Other/Unknown
- Ethnicity
  - Hispanic or Latino
  - Unknown
- Payor Type (n, %)
  - Medicaid
  - Commercial
  - Managed Care
  - Other
- Drug dependence (yes or no) as defined by one or more of the following:
  - ICD-9 diagnosis code 648.30 (Drug dependence of mother, unspecified as to episode of care or not applicable)

    OR
  - ICD-10 diagnosis code O99.32x (Drug use complicating pregnancy, childbirth, and the puerperium)

    OR
  - ICD-10 diagnosis code F11 (F11.1-F11.99) Opioid use disorder codes. One code or any combination of codes.

- Benzodiazepine used *on the same day as opioid* use (n, %) (see Appendix C for list of benzodiazepines)
    - Use of benzodiazepines
    - No use of benzodiazepines
- Year of discharge
    - 2014
    - 2015
    - 2016
- Route of administration for patients for whom an opioid was utilized (determined separately for both outcomes of interest)
    - Non-PO (IV, IM, Topical - one or any combination of the three routes)
    - PO (*per os*/oral) and non-PO
    - PO only

<u>Hospital Characteristics for both During Hospitalization and Day of Discharge</u>

- Length of stay (LOS)
    - Mean-Std Dev
    - Median
    - Interquartile Range (IQR)
    - Min-Max
- Bed size
    - <100
    - 100-199
    - 200-299
    - 300-499
    - 500+
- Nine Census Regions
    - New England
    - Mid-Atlantic
    - South Atlantic
    - NE Central
    - SE Central
    - NW Central
    - SW Central

        - Mountain
        - Pacific
    - Teaching Status
        - Teaching
        - Non-teaching
    - Urbanicity
        - Rural
        - Urban

The statistical methods started with a bivariate analysis of the study population to gain a better understanding of the patients meeting the selection criteria and included means, standard deviations, the median, and range. Categorical data were expressed as counts and percentages of patients within the corresponding categories. The bivariate analysis was performed for: 1) opioid administration during hospitalization and; 2) opioid administration on the diay of discharge. Fisher's tests were used to test for statistical differences in categorical variables, and T- or Wilcoxon Rank Sum tests were used for determination of statistical differences in continuous variables.

Co-variates with a p-value of 0.10 or greater were then included in the adjusted generalized linear mixed-effects model (GLMM). The GLMM was used to account for the possible clustering at the hospital level by including hospital as a random effect. Additionally, GLMM allows for non-normal distributions of dependent data. The GLMM approach was employed because of the interest in understanding the likelihood of each patient being administered an opioid and the relationship of the co-variates to that likelihood.

For each of the outcomes: 1) administration of opioid during the hospitalization and 2) administration of opioid on the day of discharge, GLMM models were constructed. Based on the bivariate analysis, individual variables with a significant relationship to the outcomes as defined

by a p-value of less than 0.10 were identified. These variables were then used to construct the multivariate regression model for each outcome. Model selection was determined using backward selection with a p-value threshold of 0.10 for variable inclusion in the final reported model. Variance Inflation Factors (VIF) were used to assess the absence of multicollinearity, with VIF values over 10 suggesting the presence of multicollinearity. Adjusted odds ratios were reported for each variable included in the model

As a secondary analysis, descriptive statistics were used to gain a better understanding of the routes of administration of opioids during the hospitalization and the day of discharge, including those patients utilizing an opioid via more than one route. Additionally, descriptive statistics were used to gain a better understanding of the trends over three years for the utilization of opioids during hospitalization. The categorical data were expressed as counts and percentage of patients in the category for each year.

Part II. E-Delphi Analysis:

In Part II of the study, the e-Delphi technique was employed to build consensus regarding recommendations for opioid orders during labor and delivery and on the day of discharge for NSVD patients. The purpose of Part II was to provide initial recommendations to stakeholders on appropriate opioid prescribing orders for NSVD patients. As previously noted, there are currently no national guidelines on opioid prescribing during labor and delivery. The CDC guidelines for opioid prescribing for chronic pain that were used as the basis for the proposed guidelines in this study are provided in Appendix C.

The Delphi technique was chosen as the consensus building technique for this study because it has been in use for more than fifty years and is an “accepted method for achieving

convergence of opinion concerning real-world knowledge solicited from experts within certain topic areas" (Hsu and Sandford, 2007). The advantages of the technique include anonymity of the panelists, an iterative process, controlled feedback, and statistical "group response" (von der Gracht, 2012). The Delphi process is iterative and typically takes two to three iterations; two rounds are optimal as additional rounds may cause panelist attrition (Hsu and Sandford, 2007; McMillan et al., 2016). For the purposes of this study, questions were submitted to the subject matter expert (SME) panel electronically, which has been referred to as the "e-Delphi technique." "The conduct of Delphi studies is amenable to the Internet platform where iterative collection of data can be made more efficient" (Donohoe et al., 2012).

Question composition was primarily quantitative in nature with an opportunity for qualitative input. Quantitative answers were expressed via a Likert scale with measures of central tendency reported (Hsu and Sandford, 2007). There is no standard guideline for defining consensus and researchers have used multiple approaches for measuring consensus including interquartile ranges (IQRs) and median scores (Hasson et al., 2000; Bentley et al., 2016). Using a four-point Likert scale, consensus was met if the majority of Delphi participants rated a guideline with a 3 or higher, with a median of 3.25 or higher, and the IQR was 1 or less (Hsu and Sandford, 2007; von der Gracht, 2012). The full e-Delphi protocol is available in Appendix D.

It was predetermined in the protocol that if consensus was not obtained in the first survey round, another round would be added, but there would be no more than three survey rounds. Consensus was not obtained in the initial two rounds, so a third round was necessary. Prior to each round of questions being submitted to the Panel, an amendment was submitted to the University of Illinois at Chicago (UIC) Institutional Review Board (IRB) for approval of the questions being submitted (Appendix E). The cadence of questioning and feedback was as follows:

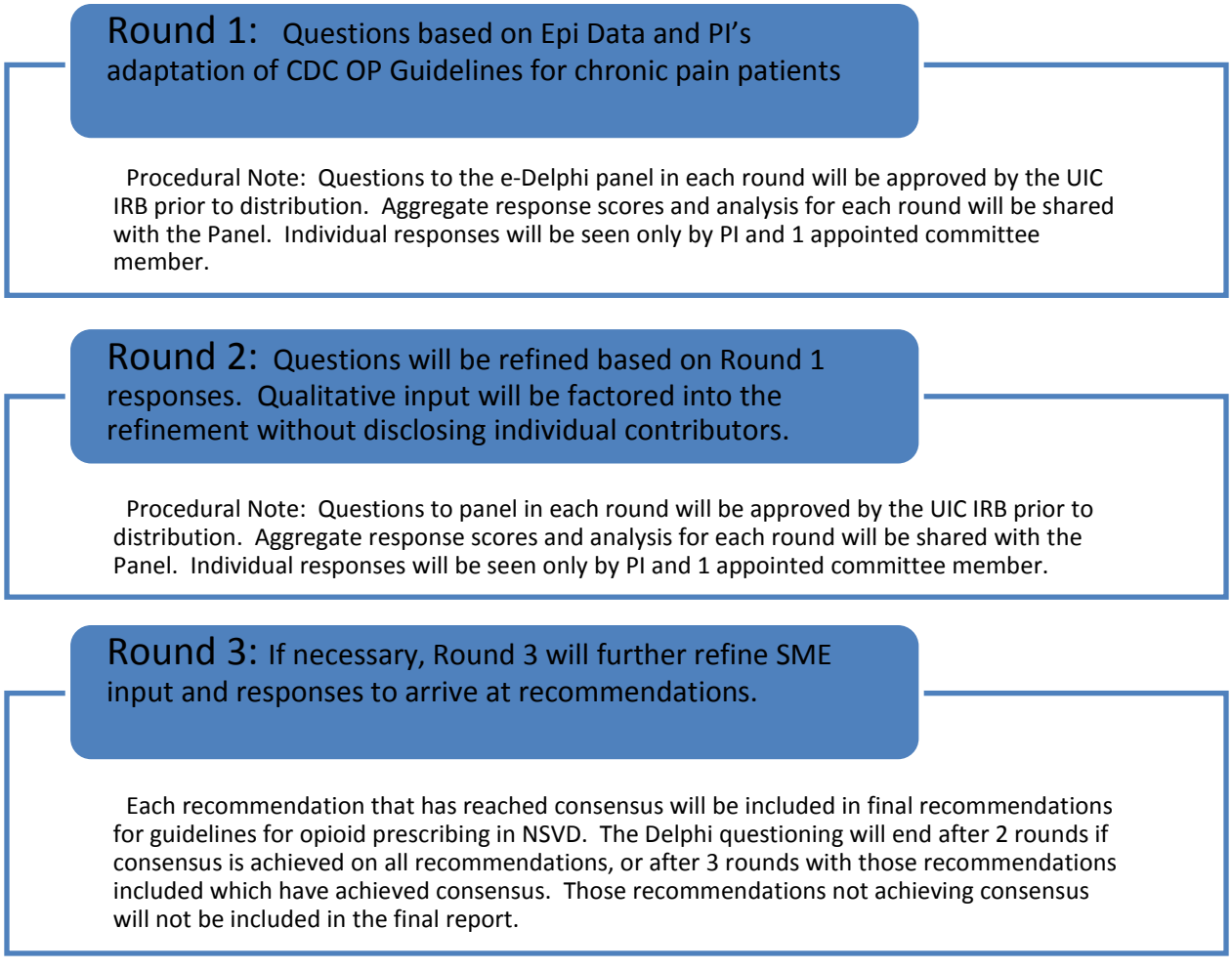
- The first round of questions was formulated by the principal investigator (PI) after Part I of the research had been conducted and analyzed. Questions were based on Part I study data and current CDC guidelines for providers prescribing opioids for chronic pain patients. The purpose of this round was twofold: To identify priority areas for formulating recommendations on opioid prescribing practices during labor and delivery for NSVD patients, and to respond to the PIs suggested adaptation of the CDC guidelines for NSVD opioid prescribing.
    - Feedback was returned to the panel reporting the median and IQR for the responses in the first round. A summation of qualitative comments (removing any identifiable details which would forfeit the anonymity of the participant providing the comment) was also provided.
    - The second round of questions was formulated and sent for IRB approval.
    - When approved, the questions were sent to the Delphi panel.
- The second round of questions were based on responses from the first round. The purpose of the second round was to resolve any outstanding questions/priorities from the epidemiological data and to further refine the adaptation of the CDC guidelines for the NSVD population. The questions were formulated by the PI with appropriate input from a Delphi-experienced member of the Dissertation Committee.
    - Feedback was returned to the panel reporting the median and IQR for the responses in the second round. A summation of qualitative comments (removing any identifiable details which would forfeit the

anonymity of the participant providing the comment) was also provided.

    - Since consensus was not achieved, a third round of questions was formulated and sent for IRB approval.
    - Once the last round of questions was approved, the third round of questions were sent to the Delphi panel.
- After analyzing the third round of questions, a summation was provided to panelists.

The survey process can be found in Figure 4 and survey instructions and results for each round are provided in Appendix F. Each round of questions was reviewed by a designated member of the Dissertation Committee with Delphi experience. Each survey link was emailed to participants with instructions for completion and return. All respondents received an individual code that only the PI and respondent knew; all data were password protected and stored electronically. The informed consent and non-disclosure agreements which were used can be found in Appendix D.

Figure 4. Survey Process for Rounds 1-3



The PI selected the Delphi panel. The invitation letter for the panel is provided in Appendix D. At the time of the surveying, all Delphi participants held a Doctor of Medicine or Doctor of Osteopathic Medicine degree and current license. Selection was based on the participants' ability to bring knowledge and experience to bear on the research question. The panel comprised fourteen subject matter experts which was within the IRB approved range of 12-20 participants. A smaller panel of SMEs was warranted as the subject matter experts will be

more homogenous in their expertise (Akins et al., 2005; Keeney et al., 2005; McMillan et al., 2016).

The SMEs were selected by the PI based on the following criteria:

- Informed consent and willingness to participate in two to three rounds of consensus building over the span of two to three months;
- Currently or previously served as a leader and/or practitioner in obstetrics and gynecology. Leader was defined as having influence in academic institutions, medical societies or policy groups and serving in a role to use said influence to affect change in the healthcare system. Examples included:
    - OBGYN physicians who had served on ACOG committees to influence guidelines and provide expert opinion;
    - OBGYN practitioners who had served in editorial roles or as reviewers for peer-reviewed publications;
- Interest in opioid prescribing and substance abuse or opioid use disorder, which was verified in the form of committee volunteering, public speaking or other professional endeavors;
- Willingness to "revise their initial or previous judgments for the purpose of reaching or attaining consensus" (Hsu and Sandford, 2007).

The SMEs completed and signed a basic intake form which reflected the above experience (Appendix D). The SMEs were also required to sign an informed consent document and non-disclosure agreement, and to allow their names to be cited as part of the process, although all responses were de-identified. The non-disclosure agreement will remain on file until after publication as unpublished data will be shared. PI work products related to Part II of the

study are kept on a password protected personal computer and will remain in possession of the PI.

d. Validity Considerations

This study is subject to several limitations. Part I of the study uses charge data from the hospital's billing system to identify use of opioids. If opioids were utilized and not coded, this would not be reflected in the data. Further, potential indications for opioid treatment were excluded, but there may be additional indications for appropriate opioid treatment that were not excluded or evaluated. Limitations were addressed through several rounds of review of the SAP over a period of four months and with the input of pharmacy, data and clinical experts including a nationally recognized maternal and child health substance abuse subject matter expert.

Part II of the study uses the Delphi Technique to build consensus through an electronic platform via the internet. The advantage of the anonymity of this approach also poses a limitation. There is a slight chance that the panelist who returned the survey is not the SME who was solicited for the study which implies the possibility of representation concerns. When designing the study, another potential limitation was using an internet-based platform as some users are more comfortable and adept at navigating this technology than others and this could hamper response rates and/or return times. This did not appear to be a challenge for the participants.

IV. MANUSCRIPTS

a. Commentary on the Manuscripts

This research required two components for it to be immediately actionable. Part I results are reported in the first manuscript and should they be published, will be the first data of their kind to be publicly available. The Journal of the American Medical Association (JAMA) was selected because its readership includes acute care providers and researchers who may read the work and decide to replicate this study in other inpatient populations to further eliminate unnecessary opioid exposures in other populations.

Part II of the study became the catalytic component of this research with national experts reviewing the data and making recommendations that can now be adopted or further refined, providing a facilitation mechanism for individual and systems level action. The intent is for the results of Part II to be submitted to Obstetrics and Gynecology, otherwise known as the Green Journal, because the manuscript provides recommendations that are best suited for the readership of this journal.

Proof of submission follows each respective manuscript.

b. Manuscript 1: Characterizing U.S. Opioid Administration for Women Undergoing Normal Spontaneous Vaginal Delivery

Prepared for submission to the Journal of the American Medical Association (JAMA)

Characterizing U.S. Opioid Administration for Women

Undergoing Uncomplicated Normal Spontaneous Vaginal Delivery

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Manuscript word count: 1200 words

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Key Points:

Question: What is the prevalence and characterization of opioid administration in uncomplicated Normal Spontaneous Vaginal Delivery patients?

Findings: In this retrospective observational study, 78.2% of women were administered an opioid. Protective characteristics included being white, married, commercially insured, and treated at a teaching facility.

Meaning: Labor and delivery is the number one reason for hospitalization in the U.S. and in uncomplicated deliveries the majority of women are exposed to an opioid.

Abstract:

Importance: The Centers for Disease Control and Prevention and other organizations have called for a review of clinical practice guidelines in response to the opioid epidemic, and although much of the prevention work to date has focused on the outpatient setting, the inpatient setting is getting more attention, with calls for avoidance of initiating opioid use, which could help prevent abuse, overdose and death.

Objective: Characterize opioid administration during hospitalization and on the day of discharge in the uncomplicated normal spontaneous vaginal delivery population.

Design and Setting: This retrospective observational study utilized data from a large, representative U.S. administrative hospital database to characterize the prevalence as well as the hospital and patient characteristics associated with opioid administration in uncomplicated normal spontaneous vaginal delivery. A bivariate analysis of opioid administration in normal spontaneous vaginal delivery patients was conducted to determine those predictors which reached a statistical significance threshold of 0.10 or

less. Variables reaching this threshold were retained and incorporated into a multilevel, multivariate logistic regression model. Adjusted odds ratios for the relationship between retained characteristics and opioid administration are presented.

Exposure: Opioid administered by any route during hospitalization and on day of discharge.

Main Outcomes: Among 49,133 normal spontaneous vaginal delivery patients, 78.2% received an opioid at some point during their hospitalization and 29.8% received an opioid specifically on the day of discharge. Being married, white, commercially insured, and treated at a teaching facility each proved to be independently protective.

Relevance: This analysis provides the first national characterization of opioid administration in a large, homogenous inpatient population.

Background:

Maternity care is the most common reason for hospitalization in the U.S.[1] Multiple data sources describe the incidence of opioid prescribing during reproductive years, pregnancy, and after discharge.[2–6] Very little has been published describing opioid prescribing in labor and delivery or on the day of discharge. Importantly, there is no national, all-payer, inpatient descriptive observational study on opioid initiation during labor and delivery. As agencies such as the Office for Women's Health (OWH) and professional organizations such as the American College of Obstetricians and Gynecologists (ACOG) continue to look for ways to prevent unnecessary opioid prescribing, the women undergoing labor and delivery present a relevant and important population to consider. This retrospective, descriptive, observational study purposed to characterize opioid administration in normal spontaneous vaginal delivery (NSVD) patients during hospitalization and on the day of discharge.

Methods:

The Premier Healthcare Database (PHD) contains hospital reported administrative data which are de-identified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rules. The data include more than 768 million patient encounters (approximately 1 in 5 U.S. discharges) from over 760 U.S. hospitals. These data comprise inpatient and hospital–based outpatient encounters from all payers including Medicaid, and have been used for research purposes by academia, pharmaceutical companies, and federal agencies including CMS, FDA, and the NIH.[7]

The study explored hospital and patient level characteristics for NSVD patients who were administered opioids at any point during their stay compared to those NSVD patients who were not administered an opioid. It also investigated the characteristics of women who were administered an opioid on the day of discharge compared to those who were not. Inclusion criteria included admitted women aged 15-44 years

hospitalized for NSVD from January 1, 2014 through December 31, 2016 based on an ICD-9 code of 650 or an ICD-10 code of O80, as determined by hospital charge master data. Exclusion criteria were aimed at achieving an uncomplicated NSVD patient population. For a full description of exclusion criteria see the online-only material, eTable 1 and eFigure 1.

The prevalence of patients receiving opioids at any point during their visit and upon discharge was calculated. Descriptive statistics were generated to document the characteristics of the patients receiving opioids during their inpatient labor and delivery visit or upon discharge. Categorical data were expressed as counts and percentages of patients within the corresponding categories. Patient level variables included age group, marital status, race, ethnicity, payer type, and length of stay. Hospital level variables included bed size, geographic region, teaching status, and urbanicity status, as defined by the U.S. Census. For a full listing of patient and hospital variables see the online-only material, e-Table 3.

Bivariate analysis was used to determine predictors of opioid administration at each time point. Chi-square tests were used to test for statistical differences between NSVD patients administered opioids versus those who were not. Covariates with a p- value of 0.10 or less were entered into a multilevel, multivariate logistic regression model using generalized linear mixed-effects modeling (GLMM). GLMM was used to estimate the adjusted odds of the patient receiving an opioid (at any point during visit/upon discharge) and to account for the clustering of patients within hospitals as well as for the non-normal distributions of dependent data.

Results:

The population of interest comprised 106,518 NSVD patients. After applying the exclusion criteria, there were 49,133 NSVD patients. Among those NSVD patients, 78.2% received an opioid at some point during their hospitalization and 29.8% received an opioid on the day of discharge (Table 1). Tables 2 and 3 provide the adjusted odds ratios for the relationship between patient and hospital characteristics and the likelihood of receiving an opioid during hospitalization (Table 2) and the likelihood of receiving an opioid on the day of discharge (Table 3). The odds for a black patient being administered an opioid during hospitalization were 42% higher than the odds for a white patient. The odds for a Medicaid patient being administered an opioid during hospitalization were 36% higher than the odds for a commercially insured patient. The odds for a patient being administered an opioid at a teaching hospital were 20% lower than the odds for patients in a non-teaching facility.

Regarding the routes of administration and the trends of utilization during hospitalization, there was little change year over year. For data on opioid administration during day of discharge over the three years, see the online-only material, eTable 2.

Discussion:

As in any procedure, a patient's perception of pain and their corresponding response will differ. Hence, there is an understanding in the medical community that uncomplicated vaginal births should, in most cases, require a different pain management approach than complicated births. Uncomplicated NSVD patients are an appropriate population to consider as healthcare leadership in the inpatient setting seek to

provide clinical guidance for opioid prescribing in non-surgical populations. These data are timely given that prescribers and hospital organizations are looking for ways to diagnose and evaluate their own systems of care relative to their respective roles in reducing the prevalence of opioid prescribing, abuse, overdose and diversion. Because there are no prevalence data, there likely has been no perceived need for national pain management guidelines related to opioid administration during NSVD procedures. The ACOG Committee on Obstetric Practice, in conjunction with the American College of Nurse-Midwives published a Committee Opinion in February of 2017 entitled, "Approaches to Limit Intervention during Labor and Birth."[8] The Committee performed an evidence review in part to "minimize the intervention for appropriate women who are in spontaneous labor at term. The desire to avoid unnecessary interventions during labor and birth is shared by health care providers and pregnant women."[8] Regardless of differing and distinguishing delivery characteristics, there is no specific guidance for pain management and narcotic use relative to complicated vs. uncomplicated births.[9] This study provides the prevalence data for opioid administration during hospitalization and on the day of discharge for uncomplicated NSVD patients.

Limitations:

Comparisons of hospital characteristics between the hospitals submitting data to PHD and the 2016 member hospitals of the American Hospital Association (AHA) are similar in distribution, although the AHA has a greater number of smaller hospitals.[7] This study uses administrative data which comes from U.S. hospitals and is based on charge master data, thus including only aspects of care for which the patient was charged and not necessarily everything the patient received. Additionally, while several potential indications for opioid treatment were excluded, there may be additional indications for appropriate opioid treatment which may have been overlooked in the exclusion parameters.

Conclusions:

These data illustrate that both patient and hospital characteristics may have a significant impact on opioid administration during NSVD procedures. As clinical and administrative leaders look for additional ways to prevent abuse, overdose and death related to opioids, these data may provide a starting point for discussions regarding opioid prescribing guidelines for inpatient populations such as NSVD patients. On a national level, the Office for Women's Health has called all stakeholders to "foster a national conversation on best practices to prevent, diagnose and treat opioid-related hazards and death among women."[10] Actionable recommendations based on this data may serve to springboard the work for which the OWH, the CDC, ACOG and others are calling.

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Tables

Table 1: Prevalence of Opioid Administration for Normal Spontaneous Vaginal Delivery (NSVD) Patients During Hospitalization and on Day of Discharge (January 1, 2014 - December 31, 2016)

Dis-charge Year	Number of Patients	NSVD Encounters with Opioid Administration During Hospitalization (any route) (n, %)	NSVD Encounters with No Opioid Administration During Hospitalization (any route) (n, %)	NSVD Encounters with Opioid Administration on Day of Discharge (any route) (n, %)	NSVD Encounters without Opioid Administration on Day of Discharge (any route), (n %)
2014	17,357	13,575 (78.2%)	3,782 (21.8%)	5,291 (30.5%)	12,066 (69.5%)
2015	17,188	13,532 (78.7%)	3,656 (21.3%)	5,238 (30.5%)	11,950 (69.5%)
2016	14,588	11,325 (77.6%)	3,263 (22.4%)	4,106 (28.1%)	10,482 (71.9%)
Total	49,133	N= 38,432 (78.2%)	N= 10,701 (21.8%)	N= 14,635 (29.8%)	N= 34,498 (70.2%)

Key: NSVD: normal spontaneous vaginal delivery

Table 2. Percents, and Adjusted Odds Ratios for the Relationship between Patient and Hospital Characteristics and the Receipt of an Opioid During Hospitalization for Normal Spontaneous Vaginal Delivery (NSVD) Patients (January 1, 2014 - December 31, 2016)

Effects	Description	% of Patients Administered Opioid During Hospitalization	Adjusted Odds Ratio	95% Wald Lower Confidence	95% Wald Upper Confidence
Age	19-34 (ref 15-18)	78.16	0.93	0.81	1.07
	35-44 (ref 15-18)	70.51	0.73	0.59	0.89
Marital Status	Married (ref Single)	74.62	0.68	0.64	0.72
	Other-Unknown status (ref Single)	70.50	0.79	0.70	0.89
Race	Black (ref White)	85.41	1.42	1.31	1.54

	Other (ref White)	73.56	0.92	0.86	0.97
Payor	Managed Care (ref Commercial - Indemnity)	74.34	1.07	0.96	1.21
	Medicaid (ref Commercial - Indemnity)	81.11	1.36	1.21	1.51
	Other Payor (ref Commercial - Indemnity)	76.93	1.04	0.91	1.19
Hospital Geographic Region	East North Central (ref West South Central)	72.01	0.46	0.32	0.66
	East South Central (ref West South Central)	85.20	1.10	0.71	1.71
	Middle Atlantic (ref West South Central)	57.49	0.30	0.20	0.46
	Mountain (ref West South Central)	83.50	0.80	0.51	1.24
	New England (ref West South Central)	62.65	0.34	0.19	0.62
	Pacific (ref West South Central)	75.12	0.52	0.38	0.73
	South Atlantic (ref West South Central)	82.83	0.78	0.58	1.05
	West North Central (ref West South Central)	81.71	1.06	0.63	1.78
Hospital Teaching Status	Teaching (ref Non-Teaching)	73.93	0.80	0.65	0.99

Key: ref: reference group

Note: All variables in Table 2 were adjusted for all other variables in Table 2.

Table 3: Percents, and Adjusted Odds Ratios for the Relationship between Patient and Hospital Characteristics and the Receipt of an Opioid on the Day of Discharge for Normal Spontaneous Vaginal Delivery (NSVD) Patients (January 1, 2014- December 31, 2016)

Effects	Description	% of Patients Administered an Opioid on Day of Discharge	Adjusted Odds Ratio	95% Wald Lower Confidence	95% Wald Upper Confidence
Age	19-34 (ref 15-18)	30.11	1.65	1.46	1.86
	35-44 (ref 15-18)	21.84	1.27	1.04	1.54
Marital Status	Married (ref Single)	25.58	0.77	0.73	0.81
	Other-Unknown status (ref Single)	24.35	0.90	0.80	1.00
Race	Black (ref White)	39.15	1.27	1.19	1.36
	Other (ref White)	24.74	0.86	0.81	0.92
Ethnicity	Hispanic (ref non-Hispanic)	25.54	0.86	0.81	0.92
Payor	Managed Care (ref Commercial - Indemnity)	23.98	1.10	0.98	1.23
	Medicaid (ref Commercial - Indemnity)	34.04	1.71	1.53	1.90
	Other Payor (ref Commercial - Indemnity)	25.72	1.22	1.07	1.40
Hospital Geographic Region	East North Central (ref West South Central)	23.86	0.44	0.32	0.60
	East South Central (ref West South Central)	38.92	0.83	0.57	1.21
	Middle Atlantic (ref West South Central)	13.55	0.24	0.17	0.36
	Mountain (ref West South Central)	32.39	0.65	0.44	0.96
	New England (ref West South Central)	12.45	0.19	0.11	0.33

	Pacific (ref West South Central)	27.15	0.57	0.43	0.77
	South Atlantic (ref West South Central)	32.11	0.62	0.48	0.80
	West North Central (ref West South Central)	34.44	0.94	0.60	1.46
Hospital Teaching Status	Teaching (ref Non-teaching)	25.54	0.79	0.65	0.95

Key: ref: reference group

Note: All variables in Table 3 were adjusted for all other variables in Table 3.

Online-Only Material

eTable 1: Exclusion Criteria: ICD-9, ICD-10, and HCPCS Codes for Exclusions

Exclusions summary:

- Patients with a contraindication to NSAIDs (see eTable 2 for definition).
- Patients undergoing caesarean delivery (see eTable 2 for definition).
- Patients with selected complicated deliveries (see eTable 2 for definition).
- Patients undergoing tubal ligation during the index hospitalization (see eTable 2 for definition).
- Death during the index hospitalization.
- Patients from hospitals with volumes below 36 deliveries within the three-year study window.
- Patients from hospitals that do not have at least one delivery in each of the three calendar years (2014-2016).

ICD-9 DM Code	Code Description	Grouping
580 – 587	Renal disease	NSAID contraindication
287.3X – 287.4X	Thrombocytopenia	NSAID contraindication
286	Coagulation disorders	NSAID contraindication
649.3X	Coagulation defects complicating pregnancy, childbirth, or the puerperium	NSAID contraindication
642.1X	Hypertension secondary to renal disease complicating pregnancy childbirth and the puerperium	NSAID contraindication
646.2X	Unspecified renal disease in pregnancy without mention of hypertension	NSAID contraindication
649.8X	Onset (spontaneous) of labor after 37 completed weeks of gestation but before 39 completed weeks' gestation, with delivery by (planned)	Caesarean delivery

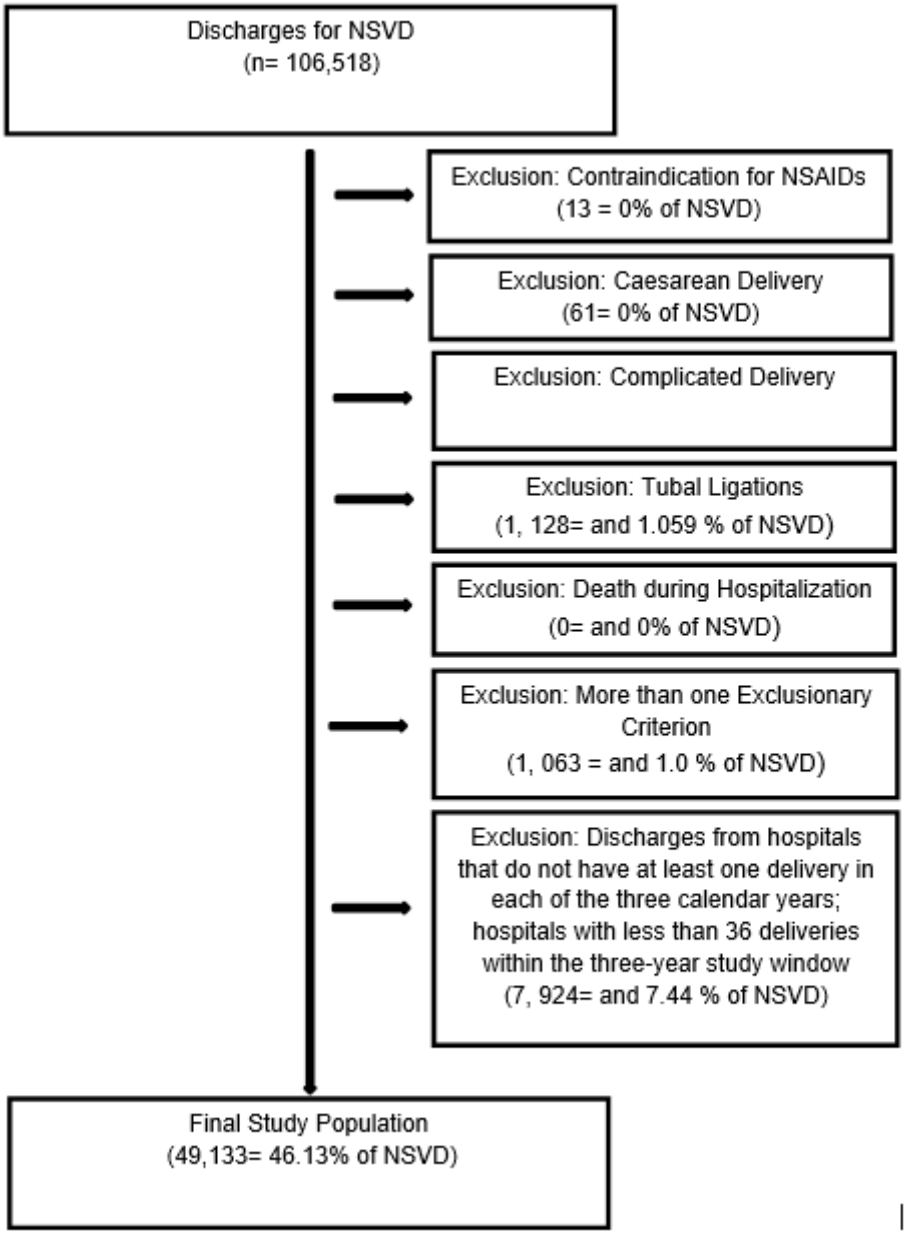
	cesarean section	
669.7	Cesarean delivery without mention of indication	Caesarean delivery
651 – 659	Care in Pregnancy, Labor, And Delivery	Complicated delivery
630 – 639	Ectopic and Molar Pregnancy and Other Pregnancy with Abortive Outcome	Complicated delivery
660 – 669	Complications Occurring Mainly in the course of Labor and Delivery	Complicated delivery
66.2X – 66.3X	Bilateral Endoscopic Destruction or Occlusion of Fallopian Tubes	Tubal ligation
ICD-9 Procedure Code	**Code Description**	**Grouping**
74	Cesarean Section and Removal of Fetus	Caesarean delivery
72	Forceps, Vacuum, And Breech Delivery	Complicated delivery
73.0X-73.4X, 73.51, 73.6X-73.9X	Other Procedures Inducing or Assisting Delivery	Complicated delivery
75.0X-75.33, 75.35-75.99	Other Obstetric Operations	Complicated delivery
ICD-10 Code	**Code Description**	**Grouping**
N00 – N19	Renal disease	NSAID contraindication
D69.3 – D69.6	Thrombocytopenia	NSAID contraindication
D65 – D68	Coagulation disorders	NSAID contraindication
O26.83	Pregnancy related renal disease	NSAID contraindication
O99.1	Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism complicating pregnancy, childbirth and the puerperium	NSAID contraindication
O82	Encounter for cesarean delivery without indication	Caesarean delivery

O00 – O08	Pregnancy with abortive outcome	Complicated delivery
O61 – O71	Complications of labor and delivery	Complicated delivery
O75.4 – O75.8	Complications of labor and delivery	Complicated delivery
0W8NXZZ	Division of Female Perineum, External Approach	Complicated delivery
0UL7	Fallopian Tubes, Bilateral	Tubal ligation
102	Obstetrics, Pregnancy, Change	Complicated delivery
109	Obstetrics, Pregnancy, Drainage	Complicated delivery
10A	Obstetrics, Pregnancy, Abortion	Complicated delivery
10D	Obstetrics, Pregnancy, Extraction	Caesarean delivery
10H	Obstetrics, Pregnancy, Insertion	Complicated delivery
10J	Obstetrics, Pregnancy, Inspection	Complicated delivery
10P	Obstetrics, Pregnancy, Removal	Complicated delivery
10Q	Obstetrics, Pregnancy, Repair	Complicated delivery
10S	Obstetrics, Pregnancy, Reposition	Complicated delivery
10T	Obstetrics, Pregnancy, Resection	Complicated delivery
10Y	Obstetrics, Pregnancy, Transplantation	Complicated delivery
HCPC Code	**Code Description**	**Grouping**
1961	Anesthesia for Cesarean Delivery	Caesarean delivery
1963	Anesthesia for Cesarean Hysterectomy without any Labor Analgesia/Anesthesia Care	Caesarean delivery
1968	Anesthesia for Cesarean Delivery Following Neuraxial Labor Analgesia/Anesthesia	Caesarean delivery
1969	Anesthesia for Cesarean	Caesarean delivery

	Hysterectomy Following Neuraxial Labor Analgesia/Anesthesia	
59510	Routine Obstetric Care Including Antepartum Care, Cesarean Delivery and Postpartum Care	Caesarean delivery
59514	Cesarean Delivery Only	Caesarean delivery
59515	Cesarean Delivery Only; Including Postpartum Care	Caesarean delivery
59618	Routine Obstetric Care Including Antepartum Care, Cesarean Delivery, and Postpartum Care, Following Attempted Vaginal Delivery After Previous Cesarean Delivery	Caesarean delivery
59620	Cesarean Delivery Only, Following Attempted Vaginal Delivery After Previous Cesarean Delivery	Caesarean delivery
59622	Cesarean Delivery Only, Following Attempted Vaginal Delivery After Previous Cesarean Delivery; Including Postpartum Care	Caesarean delivery
59300	Episiotomy or Vaginal Repair, by other than Attending	Complicated delivery
58600 - 58615	Tubal Ligation	Tubal ligation

Key: ICD: International Classification of Diseases; HCPC: Healthcare Common Procedure Coding System

eFigure 1: Study Population Identification



Key: NSVD: normal spontaneous vaginal delivery; NSAIDs: nonsteroidal anti-inflammatory drugs

e-Table 2. Opioid Administration by Route During Hospitalization in U.S. NSVD Patients January 1, 2014-December 31, 2016

Population	Overall (%)	2014 (%)	2015 (%)	2016 (%)
NSVD, n	49,133	17,357	17,188	14,588
NSVD, without any opioid, n (%)	10,701 (21.8%)	3,782 (21.8%)	3,656 (21.3%)	3,263 (22.4%)
NSVD with any opioid during hospitalization, n (%)	38, 432 (78.2%)	13,575 (78.2%)	13,532 (78.7%)	11,325 (77.6%)
NSVD with only non-PO opioid during hospitalization, n (%)	14,673 (29.9%)	4,957 (28.6%)	5,078 (29.5%)	4,638 (31.8%)
NSVD with only PO opioid during hospitalization, n (%)	7,760 (15.8%)	2,841 (16.4%)	2,775 (16.1%)	2,144 (14.7%)
NSVD with both PO and non-PO opioid during hospitalization, n (%)	15,999 (32.6%)	5,777 (33.3%)	5,679 (33.0%)	4,543 (31.1%)

Key: NSVD: normal spontaneous vaginal delivery; PO: *per os*/oral

e-Table 3. Patient and Hospital Variables for Each Patient Discharge for Opioid Administration During Hospitalization and on Day of Discharge

Patient Variables for Each Discharge Included in Bivariate Analysis	
Age	15-18
	19-34
	35-44
Marital Status	Married
	Single
	Other/Unknown

Race	White
	Black
	Other/Unknown
Ethnicity	Hispanic or Latino
	Unknown
Payor Type	Medicaid
	Commercial
	Managed Care
	Other
Drug Dependence (as defined by ICD-9 Diagnoses Codes 648.3 or ICD-10 Diagnoses Codes O99.32x or F11 (F11.1-F11.99)	Yes
	No
Benzodiazepine used on Same Day as Opioid	Benzodiazepine used on Same Day
	No use of benzodiazepines
Year of Discharge	2014
	2015
	2016
Route of Administration of Opioid (determined separately for both during hospitalization and on day of discharge)	Non-PO (Iv, IM, Topical – one or any combination of the three routes)
	PO and non- PO
	PO only
Hospital Variables for Each Discharge Included in Bivariate Analysis	
LOS	Mean-Std Dev
	Median
	IQR
	Min/Max
Bed Size	<100
	100-199

	200-299
	300-499
	500+
Nine Census Regions	New England
	Mid-Atlantic
	South Atlantic
	NE Central
	SE Central
	NW Central
	SW Central
	Mountain
	Pacific
Teaching Status	Teaching
	Non-teaching
Urbanicity	Rural
	Urban

Proof of Submission: Detailed Status Information

Manuscript #	JAMA18-3719
Current Revision #	0
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Title	Characterizing U.S. Opioid Administration for Women Undergoing Uncomplicated Normal Spontaneous Vaginal Delivery
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Coauthors	J. Mills (corr_auth) , Mimi Huizinga , Scott Robinson , Teresa Davis , Kee Chan
Group Authorship	Group Name: NSVD Opioid Study

c. Manuscript 2: Opioid Prescribing Guidelines for Uncomplicated Normal Spontaneous Vaginal Birth Patients During Hospitalization and on the Day of Discharge

Prepared for submission to Obstetrics and Gynecology (The Green Journal)

Opioid Prescribing Guidelines for Uncomplicated Normal Spontaneous Vaginal Birth Patients During Hospitalization and on the Day of Discharge

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Short title: Expert Guidelines: Opioid Prescribing in NSVD

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leadership practice work in this very arena. Special thanks to Jeanne Mahoney, Mimi Huizinga, Bruce Bowdy, Suzanne Coleman and Tony Dubitsky for their advice and counsel in this research.

Precis: New Expert Guidelines Developed for Informing Opioid Prescribing in Uncomplicated Normal Spontaneous Vaginal Delivery

Abstract:

Maternity care is the most common reason for hospitalization in the US. While the Centers for Disease Control and Prevention (CDC) has urged clinicians to improve opioid prescribing behavior, there are no clinical practice guidelines for opioid prescribing during labor and delivery and at discharge for uncomplicated Normal Spontaneous Vaginal Delivery (NSVD) patients. The most recent national NSVD pain management recommendations, from the American College of Obstetricians and Gynecologists (ACOG), are general. Given the national opioid epidemic and the escalating numbers of women who have overdosed or died, it may be time to reevaluate prescribing guidelines in NSVD. There are new national data on the prevalence of opioid prescribing in uncomplicated NSVD patients, which helped frame an adaptation of the CDC's chronic pain guidelines. The adapted guidelines were then used to survey a Delphi panel of leading obstetricians/gynecologists to develop consensus on guidelines for prescribing opioids for women during labor and delivery and on the day of discharge. The panel was surveyed for three rounds, resulting in draft guidelines for appropriate opioid prescribing for the uncomplicated NSVD population. Recommendations informed by national data on current opioid prescribing for uncomplicated NSVD patients might reduce unnecessary exposure to opioids in maternal and newborn populations and reduce the opportunity for opioid diversion. Leaders in public health policy, clinical practice, and hospital administration have an opportunity to deploy newly developed recommendations in the advancement of prevention efforts to address the U.S. opioid crisis.

Background:

Opioid related deaths are rising in the U.S. and contribute to sixty-six percent of drug overdose deaths.[1,2] Agency and organizational leaders are looking for opportunities to employ

primary, secondary, and tertiary prevention strategies. For leaders who have clinical and administrative responsibility across state lines, these prevention efforts may be more difficult because of significant variation in opioid prescribing patterns. Reported prescribing variations do not correlate with patient acute and chronic pain levels and providers in the highest opioid prescribing U.S. states write three times the prescriptions for opioids as prescribers in the lowest opioid prescribing states.[3,4] Providers in both inpatient and outpatient settings might unknowingly contribute to high prescribing rates due to a lack of awareness about their own prescribing patterns compared to their peers. Further, recent national public opinion data show U.S. citizens place the majority of responsibility for the growing opioid epidemic on inappropriate physician prescribing, even though there are several significant contributing factors to the epidemic.[5]

Responding to the opioid epidemic, the CDC published guidelines for outpatient opioid prescribing for chronic pain patients in 2016. Shortly after the guidelines were published, Dr. Tom Frieden, CDC Director, published an editorial in the New England Journal of Medicine acknowledging that, "Although the guideline addresses chronic pain, many patients become addicted to opioids after being treated for acute pain."[6] Thought leaders in public health and policy have called for a more comprehensive view of opioid prescribing to include the inpatient setting and have reiterated that opioid exposure avoidance is critical in prevention efforts.[7–9]

The literature points to the significance of receiving an opioid as an inpatient and how that portends for continued prescribing post discharge. In opioid naïve patients (patients who have not been exposed to an opioid), opioid receipt at hospital discharge increases future chronic opioid use.[10] As noted by Lail et al. in the Canadian Journal of Hospital Pharmacy, "Harms associated with prescription opioids are a major and increasing public health concern. Prescribing opioids for inpatients may contribute to the problem, especially if primary care

practitioners continue opioid therapy that is initiated in the hospital".[11] Both the inpatient setting and the discharge disposition play a role in patients' exposure to opioids and subsequent risk for abuse, overdose, addiction and possible death.

When considering inpatient populations that might be targeted for reducing opioid exposure, the NSVD population is a strong contender for several reasons. First, labor and delivery is the most common reason for hospitalization and therefore has a significant impact on pharmacy supply, demand, and diversion. Second, a subset of this population, NSVD patients without complications, are more homogenous in their presentation and treatment than other patient groups since they are more similar in age, presentation, and outcomes relative to their diagnosis codes. Third, the NSVD population is typically discharged home to care for an infant, meaning two patients are exposed to the opioid versus just one. Fourth, improving the health of mothers, infants and children is a Federal priority and part of the U.S. public health goals.[12]

Labor and delivery are times of acute pain, and while some opioid use may be appropriate, other pharmacologic approaches could be considered in low risk, straightforward procedures such as uncomplicated NSVD. The American College of Obstetricians and Gynecologists (ACOG) has stated that pain management during delivery is appropriate, and providers should consider both pharmacologic and non-pharmacologic interventions. However, there is no direct guidance for inpatient opioid orders in the NSVD population, nor are there national data for benchmarking. The most relevant guidance is a 2017 ACOG committee opinion based on fourteen-year-old data stating, "in the hospital setting, pharmacologic analgesia should be available for all women in labor who desire medication."[13]

The objective of this study was to use expert input and recently generated national observational data to inform opioid prescribing recommendations in the uncomplicated NSVD patient population. The findings from this study may benefit multiple stakeholders and create a

more thoughtful approach to opioid prescribing for women during labor and delivery and at postpartum discharge.

Methods:

A panel of OB-GYN clinical leaders was invited to participate in a Delphi panel for three rounds of surveying from December 2017 through February 2018. The purpose of the panel was to provide consensus on eight recommendations for opioid prescribing guidelines for labor and delivery and on the day of discharge for the uncomplicated NSVD population. The Delphi technique was chosen because it is a consensus building technique with a fifty-year history as an appropriate method for assimilating and integrating opinions from panelists who have in-depth knowledge within a given topic.[14] The advantages of the technique include panelist anonymity, and a statistical group response from an iterative process with controlled feedback.[15] Because questions were submitted to the Delphi panel electronically and responses were also gathered electronically, this study utilized what has been referred to as the e-Delphi approach.[16]

The protocol required that all e-Delphi participants held a current MD or DO license; selection was based on participants' ability to bring clinical knowledge and leadership experience to the research question. The panel comprised fourteen participants (Table 2). This panel size was chosen because the participants were homogenous in their expertise and the literature suggests that size of the panel should correlate to goals of the panel and the homogeneity needed.[17–19] The panelists were selected by the principal investigator (PI) based on the following criteria:

- Informed consent and willingness to participate in two to three rounds of consensus building over the span of 2-3 months;
- Currently and/or previously served as a leader and/or practitioner in obstetrics and gynecology. Leader was defined as having influence in

academic institutions, medical societies or policy groups and serving in a role to use that influence to affect change in the healthcare system.

- Interest in opioid prescribing and substance abuse or opioid use disorder (OUD), which was verified in the form of serving on professional committees, public speaking or other professional endeavors;
- Willingness to revise initial responses for the purpose of reaching consensus.[14]

Prior to recruiting the e-Delphi panelists, the researchers conducted a national observational study to characterize opioid administration in uncomplicated NSVD patients during hospitalization and on the day of discharge. Data for the study were derived and analyzed from the Premier Healthcare Database (PHD), which is the nation's largest hospital-reported administrative database. The data were de-identified in accordance with the HIPAA Privacy Rule per 45 CFR 164.506(d)(2)(ii)(B) and included more than 768 million patient encounters (approximately 1 in 5 U.S. discharges) from over 760 U.S. hospitals. These data comprise inpatient and hospital–based outpatient encounters from all payers including Medicaid, and have been used for research purposes by academia, pharmaceutical companies, and U.S. Department of Health and Human Services agencies.[20]

The primary outcome of interest was whether an uncomplicated NSVD patient received an opioid during hospitalization and/or on the day of discharge from January 1, 2014 through December 31, 2016. The recently generated data submitted to the Delphi panelists showed a 78.2% prevalence of opioid administration in uncomplicated NSVD patients during hospitalization and a 29.8% prevalence on the day of discharge (Mills unpublished data, 2018). After reviewing the data, the panelists were surveyed to assess the level of their agreement on eight proposed NSVD opioid prescribing guidelines to be applied during hospitalization and on

the day of discharge. These initial eight guidelines were adapted from the CDC chronic pain opioid prescribing guidelines.[21] The CDC guidelines from which the adapted guidelines originated can be found at https://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm.

The e-Delphi panelists were presented a summary of the national data which described opioid administration prevalence in uncomplicated NSVD patients in U.S. hospitals. The panelists were then individually surveyed to assess their respective agreement regarding each of the eight drafted guidelines. Survey question composition was quantitative in nature with an opportunity for qualitative input following review of each of the eight proposed guidelines. The quantitative answers were expressed via Likert scale with measures of central tendency reported.[14] There is no standard guideline for defining consensus; researchers have used multiple approaches including interquartile ranges (IQRs) and median scores.[22,23] Using a four-point Likert scale, consensus was met for each guideline if the majority of Delphi participants rated the guideline with a three or higher, with a median of 3.25 or higher, and the IQR was 1 or less.[14,15] Before each survey round commenced, a survey link was emailed to participants with instructions for completion and return. All respondents received an individual code that only the PI and respondent knew; all data were password protected and stored electronically.

The protocol stated that if consensus was not obtained in the first survey round, another round would be added, but there would be no more than three survey rounds. In this study, consensus was not obtained for all guidelines in the initial two rounds, so a third round was necessary. The first round of survey questions was based on the opioid administration prevalence data and the adapted CDC guidelines for providers prescribing opioids for chronic pain. The questions were submitted to the de-identified panelists via Survey Monkey™. The primary purpose of this round was to identify priority areas for formulating recommendations on opioid prescribing practices during labor and delivery for NSVD patients and to respond to the

suggested adaptation of the CDC guidelines for NSVD opioid prescribing. The patient population was defined as NSVD patients without complications (tubal ligation, patients with a contraindication to NSAIDs, patients undergoing caesarean delivery, deliveries with fetal distress, episiotomy, use of forceps/assisted delivery, any level of laceration). Two subsequent rounds of surveying occurred. See Figure 1 for a description of the e-Delphi process.

Institutional Review Board (IRB) approval for this project was secured through the University of Illinois, Chicago.

Results:

All fourteen panelists participated in the three rounds of surveying and scored each adapted guideline for every round of surveying, resulting in zero attrition and a 100% response rate over three months. The final adapted guidelines for opioid prescribing for uncomplicated NSVD patients during labor, delivery and on the day of discharge are provided in Table 1, which also illustrates the round in which consensus was achieved, indicating how quickly agreement was obtained. Consensus was reached for seven of the eight proposed guidelines after three rounds of surveying.

Discussion:

Despite local and national efforts to reduce opioid use and abuse, there has been an increase in prevalence for all populations, including pregnant women and women of reproductive age.[24] Approximately 2.7 million vaginal deliveries occurred in the U.S. during 2015.[25] New national data show that approximately 79% of women undergoing uncomplicated NSVD are administered an opioid during hospitalization and almost 30% are administered an opioid on the day of discharge (Mills unpublished data, 2018). The size of this population suggests that additional consideration be given with respect to whether and how opioids are used during labor

and delivery and on the day of discharge. As leaders in agencies such as the CDC and the Office for Women's Health (OWH) and professional organizations like ACOG continue to look for ways to prevent unnecessary opioid use, abuse, overdose and death, the uncomplicated NSVD population is a relevant and important population to consider. Further, because of the opioid epidemic, it is incumbent on leaders in clinical practice, public health policy, and hospital administration to consider their respective formularies, protocols, policies and prescribing disciplines for this class of drugs.[26,27]

The seven proposed guidelines in Table 1 could serve as a starting point for obstetric health clinicians as they consider practical ways to limit opioid exposure for their patients. While consensus was not achieved for Guideline 5, it received considerable qualitative commentary. Based on the comments and divergent scoring, it is likely that consensus would not have been reached even with additional rounds. The qualitative commentary showed that validation of this guideline came from panelists who either wanted more support and accountability for providers, and/or those who believed that opioid use should be treated as a medical condition. Further, panelists commented that pain management personnel and neonatology should be consulted regarding opioid use because of its impact on the approach providers use to care for both the mother and baby. Those who did not endorse Guideline 5 commented that this guideline places an onerous burden on the physician and is unrealistic. Further, in some communities, it may not be feasible to involve other clinicians to counsel the patient on neonatal abstinence syndrome (NAS) and other risks associated with opioid utilization.

Addressing the opioid epidemic presents many challenges and there is no singular solution. However, national data indicates that receiving a prescription for opioids is the harbinger for many who eventually suffer from opioid use disorder. The results of this study may be used by healthcare leaders and other stakeholders as the basis for a final set of guidelines for

opioid prescribing for the uncomplicated NSVD population. Similar approaches may be considered for the complicated NSVD and caesarean section populations.

Limitations:

There are several limitations to this study. First, the panel only comprised physicians; midwives and other clinicians were not represented. Second, the proposed guidelines were adapted from existing CDC guidelines for a different patient population and did not originate from the panelists themselves. Third, a more robust and cohesive set of recommendations may have been achieved if the process for consensus building had been conducted in a live versus online format, as it would have allowed for more back and forth between the leader practitioners. Fourth, the guidelines are specifically for uncomplicated NSVD patients, yet, during the e-Delphi process, a few of the panelists questioned what should be done when there are lacerations or other complications. Although these exclusions were included in the instructions, it may be that some panelists thought they were voting on NSVD guidelines in general versus guidelines for uncomplicated NSVD deliveries. Finally, the advantage of the anonymity of this approach also poses a limitation. The study uses an electronic platform and there is not complete confidence that a panelist who returned the survey is actually the panelist who was solicited for the study, which implies the possibility of representation concerns.

Conclusions:

Until recently the prevalence of opioid administration during hospitalization and on the day of discharge was unknown in the U.S. New national data informed the generation of seven opioid prescribing guidelines for obstetric clinicians during labor and delivery and on the day of discharge. Limiting opioid exposure when the benefit of opioid administration does not outweigh the risk is not only important in the outpatient population, but the inpatient population as well. These new prescribing guidelines can serve as a starting point for discussions in local

hospitals, national integrated delivery networks, clinical and public health professional organizations, and federal agencies on how to limit opioid exposure and consider other multi-modal pain management approaches in the uncomplicated NSVD population.

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Table 1: Final Recommendations and Associated Consensus Status in Each Round of Surveying

Guideline (G)	Recommendation	Consensus Yes/No	Round 1	Round 2	Round 3
G1	Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for normal spontaneous vaginal delivery patients with no complications. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.	**Yes**	**X**		
G2	Options and expectations for intra- and post-partum pain management should be an essential component of every patient's care and be customized to each woman's needs and history. It is recommended that clinicians address these options with their patients as part of the labor and birth goals discussion. The clinician should document that pain management options were discussed, questions answered, and the patient appeared to understand.	**Yes**			**X**
G3	Long-term opioid use often begins with the treatment of acute pain. When opioids are started, clinicians should order the lowest effective dosage and prescribe no greater quantity of opioids than	**Yes**	**X**		

	needed for the expected duration of such pain severe enough to require opioids.				
G4	When starting opioid therapy, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting opioids. This is especially important on the day of discharge.	**Yes**	**X**		
G5:	Clinicians should review the patient's history of controlled substance use. If the clinician determines the patient is utilizing opioids (prescribed or unprescribed), the clinician should work with pain management personnel to develop a plan for intra- and post-partum pain medication. A prenatal consult with neonatology or a pediatrician, to counsel the patient about the risk for Neonatal Abstinence Syndrome, should be strongly advised.	**No**			
G6	Clinicians should avoid prescribing opioid pain medications and benzodiazepines concurrently whenever possible.	**Yes**	**X**		
G7	Clinicians and hospital administration should consider implementing a protocol for opioid prescribing for NSVD patients during and after delivery. This could help prevent opioid orders becoming routine in NSVD patients where the benefit may not outweigh the risk for mother and fetus.	**Yes**		**X**	
G8	When clinicians identify a patient with Opioid Use	**Yes**	**X**		

	Disorder or OUD, treatment discussions should be prioritized during hospitalization, upon discharge and at the postpartum appointment.				

Key: NSVD normal spontaneous vaginal delivery

Table 2: Panel Participants and Credentials (in alphabetical order):

Name	**Leadership Role and Affiliation(s)**
Tamika Auguste, MD	Associate Medical Director, Medstar Health Simulation Training & Education Lab Associate Professor, Obstetrics and Gynecology, Georgetown School of Medicine
Peter Bernstein, MD, MPH	Director, Division of Maternal Fetal Medicine Professor of Obstetrics & Gynecology and Women's Health Albert Einstein College of Medicine/Montefiore Medical Center
Ann E.B. Borders, MD, MSc, MPH	Maternal-Fetal Medicine, Evanston Hospital, NorthShore University HealthSystem Clinical Associate Professor, University of Chicago, Pritzker School of Medicine Adjunct Assistant Professor Department of Medical Social Sciences, Center for Healthcare Studies, Institute for Policy Research, Northwestern University

	Executive Director, Illinois Perinatal Quality Collaborative
Siobhan Dolan, MD	Professor and Vice Chair, Research, Department of Obstetrics and Gynecology and Women's Health, Montefiore Health System
Timothy J. Fisher, MD, MS	Obstetrics and Gynecology Residency Program Director Interim Director, Division of General Obstetrics and Gynecology Assistant Professor, Obstetrics and Gynecology Dartmouth-Hitchcock Medical Center and The Geisel School of Medicine at Dartmouth Medical Director, Northern New England Perinatal Quality Improvement Network
Alex Friedman, MD	Assistant Professor, Obstetrics & Gynecology, Columbia University College of Physicians and Surgeons
William Grobman, MD,	Arthur Hale Curtis Professor Vice Chair, Department of Obstetrics and Gynecology Medical Director, NMG Women's Health Feinberg School of Medicine at Northwestern University
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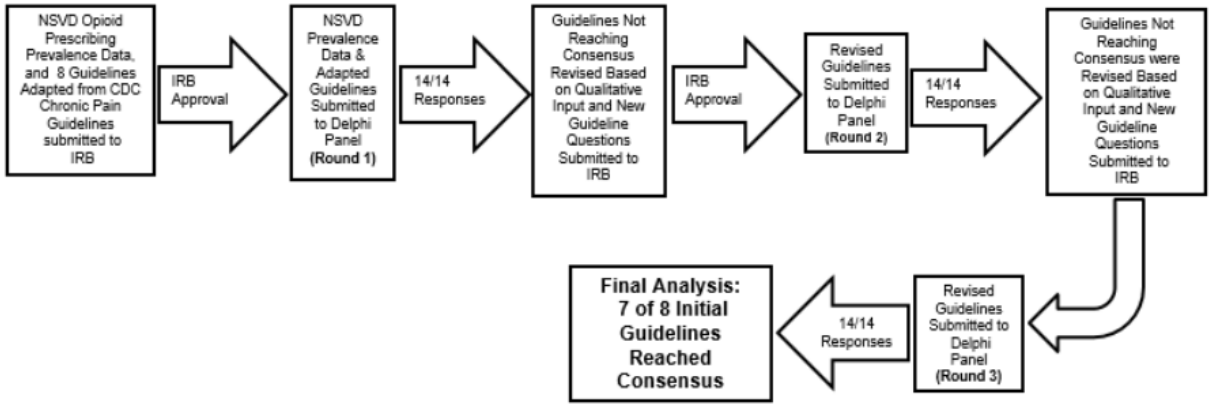
	Associate Professor of Obstetrics & Gynecology, Zucker School of Medicine at Hofstra/Northwell Perinatalogist, Department of Obstetrics and Gynecology, North Shore University Hospital.
David Lagrew, MD	Executive Medical Director of Women's Service, St. Joseph-Hoag Health Region of Providence Healthcare
Elliott Main, MD	Medical Director, California Maternal Quality Care Collaborative
Christian Pettker, MD	Associate Professor of Obstetrics, Gynecology, and Reproductive Sciences Chief of Obstetrics, Yale School of Medicine and Yale-New Haven Hospital Medical Director, Labor & Birth Unit and Maternal Special Care Unit, Yale-New Haven Hospital
Mona Prasad, DO, MPH	Assistant Professor, Department of OB/GYN, Division of Maternal Fetal Medicine, The Ohio State University Medical Center
Mishka Terplan, MD, FACOG	Associate Medical Director, MedStar Health Simulation Training & Education Lab (SiTEL) Associate Professor, Obstetrics and Gynecology, Georgetown School of Medicine
Tricia Wright, MD, MS, FACOG,	Associate Professor Department of Obstetrics, Gynecology

FASAM	and Women's Health Clinical Associate Professor, Department of Psychiatry University of Hawaii John A. Burns School of Medicine

Figure Legend

Figure 1: IRB and Delphi Process for Consensus Based Guidelines

(October 2017- February 2018)



Key: NSVD normal spontaneous vaginal delivery; CDC Centers for Disease Control and Prevention; IRB Institutional Review Board

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Opioid Prescribing Guidelines for Uncomplicated Normal Spontaneous Vaginal Birth Patients During Hospitalization and on the Day of Discharge

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Article Type:	Guidelines
Manuscript Classifications:	Anesthesia and obstetric anesthesia; Health policy and health economics; Labor; Labor, general; Labor, management; Pharmacology
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V. DISCUSSION AND CONCLUSION

a. Discussion and Implications for Public Health

Prior to this research there were no data on opioid administration for one of the largest hospital inpatient populations in the U.S. This is problematic because the literature points to an opioid prescription as the number one risk factor for opioid abuse (CDC, 2017d). Opioids are highly addictive substances and initiating even short-term opioid therapy requires careful consideration. In systems of care, clinical decision-making algorithms are designed to foster standardized medication practices to prevent protocol deviation. This is done so that patients with a given diagnosis or procedure receive the "standard of care" regardless of who the provider is or the time of day or shift in which care is provided. Given the prevalence of opioid prescribing and the associated risks, healthcare systems may be at a crossroads that necessitates reevaluating their respective pain management protocols and specifically, how and when opioids are administered.

The purpose of Part I of the research (the observational study) was to determine to what extent opioids are being administered in the NSVD population, because there would have been no need to devote attention to recommendations for prescribing where there was little to no opioid administration. The analysis resulting from Part I revealed a high prevalence of opioid administration in the NSVD population with independent patient and hospital characteristics reported as predictors. This new data and analysis pointed to a broader challenge: How can the administration of opioids in this particular inpatient population, NSVD patients, be better aligned with the medical mantra, "First Do No Harm?" The risk/benefit scenario of opioid administration in women undergoing uncomplicated NSVD and being discharged to care for an infant needed to

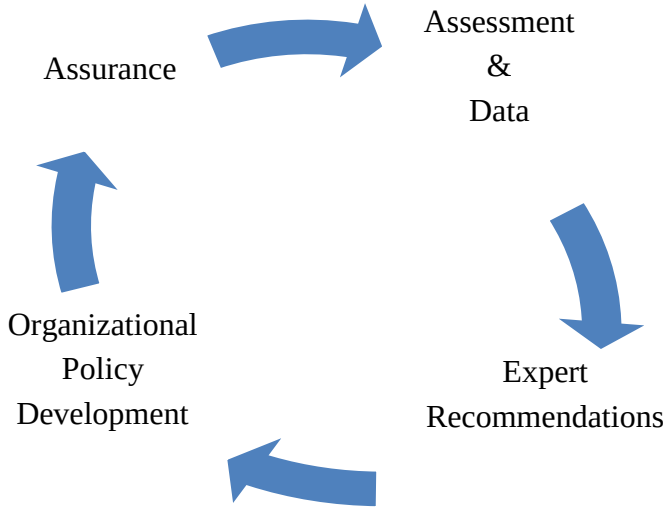
be evaluated by clinician leaders, not data experts, in order to obtain meaningful results. Thus, because recommendations were needed to make the research actionable from a leadership perspective, Part II of the research was added resulting in an overall mixed methods approach.

The purpose of Part II (the e-Delphi study) was to arrive at consensus on guidelines for leaders in maternal health for opioid prescribing in uncomplicated NSVD patients. The data and adapted CDC chronic pain guidelines were used in parallel to provide initial PI-drafted recommendations for opioid prescribing to the e-Delphi panel of OBGYN experts who were surveyed. As covered in Chapter 4, after three rounds of surveying, the Panel agreed on seven recommendations which reached consensus, resulting in guidelines for both clinician leaders and policy stakeholders with regard to opioid administration in NSVD patients.

Thinking of the application of this research to the healthcare system requires considering where the opioid challenge started. The Conceptual Framework introduced in Chapter 2 succinctly illustrates the opioid phenomenon in the context of the U.S. healthcare system (Peters, 2014). The conceptual framework illustrates that with the advent of "Pain as the 5th Vital Sign", hospitals were reimbursed based on how effectively pain was managed from the patient's perspective. Consequently, opioid prescribing increased and so did abuse, addiction, overdose and death. Historically, with regard to opioid prescribing, the unsuccessful implementation of prevention efforts has been due to the siloed perspective of manufacturers, policy makers and prescribers. Manufacturers are for-profit entities and are in business to make money, which requires sales and the associated marketing practices to prescribers and consumers. To exacerbate the situation, policy makers did not appreciate how the "Pain as the 5th Vital Sign" policy affected an array of connected influencers, including practitioners who were rewarded for effectively relieving their patients' pain through CMS' value-based purchasing program.

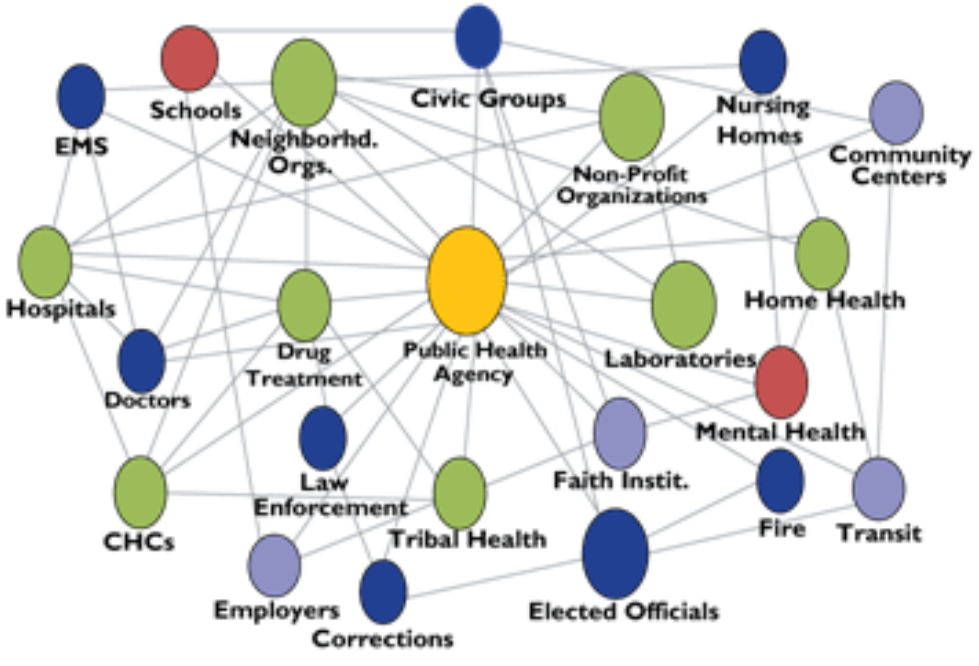
Understanding this history created an opportunity to use a systems approach in this study by introducing the observational data to influence the recommendations made by obstetric leaders. These recommendations may then inform policy making and highlight the need for pattern assessment and assurance regarding prescribing practices in maternal and child health. See Figure 5.

Figure 5. Systems Approach to Decreasing NSVD Opioid Exposure



The public health system is made up of numerous interconnected entities and each can have an impact on the opioid epidemic and this includes hospitals and clinician stakeholders. Examining these individual actors and the network of which they are an inherent part is important as their actions impact and influence the community in multiple ways in regards to opioid prescribing. The diagram in Figure 6 depicts these relationships.

Figure 6. The Public Health System



Source: CDC, 2014b

Once the prescribing guidelines from Part II are shared widely, stakeholders within the public health system can benefit from this research in a myriad of ways including the reduction of the opioid supply in their communities, the addition of prescribing guidelines for a discreet inpatient population and data that can be used for benchmarking and measurement purposes. One example would be employers who are self-insured working with local hospitals and providers to incentivize them to use new, evidence-based opioid prescribing protocols in the NSVD population, and then measuring progress against historical or baseline performance. Another example would include public health agencies, community centers, hospitals and other

entities which provide education for expectant mothers. These data and recommendations could be used to inform the educational material that is provided so that women.

This research applies to public health practice in a number of ways, but most importantly, it applies to the core mission of public health, prevention. The literature review cites many of the morbidity and mortality statistics associated with the resulting opioid epidemic. Part of the challenge is getting prescribers to think of avoiding narcotics much in the same way they lean into vaccination – it is a prevention mindset with resulting clinical decisions to support good public health practice. “If public health professionals were pressed to provide a one-word synonym for public health, the most frequent response would probably be prevention. In general, prevention characterizes actions that are taken to reduce the possibility that something will happen or in hopes of minimizing the damage that may occur if it does happen” (Turnock, 2009). This research contributes to that goal within the framework of the three core functions of public health in several ways as depicted in Table V.

TABLE V: EPI AND E-DELPHI RESEARCH AND CONTRIBUTIONS TO THE THREE CORE PUBLIC HEALTH FUNCTIONS[a]

Assessment Evaluation of Health Status and Hazards of a Community or Population	**Policy Development** Creation of Plans and Policies to Address and Deal with Community's Health Hazards	**Assurance** Implementation of Plans Developed and Inform and Educate
Part I of the research (Epi Study) describes prevalence of opioid administration to NSVD patients.	Part II of the research (e-Delphi Study) adapts the CDC's chronic pain opioid prescribing guidelines to the NSVD population.	Part I will be submitted for publication and could assist in improving awareness with regard to the prevalence of opioid prescribing.
Part I characterizes patient and hospital factors predictive of opioid administration.	Part II points to which areas may be more difficult to get clinicians to agree upon with respect to changing prescribing behavior by illuminating which guideline did not gain consensus and how long it took to gain consensus on the other guidelines.	Part II will be submitted for publication and could assist clinicians with a set of guidelines for opioid prescribing in the uncomplicated NSVD population. In QI efforts, such as the ACOG Safety Bundles and Preinatal Quality Improvement Collaborative.

[a]Definitions adapted from Rowitz, 2009

Table V illustrates the interrelatedness of the research goals and the corresponding opportunity for impact on the three core functions of public health. Using a systems thinking approach, we can apply the outcomes from this body of research in the individual areas of assessment, assurance, and policy development.

Part I of the research (the epidemiology study) provided the investigatory analysis of the prevalence of opioid administration. The analysis also included insight into patient, hospital and geographical characteristics for which there was a stronger likelihood of opioid administration and thus the risk of addiction and/or diversion. This part of the research primarily falls into the assessment function of public health. Though the data and analysis from Part I are helpful in raising awareness and contribute to the research field in their own right, they are not actionable.

Part II (the e-Delphi study) falls into the policy/plan development function of public health as it provided an actionable catalyst whereby protocols and prescribing plans could be informed by the recommendations that resulted from Part II. The recommendations from Part II were the culmination of the e-Delphi panelists' responses to three rounds of surveys which were informed by the Part I analyses and the CDC guidelines for chronic pain opioid prescribing. These recommendations may now serve as an evidence-based tool to empower clinical and administrative leaders to prevent unnecessary administration of these highly addictive substances. Reducing administration reduces the demand, and thus supply, of opioids and could subsequently have an impact on reducing opioid abuse, and also impact the diversion of opioids in the hospital and in the community. The results of Part I and Part II, as found in Chapter 4, through publication can offer new data and increase awareness of the prevalence of prescribing and available recommendations to mitigate opioid exposure in the NSVD population.

b. Practice and Leadership Implications

An adaptive challenge can be defined as "the gap between the values people stand for and the reality that they face" (Heifetz et al., 2009); adaptive leadership can be defined as a leadership approach and language "to help organizations thrive amidst uncertain change" (Ulstad, 2016). As discussed in Chapter 2, an adaptive leadership approach is needed as healthcare systems tackle the adaptive challenge of both implementing and operationalizing changes to improve maternal health in the U.S. Since the well-being of mothers and babies is a top priority for U.S. public health it is important to characterize what is transpiring in practice relative to that priority.

In a recent six-month investigation examining maternal mortality in the U.S., more women were reported dying due to pregnancy-related complications than in any other developed country (Martin and Montagne, 2017a). The investigation cited one of the reasons for this

increase as, “the hodgepodge of hospital protocols for dealing with potentially fatal complications, allowing for treatable complications to become lethal.” This speaks to the need for recognizing the roles of protocols and processes or lack thereof in every setting of care. Applying this research to a hospital system or an accountable care organization requires leadership to first determine the strategy of the organization as it pertains to appropriate opioid administration protocols relative to their goals and values in their respective system and community, and then establishing thresholds with appropriate stakeholder input. This is both a technical challenge and an adaptive challenge. Dr. Elliott Main, a member of the e-Delphi panel and a professor in obstetrics and gynecology at Stanford and the founder of the California Maternal Quality Care Collaborative, stated the following in relation to reducing maternal harm, "Prevention isn't a magic pill.... It’s actually teamwork [and having] a structured, organized, standardized approach" to care (Martin and Montagne, 2017b). Designing a protocol to standardize the avoidance of opioid exposure whenever possible is a technical challenge. Similarly, the research in Part I (the epidemiological study) was a technical challenge since it involved a predictable process and associated steps as written in the statistical analysis plan. Leading the labor and delivery clinicians at a hospital system in changing their thinking about avoiding opioid exposure as a preventive practice is an adaptive challenge. Likewise, Part II of the research (the e-Delphi study) required adaptive work and would be considered an adaptive challenge since it required new learning, multiple perspectives, changing behavior/attitudes and the possibility for resistance (Ulstad, 2016).

Once leaders diagnose whether and to the extent there is a prescribing problem, they must act on a system level to resolve the problem, reduce risk and improve care. Although baseline data will be important to diagnose and assess subsequent changes in prescribing behavior, action is needed to deploy sustainable change. As discussed in Chapter 2, healthcare leaders understand

the concept of diagnosis and treatment relative to patients, but they must also apply it to their own systems. Heifetz et al. address this systems' application in terms of mobilization with the goal of tackling an adaptive challenge and moving from where the organization is currently to where it purposes to be (Heifetz et al., 2009). To properly attend to the adaptive challenge, adaptive leaders must adhere to five guiding principles:

1) Distinguish between technical and adaptive challenges when diagnosing and treating a challenge;
2) Ensure productive work tension – teams are challenged but not overburdened;
3) Understand and lead with the knowledge of the difference between the role of authority and the exercise of leadership;
4) Recognize and address work avoidance and resistance behaviors by staff;
5) See the big picture but also spend time in the trenches (spends time on the balcony and the dance floor).

(adapted from Heifetz et al., 2009, and Ulstad, 2016).

The first principle, distinguishing between a technical and adaptive challenge, was discussed above and arguably can be discerned more readily than distinguishing whether there is productive work tension. Clinicians and staff need to have enough tension to feel challenged but not so much tension that it creates a negative balance. This is especially difficult in hospital settings where there is naturally a lot of tension and stress associated with care delivery. It is likely that wherever and whenever leadership initiates a change in protocols for medication management, opioids or otherwise, there will be resistance at some level because practitioners may feel that they are being dictated to and are subsequently being asked to relinquish authority or autonomy in decisions related to their patients. The complexity of the adaptive change may be

helping prescribers adjust their perspective regarding the new opioid administration guidelines and how these guidelines reinforce the values of the organization and community in preventing further harm related to opioid abuse, addiction, overdose and diversion. Adaptive leaders are needed to diagnose and provide guidance for navigating complex challenges and leading the overall strategy.

The third principle, "Understands and leads with the knowledge of the difference between the role of authority and the exercise of leadership", is especially key in an arena where credentials and titles are important to distinguish to the patient and staff who is ultimately accountable for life and death decisions. Irrespective of how authority is ascribed, by position or influence, leadership is an action that helps people see how to get from point A to point B, why that work is important and what each team member's role is in that effort.

Applying the fourth principle, recognizes and addresses work avoidance and resistance behaviors by staff, to the labor and delivery setting would require a leader to have their eyes and ears open and participate actively in meetings and rounds so that they could observe firsthand whether staff are avoiding work because they do not agree (perhaps because they were not part of the collaborative effort to decide on the adaptive change), they feel overwhelmed or think they may have a disproportionate amount of the work assigned to them. Stakeholder engagement and open communication are key, as well as being aware of and addressing behavior that is negative or obstructionist in its approach, which ties directly into the fifth principle.

The fifth principle demands that the leader is in the trenches experiencing the successes and failures, progress and setbacks beside his or her team. It provides the leader a front row seat to what is working/adapting and what is not working. It also helps the team see the leader as part of the collective team, not outside of it. The juxtaposition of the trench is the balcony and adaptive leaders also need a balcony perspective so that they can see the overall effect of what

they are implementing. This helps address the age-old leadership challenge of not being able to see the forest for the trees and ensures the activity is connected to the purpose.

Applying these principles to this research means that once leaders have diagnosed the adaptive challenges and the technical challenges, they can determine the best approach to managing each in their own system. For example, once the data source for analyzing opioid prescribing in the maternal health population has been decided on, the leader can then determine the best measurement approach and benchmarks and subsequent protocols for opioid prescribing. Setting up the data analyses is technical; gaining agreement on the specifics – the what and who and how clinicians are measured relative to benchmarks – will be highly adaptive.

It is beyond the scope of this research to determine what is an appropriate goal or threshold for opioid prescribing because individual systems will have different patient populations and different care delivery approaches. Regardless of the threshold, to diagnose the system, leaders must have data, and to improve system performance, leaders must measure. The data from Part I of the research are in aggregate form and the analysis does not drill down to the individual hospital level due to HIPAA privacy requirements. Leaders will have to adapt the methodology used in Part I for their own system. This is feasible depending on the software and quality improvement tools they have at their disposal. The inclusionary and exclusionary criteria found in Appendix A can be used in any system. If a hospital does not have an electronic medical record or form of quality improvement software, a random chart review could be conducted by administrative personnel to assess the prevalence of opioid administration in the NSVD population. Regardless of the technology available, the work can be done, but the system's leadership must see the role they can play in addressing the larger opioid epidemic and have a will to engage in prevention activities. They must foster this same will with their staff without overwhelming them (Principles 2 and 3). As part of the mobilization, once the data is

collected for the system, leaders can assess if and where there is a higher prevalence of opioid administration and whether it is provider-specific, hospital-specific or a broader challenge. Whether or not there is an unacceptable amount of opioid administration relative to the system's goals, it may be prudent to reevaluate any clinical decision-making tools that are in place for the NSVD population and then evaluate if and how the recommendations in Part II could be adapted and deployed. The risk-benefit tension of this adaptive challenge is that it invites protocols and clinical decision-making tools into the process. These tools can help if they are evidence-based and are reviewed regularly against the latest research.

Hospital leadership will need to remember that clinicians play a larger role than just prescribers, as they are an inherent part of the U.S. public health system. Part of what drives this adaptive challenge is the complexity around individual provider behavior and the corresponding motivations. "To drive quality improvement and patient safety forward, you have to have the passionate engagement of clinicians — healthcare's smart cogs. Experiences in other industries have demonstrated that spreading new, innovative ideas can be accomplished by paying attention to the so-called opinion leaders that exist in all groups of people of sufficient size. The same approach works in healthcare" (Tinker and Faulk, 2017). Physicians have long ascribed to the medical mantra of "First, do no harm." For any system that has physicians prescribing highly addictive substances, the risk must be outweighed by the benefit. The question here becomes what is the risk both for the patient and the population? What is the benefit? These questions are important when considering the needs of an individual patient relative to the overall epidemic of opioid use, abuse, overdose and death. This is an opportunity for health system leaders, whether clinical or administrative, to invite prescribers to protect the values of the organization and the provider community as they consider their role in opioid prescribing (Rowitz, 2009). It is inviting them to participate in the adaptive challenge and be a stakeholder versus a bystander.

Both Parts I and II of this research offer contributions to leaders, so that they may participate as “an agent of social change by identifying health problems and risks and stimulating actions toward their elimination” (Turnock, 2009). For clinical and administrative leaders evaluating this data, it could be easy to dismiss the results since the analysis is in aggregate and does not point to a particular health system or city. However, large systems delivering care in the U.S. South-Central census region (Louisiana, Texas, Oklahoma and Arkansas) should give particular notice to this data on opioid administration, especially on the day of discharge. Receiving care as an NSVD patient in one in these states independently predisposes the patient to opioid administration on the day of discharge compared to all other regions. The same holds true for opioid administration during hospitalization with the exception of the East South Central and West North Central regions. As leaders consider intervention and prevention opportunities, prioritizing assessment of and education for prescribers in this geography may prove efficacious.

Similarly, leaders in non-teaching hospitals need to be aware that the risk for opioid exposure versus no exposure is higher in their institutions, even when all other patient characteristics are constant. Refer to Tables VI and VII for specific odds ratios for each independent predictor for opioid administration both during hospitalization and on the day of discharge.

TABLE VI. PERCENTS, AND ADJUSTED ODDS RATIOS FOR THE RELATIONSHIP BETWEEN PATIENT AND HOSPITAL CHARACTERISTICS AND THE RECEIPT OF AN OPIOID DURING HOSPITALIZATION FOR NORMAL SPONTANEOUS VAGINAL DELIVERY (NSVD) PATIENTS (JANUARY 1, 2014 - DECEMBER 31, 2016)

Effects	Description	% of Patients Administered Opioid During Hospitalization	Adjusted Odds Ratio	95% Wald Lower Confidence	95% Wald Upper Confidence
Age	19-34 (ref 15-18)	78.16	0.93	0.81	1.07
	35-44 (ref 15-18)	70.51	0.73	0.59	0.89
Marital Status	Married (ref Single)	74.62	0.68	0.64	0.72
	Other-Unknown status (ref Single)	70.50	0.79	0.70	0.89
Race	Black (ref White)	85.41	1.42	1.31	1.54
	Other (ref White)	73.56	0.92	0.86	0.97
Payor	Managed Care (ref Commercial - Indemnity)	74.34	1.07	0.96	1.21
	Medicaid (ref Commercial - Indemnity)	81.11	1.36	1.21	1.51
	Other Payor (ref Commercial - Indemnity)	76.93	1.04	0.91	1.19
Hospital Geographic Region	East North Central (ref West South Central)	72.01	0.46	0.32	0.66
	East South Central (ref West South Central)	85.20	1.10	0.71	1.71
	Middle Atlantic (ref West South Central)	57.49	0.30	0.20	0.46
	Mountain (ref West South	83.50	0.80	0.51	1.24

	Central)				
	New England (ref West South Central)	62.65	0.34	0.19	0.62
	Pacific (ref West South Central)	75.12	0.52	0.38	0.73
	South Atlantic (ref West South Central)	82.83	0.78	0.58	1.05
	West North Central (ref West South Central)	81.71	1.06	0.63	1.78
Hospital Teaching Status	Teaching (ref Non-Teaching)	73.93	0.80	0.65	0.99

Key: ref: reference group

Note: All variables in Table 2 were adjusted for all other variables in Table 2.

TABLE VII: PERCENTS, AND ADJUSTED ODDS RATIOS FOR THE RELATIONSHIP BETWEEN PATIENT AND HOSPITAL CHARACTERISTICS AND THE RECEIPT OF AN OPIOID ON THE DAY OF DISCHARGE FOR NORMAL SPONTANEOUS VAGINAL DELIVERY (NSVD) PATIENTS (JANUARY 1, 2014- DECEMBER 31, 2016)

Effects	Description	% of Patients Administered an Opioid on Day of Discharge	Adjusted Odds Ratio	95% Wald Lower Confidence	95% Wald Upper Confidence
Age	19-34 (ref 15-18)	30.11	1.65	1.46	1.86
	35-44 (ref 15-18)	21.84	1.27	1.04	1.54
Marital Status	Married (ref Single)	25.58	0.77	0.73	0.81
	Other-Unknown status (ref Single)	24.35	0.90	0.80	1.00
Race	Black (ref White)	39.15	1.27	1.19	1.36
	Other (ref White)	24.74	0.86	0.81	0.92
Ethnicity	Hispanic (ref non-Hispanic)	25.54	0.86	0.81	0.92
Payor	Managed Care (ref Commercial - Indemnity)	23.98	1.10	0.98	1.23
	Medicaid (ref Commercial - Indemnity)	34.04	1.71	1.53	1.90
	Other Payor (ref Commercial - Indemnity)	25.72	1.22	1.07	1.40
Hospital Geographic Region	East North Central (ref West South Central)	23.86	0.44	0.32	0.60
	East South Central (ref West South Central)	38.92	0.83	0.57	1.21
	Middle Atlantic (ref West South Central)	13.55	0.24	0.17	0.36
	Mountain (ref West South Central)	32.39	0.65	0.44	0.96

	New England (ref West South Central)	12.45	0.19	0.11	0.33
	Pacific (ref West South Central)	27.15	0.57	0.43	0.77
	South Atlantic (ref West South Central)	32.11	0.62	0.48	0.80
	West North Central (ref West South Central)	34.44	0.94	0.60	1.46
Hospital Teaching Status	Teaching (ref Non-teaching)	25.54	0.79	0.65	0.95

Key: ref: reference group

Note: All variables in Table 3 were adjusted for all other variables in Table 3.

To execute these changes successfully it may be useful to appreciate the history of how change has been managed within the health system and help providers focus forward with the goal of improving care and preventing harm. “Leaders should help constituents view the organization and organizational change in the context of relevant social, political, economic, and technical systems and trends. They should take a long view backward over the organization’s history and even its prehistory in order to help people in the organization think more wisely about the future” (Bryson, 2004). Leaders may avoid repeating mistakes of the past by understanding cultural barriers within the organization when initiating quality improvement plans with providers. As Bryson mentions, using the political landscape could prove useful. In the maternal health population there has been considerable press regarding how the U.S. is lagging behind other developed countries on morbidity and mortality in pregnancy and delivery. In considering ways to improve maternal health, fostering responsible opioid prescribing presents a timely and valuable opportunity. In reviewing the qualitative feedback received in Part II, the e-Delphi Panel agreed. See Table 2 (Manuscript 2) in Chapter 4 for e-Delphi participants’ credentials.

In conclusion, the mixed method approach was ideal for this study and resulted in new research and recommendations for clinical and administrative leadership as well as policy stakeholders. The data and analysis in Part I filled an important gap in the literature regarding the prevalence of opioid administration in the inpatient maternal health population as depicted in the Conceptual Framework in Chapter 2. The recommendations in Part II inform and may empower clinicians and leaders to take initial steps to reduce unnecessary opioid administration in a large and well-defined population.

c. Limitations

There are limitations in both Part I and Part II of the research. These limitations are important to weigh, especially for those considering duplicating this work in different inpatient populations or in their own respective NSVD population. For the epidemiological study, Part I, there were three distinct limitations: 1) administrative data, 2) exclusionary criteria, and 3) hospital characteristics. For the e-Delphi study, Part II, limitations to the study design were related to 1) representation, 2) instruction compliance, and 3) guideline origination. The limitations are detailed in Table VIII to help provide guidance for future studies in using this approach. These limitations should be considered as leaders contemplate how to implement their own data collection on opioid prescribing in their own organizations and adopt the proposed guidelines discussed in this study. At a national level, the findings from both arms of the study are timely and relevant and may prove useful in making policy changes in opioid prescription practice in maternal and child health.

TABLE VIII: PART 1 AND PART 2 STUDY LIMITATIONS

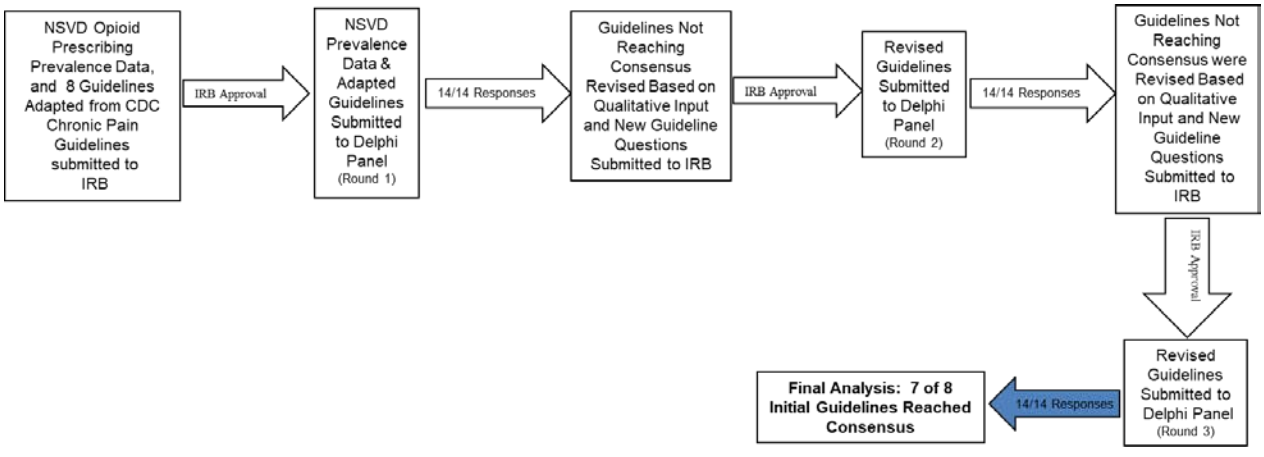
Part 1 Limitations	
Administrative Data	This study uses administrative data which comes from U.S. hospitals and is based on charge master data. The data captures only what the patient was charged and not necessarily everything the patient received.
Exclusionary Criteria	While several potential indications for opioid treatment were excluded, there may be additional indications for appropriate opioid treatment which may have been overlooked in the exclusion parameters.
Hospital Characteristics	Comparisons between hospital characteristics for the hospitals submitting data to Premier and the 2016-member hospitals of the American Hospital Association (AHA), demonstrate a similar distribution, although the AHA has a greater number of smaller hospitals.
Part 2 Limitations	
Representation	The Panel only comprised physicians; midwives and other clinicians were not represented and [why this is important/a limitation]; the study uses an electronic platform and as such, there is not complete confidence that the panelist who returned a survey is actually the panelist who was solicited for the study.
Instruction Compliance	The guidelines given to the panel were specifically for uncomplicated NSVD patients. Yet, during the e-Delphi process, a few of the participants questioned what should be done when there were lacerations or other complications. Although these exclusions were included in the instructions, it may be that some panelists thought they were voting on NSVD guidelines in general versus guidelines for uncomplicated NSVD deliveries.
Guideline Origination	The guidelines were adapted from existing CDC guidelines for the chronic pain patient population and did not originate from the panelists. It is likely a more robust and cohesive set of recommendations could have been achieved had the conduit for consensus building been conducted live with the Panel starting from scratch versus using the PI's adaptation of the CDC chronic pain guidelines.

d. Institutional Review Board

Both Part I and Part II of this research were approved by the University of Illinois Institutional Review Board on October 3, 2017 and assigned protocol number 2017-0781. The statistical analysis plan associated with Part I is provided in Appendix A and the e-Delphi protocol associated with Part II can be found in Appendix D. Figure 7 depicts the IRB process.

The study was determined to be of low risk because Part I contained no identifiable data and was in compliance with HIPAA requirements. Details on the specific data used for Part I can be found in the SAP in Appendix A as well as in Chapter 2. Part II of the study was deemed low risk. The participants were not considered a vulnerable population as they were licensed MDs or DOs. Further, only the PI had access to the identity of the e-Delphi panelist associated with each survey response. All approved documents related to the e-Delphi work in Part II, including the Informed Consent and e-Delphi protocol can be found in Appendix D. Once the initial protocol was approved, the subsequent amendments were expedited. Amendments included revised questions for the second and third survey rounds. The revised questions were necessary as they each incorporated the qualitative feedback provided by the e-Delphi committee in the previous round.

Figure 7. Institutional Review Board Process.



e. Conflict of Interest Statement

The Principal Investigator submitted a “Significant Financial Interest – Disclosure and Management Plan” to the Office of the Vice Chancellor for Research on July 7, 2017. The management plan was approved by the Chair of the PI’s Dissertation Committee and the Head of the DrPH Program on 7/26/2017. The plan received final approval by the Chancellor’s Office for Research on 8/3/17 and is on file with the Chancellor’s Office and the IRB office at the University of Illinois, Chicago.

APPENDICES

Appendix A: Statistical Analysis Plan

Comprehensive, Descriptive, Epidemiological Study to Better Understand Factors Associated with Clinician Opioid Utilization in Normal, Spontaneous, Vaginal Delivery

Version 2.3

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Appendix A (continued)

Table 1. Statistical Analysis Plan Revision History

Date	Version	Description	Author
02/18/2017	1.0	Initial Document	J. Rebecca Mills
03/26/2017	1.1	Document with edits by MM and RM to version 1.0	Huizinga and Mills
4/14/17	1.2	Draft to keep with final Edits	Mills
5/10/17	1.3	Draft with Dr. Bowdy and Dr. Taylor Edits and Huizinga review	Mills
5/25/17	1.4	Edits with Dr. Handler and Dr. Terplan's Input	Huizinga and Mills
5/30/17	1.5	Edits with Bowdy and Huizinga input following 1.4	Mills
6/7/17	1.6	Edits with Davis, Bowdy, Huizinga, Mills input relative to exclusion criteria	Mills
6/9/17	1.7	Final edited version with updated opioid list	Mills
6/12/17	1.8	Clarification on outcomes and added clarity around NSVD and PO vs. Non-PO	Mills
6/26/17	1.9	Clarity around LOS, age and final analyst edits	Davis and Mills
7/21/17	2.0	Added exclusionary criteria for hospitals w/lower delivery volumes	Mills
10/22/17	2.1	Refined Figure 1 and Tables 5 and 8 to reflect mutually exclusive groups and changed payor type to patient characteristic vs. hospital characteristic. Insert data.	Mills and Robinson

01/11/2017	2.2	Further refine verbiage for clarity based on Dr. Huizinga's feedback.	Mills and Robinson
2/10/2017	2.3	Last round of edits including verbiage and clarity in terminology, removed intro and age (kept categorical age), added VIF	Mills, Robinson, Bowdy

Appendix A (continued)

AMENDMENTS FROM PREVIOUS VERSION(S)

Version 2.3

1.1. Study Design

This study will be a retrospective, observational study to understand the demographic and clinical characteristics of patients in which opioid medications are utilized during normal vaginal delivery. The study will utilize the Premier Healthcare Database (PHD). The PHD is a HIPAA compliant and de-identified database. Descriptive statistics (i.e., mean, standard deviation, median, and interquartile range for continuous variables; counts and percentages for categorical variables) will be provided to characterize patients of interest. The association between each covariate and the opiate use (patient receiving an opioid) will be assessed through appropriate statistical testing. The covariates with a significant association with the outcome opiate use will be included in multivariate regression models.

1.1.1. Study Population and Period

Patients meeting all the following inclusion criteria will be eligible for inclusion into the study:

- Inpatients 15-44 years of age;
- Hospital discharge dates between January 2014 and December 2016;
- At least one service day in the hospital as determined by hospital charge master data;
- At least one of the following ICD-9 or ICD-10 codes for Normal Spontaneous Vaginal Delivery:

Table 2. ICD-9 and ICD-10 codes for Spontaneous Vaginal Delivery

ICD-9 Code	**Code Description**	**Grouping**
650	Normal delivery	Normal Vaginal Delivery
ICD-10 Code	**Code Description**	**Grouping**
O80	Encounter for full-term uncomplicated delivery	Normal Vaginal Delivery

Exclusions:

- Patients with a contraindication to NSAIDs (see Table 2 for definition).
- Patients undergoing caesarean delivery (see Table 2 for definition).
- Patients with selected complicated deliveries (see Table 2 for definition).
- Patients undergoing tubal ligation during the index hospitalization (see Table 2 for definition).

Appendix A (continued)

- Death during the index hospitalization.
- Patients from hospitals with volumes below 36 deliveries within the three-year study window.
- Patients from hospitals that do not have at least one delivery in each of the three calendar years (2014-2016).

Table 3. ICD-9, ICD-10, and HCPCS Codes for Exclusions

ICD-9 DM Code	**Code Description**	**Grouping**
580 – 587	Renal disease	NSAID contraindication
287.3X – 287.4X	Thrombocytopenia	NSAID contraindication
286	Coagulation disorders	NSAID contraindication
649.3X	Coagulation defects complicating pregnancy, childbirth, or the puerperium	NSAID contraindication
642.1X	Hypertension secondary to renal disease complicating pregnancy childbirth and the puerperium	NSAID contraindication
646.2X	Unspecified renal disease in pregnancy without mention of hypertension	NSAID contraindication
649.8X	Onset (spontaneous) of labor after 37 completed weeks of gestation but before 39 completed weeks' gestation, with delivery by (planned) cesarean section	Caesarean delivery
669.7	Cesarean delivery without mention of indication	Caesarean delivery
651 – 659	Care in Pregnancy, Labor, And Delivery	Complicated delivery
630 – 639	Ectopic and Molar Pregnancy and Other Pregnancy with Abortive Outcome	Complicated delivery
660 – 669	Complications Occurring Mainly in the course of Labor and Delivery	Complicated delivery
66.2X – 66.3X	Bilateral Endoscopic Destruction or Occlusion of Fallopian Tubes	Tubal ligation
ICD-9 Proc Code	Code Description	**Grouping**
74	Cesarean Section and Removal of Fetus	Caesarean delivery

72	Forceps, Vacuum, And Breech Delivery	Complicated delivery
73.0X-73.4X, 73.51, 73.6X-73.9X	Other Procedures Inducing or Assisting Delivery	Complicated delivery
75.0X-75.33, 75.35-75.99	Other Obstetric Operations	Complicated delivery
ICD-10 Code	**Code Description**	**Grouping**
N00 – N19	Renal disease	NSAID contraindication
D69.3 – D69.6	Thrombocytopenia	NSAID contraindication
D65 – D68	Coagulation disorders	NSAID contraindication
O26.83	Pregnancy related renal disease	NSAID contraindication
O99.1	Other diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism complicating pregnancy, childbirth and the puerperium	NSAID contraindication
O82	Encounter for cesarean delivery without indication	Caesarean delivery
O00 – O08	Pregnancy with abortive outcome	Complicated delivery
O61 – O71	Complications of labor and delivery	Complicated delivery
O75.4 – O75.8	Complications of labor and delivery	Complicated delivery
0W8NXZZ	Division of Female Perineum, External Approach	Complicated delivery
0UL7	Fallopian Tubes, Bilateral	Tubal ligation
102	Obstetrics, Pregnancy, Change	Complicated delivery
109	Obstetrics, Pregnancy, Drainage	Complicated delivery
10A	Obstetrics, Pregnancy, Abortion	Complicated delivery
10D	Obstetrics, Pregnancy, Extraction	Caesarean delivery
10H	Obstetrics, Pregnancy, Insertion	Complicated delivery
10J	Obstetrics, Pregnancy, Inspection	Complicated delivery
10P	Obstetrics, Pregnancy, Removal	Complicated delivery
10Q	Obstetrics, Pregnancy, Repair	Complicated delivery
10S	Obstetrics, Pregnancy, Reposition	Complicated delivery
10T	Obstetrics, Pregnancy, Resection	Complicated delivery

10Y	Obstetrics, Pregnancy, Transplantation	Complicated delivery
HCPC Code	**Code Description**	**Grouping**
1961	Anesthesia for Cesarean Delivery	Caesarean delivery
1963	Anesthesia for Cesarean Hysterectomy without any Labor Analgesia/Anesthesia Care	Caesarean delivery
1968	Anesthesia for Cesarean Delivery Following Neuraxial Labor Analgesia/Anesthesia	Caesarean delivery
1969	Anesthesia for Cesarean Hysterectomy Following Neuraxial Labor Analgesia/Anesthesia	Caesarean delivery
59510	Routine Obstetric Care Including Antepartum Care, Cesarean Delivery and Postpartum Care	Caesarean delivery
59514	Cesarean Delivery Only	Caesarean delivery
59515	Cesarean Delivery Only; Including Postpartum Care	Caesarean delivery
59618	Routine Obstetric Care Including Antepartum Care, Cesarean Delivery, and Postpartum Care, Following Attempted Vaginal Delivery After Previous Cesarean Delivery	Caesarean delivery
59620	Cesarean Delivery Only, Following Attempted Vaginal Delivery After Previous Cesarean Delivery	Caesarean delivery
59622	Cesarean Delivery Only, Following Attempted Vaginal Delivery After Previous Cesarean Delivery; Including Postpartum Care	Caesarean delivery
59300	Episiotomy or Vaginal Repair, by other than Attending	Complicated delivery
58600 - 58615	Tubal Ligation	Tubal ligation

Appendix A (continued)

1.1.2. Data sources

1.1.2.1. Premier healthcare database (PHD)

Data for the study described in the Dissertation Proposal will be derived from the statistically de-identified Premier Healthcare Database described in Appendix A of the SAP.

1.2. Study Objectives

1. Describe prevalence of opioid utilization during the hospitalization and on the day of discharge for normal spontaneous vaginal delivery (NSVD) admission to U.S. hospitals contributing data to the PHD;
2. Investigate patient characteristics associated with opioid utilization during hospitalization and opioid utilization on the day of discharge;
3. Describe the characteristics of hospitals for patients who utilized opioids during their hospital stay;
4. Analyze opioid utilization trends in NSVD patients.
5. Describe prevalence of opioid utilization during NSVD for patients with documented drug dependence during pregnancy;
6. Describe prevalence of concomitant benzodiazepine-opioid utilization;
7. Characterize what is considered normal practice in the United States for pain medication utilization during normal, spontaneous, vaginal delivery and place opioid utilization in context.

1.3. Specific Aims and Study Outcomes

Specifically, an analysis will be performed to descriptively characterize in NSVD patients:

- Utilization of any opioid medication (list of opioids in Appendix B) at any time during the hospitalization.
- Utilization of any opioid medication (list of opioids in Appendix B) on the day of discharge.

Four secondary descriptive analyses will be performed to further characterize opioid utilization:

- Utilization of opioid during the hospitalization by route of administration (no opioid, any opioid, non-PO, PO, both PO and non-PO)
- Utilization of opioid on the day of discharge by route of administration (no opioid, any opioid, non-PO, PO, both PO and non-PO)
- Utilization of opioid (no opioid, any opioid, non-PO, PO, both PO and non-PO) during the hospitalization by year of discharge
- Utilization of opioid (no opioid, any opioid, non-PO, PO, both PO and non-PO) on the day of discharge by year of discharge

Appendix A (continued)

2. ANALYSES

Initial analyses will include a descriptive analysis to understand the demographic and clinical characteristics of patients and to describe opioid utilization during normal spontaneous vaginal delivery.

3. HYPOTHESES AND DECISION RULES

The study hypothesis is there are differences in opioid utilization by patient and hospital characteristics for normal, spontaneous, vaginal delivery patients.

3.1. Statistical Hypothesis

The null hypothesis is:

H_0: there are no differences by patient or hospital characteristics for the receipt of opioids for normal vaginal delivery patients.

3.2. Statistical Decision Rules

An alpha of 0.05 for any bivariate tests will be considered statistically significant. For inclusion in models, both clinical and statistical significance will be considered. Statistical significance at an alpha of 0.10 will be considered for modeling purposes

1. ANALYSIS SETS/POPULATIONS

An analytic file will be built with patient data extracted from the PHD based on the patient selection criteria described in 2.1.1. The analytic file will contain all variables, including endpoints, exposure, and covariates. All analyses will be performed using the de-identified analytic file.

2. OUTCOMES AND COVARIATES

2.1. Outcomes

The following study outcomes will be created in the analytic file:

- Utilization of an opioid at any time during the index admission as defined by the presence of a charge for a medication listed in Appendix B.
- Utilization of an opioid on the day of discharge as defined by the presence of a charge for a medication listed in Appendix B with a charge date equal to the discharge date.

Each outcome will be coded as a binary yes/no variable and analyzed separately.

2.2. Descriptive Variables and Covariates

The following covariates will be created to describe the patient population. Selected variables will be included in the multivariable regression models as covariates.

- Patient Characteristics for each Discharge
    - Age
        - By age-group
            - 15-18
            - 19-34
            - 35-44

Appendix A (continued)

- Marital Status
  - Married
  - Single
  - Other/Unknown
- Race
  - White
  - Black
  - Other/Unknown
- Ethnicity
  - Hispanic or Latino
  - Unknown
- Payor Type (n, %)
  - Medicaid
  - Commercial
  - Managed Care
  - Other
- Drug dependence (yes or no) as defined by one or more of the following:
  - ICD-9 diagnosis code 648.30 (Drug dependence of mother, unspecified as to episode of care or not applicable)

    OR
  - ICD-10 diagnosis code O99.32x (Drug use complicating pregnancy, childbirth, and the puerperium)

    OR
  - ICD-10 diagnosis code F11 (F11.1-F11.99) Opioid use disorder codes. One code or any combination of codes.
- Benzodiazepine used *on the same day as opioid* use (n, %) (see Appendix C for list of benzodiazepines)
  - Use of benzodiazepines
  - No use of benzodiazepines
- Year of discharge
  - 2014
  - 2015
  - 2016
- Route of administration for patients for whom an opioid was utilized (determined separately for both outcomes of interest)
  - Non-PO (IV, IM, Topical - one or any combination of the three routes)
  - PO and non-PO
  - PO only

- Hospital Characteristics
  - LOS
    - Mean-Std Dev
    - Median
    - IQR

- Min-Max

Appendix A (continued)

- Bed size
  - <100
  - 100-199
  - 200-299
  - 300-499
  - 500+
- Nine Census Regions
  - New England
  - Mid-Atlantic
  - South Atlantic
  - NE Central
  - SE Central
  - NW Central
  - SW Central
  - Mountain
  - Pacific
- Teaching Status
  - Teaching
  - Non-teaching
- Urbanicity
  - Rural
  - Urban

As described in 6.1, binary flags for the two outcomes will be created and included in the analytics file. Additional flags will be created for identifying patients who have received a non-PO opioid at any time during the hospitalization and /or on the day of discharge. Flags will be created for patients who received PO at any time and/or on the day of discharge. A flag will be created for patients who received both PO opioids and the other forms of opioids. Patients may receive an opioid by any or all four routes (IM, IV, Topical, PO) either during the hospitalization and/or on the day of discharge. See Appendix B for a listing of opioids and possible routes. For the cohort of patients receiving opioids, the route of administration will be determined by the description of the item charged on the hospital charge master and will be flagged as belonging to one of the following groups: 1) Non-PO opioid 2) PO only 3) Both PO and Non-PO.

3. HANDLING OF MISSING VALUES

For categorical and continuous variables such as age, missing records will be excluded from analysis. The percentage of missing data will be examined to ensure there is no loss of generalizability. Outliers in the continuous outcome variables will be evaluated by the PI and Committee to determine if there is a value above or below which they should be excluded from analyses.

Appendix A (continued)

4. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSIS

4.1. Statistical Methods

Analytic files as described above containing all the variables will be generated based on the population selection criteria and variable definitions. All analyses will be performed using these analytic files. The statistical methods will include a bivariate analysis of the study population and a multilevel multivariate regression to control for hospital characteristics.

Descriptive analysis will be performed on our outcomes and covariates of interest, testing for differences between those populations who received an opioid during their hospital stay and/or on the day of discharge and those populations who received no opioid. Co-variates with a p-value of 0.100 or less will be included in the adjusted generalized linear mixed-effects model (GLMM). The GLMM will account for likely clustering at the hospital level by including hospital as a random effect. GLMMs allow for non-normal distributions of dependent data. The GLMM will be based on a binomial distribution of data given the binary response options for each given outcome (received an opioid vs. did not receive an opioid). GLMM was selected instead of Generalized Estimating Equations (GEE) because the likelihood of each patient receiving an opiate and relationship of the co-variates to that likelihood is the key question of interest.

4.1.1. Descriptive Methods

Descriptive statistics will be used to gain a better understanding of the patients meeting the selection criteria to better understand the characteristics between those patients who received an opioid and those who did not receive an opioid. Descriptive statistics for a continuous scale will include mean, standard deviation, median, and interquartile range. Categorical data will be expressed as counts and percentages of patients in the categories. Bivariate analysis tables will compare outcomes of interest across treatment groups as characterized in 6.1.1. Chi-square or Fisher's tests will be used to test for statistical differences in categorical variables, and T- or Wilcoxon Rank Sum tests will be utilized for determination of statistical differences in continuous variables as appropriate.

4.1.2. Multivariate regression

A GLMM will be constructed to include utilization of opioid during the hospitalization and utilization of opioid on the day of discharge. Based on the bivariate analysis, we will identify the individual variables with a significant relationship to the outcomes as defined by a p-value of or less than 0.1000. These variables will be used to construct the multilevel multivariate logistic regression model for each outcome.

The primary outcome measures will be analyzed using a generalized linear mixed-effects model (GLMM) approach. Under this approach, a GLMM with a binomial distribution

and logit link function will be fitted to estimate the likelihood of an individual patient receiving

an opioid. Separate models will be constructed for receiving opioids at any time during the hospitalization and receiving an opiate on the last day of the hospitalization. It will include covariates listed above. The hospital will be included as a random effect to account for likely clustering. Significance testing will be based upon maximum likelihood and odds ratio estimates. The final set of predictors will be determined using backward selection with a p-value threshold of 0.100 for inclusion in the final reported model.

Variance Inflation Factors (VIF) will be used to assess the absence of multicollinearity, with VIF values over 10 suggesting the presence of multicollinearity. VIF were run and all values for the variables included in the final model were less than 10 suggesting no presence of multicollinearity. The majority of variables were categorical therefore no scatter plots were run.

4.1.3. Secondary analyses

4.1.3.1. Utilization of opioid during the hospitalization by route of administration (PO only, Non-PO Only and PO and Non-PO)

Descriptive statistics will be used to gain a better understanding of the routes of administration of opioids during the hospitalization including those patients receiving more than one route. The categorical data will be expressed as counts and percentage of patients in the category. As the data may be correlated, we will use the Chi-Squared test to examine differences in patient and hospital characteristics by route of administration.

4.1.3.2. Utilization of opioid on the day of discharge by route of administration (PO only, Non-PO Only and PO and Non-PO)

Descriptive statistics will be used to gain a better understanding of the routes of administration of opioids on the day of discharge. The categorical data will be expressed as counts and percentage of patients in the category. Each discharge may have more than one route of opioid administration and these categories are not mutually exclusive for each discharge. As the data may be correlated, we will use the Chi-Squared test to examine differences in patient and hospital characteristics by route of administration.

4.1.3.3. Utilization of opioid during the hospitalization by year of discharge

Descriptive statistics will be used to gain a better understanding of the trending over the three years of the study for of opioids during the hospitalization. The categorical data will be expressed as counts and percentage of patients in the category for each year.

Appendix A (continued)

4.1.3.4. Utilization of opioid on the day of discharge by year of discharge

Descriptive statistics will be used to gain a better understanding of the trending over the three years of the study for of opioids on the day of discharge. The categorical data will be expressed as counts and percentage of patients in the category for each year.

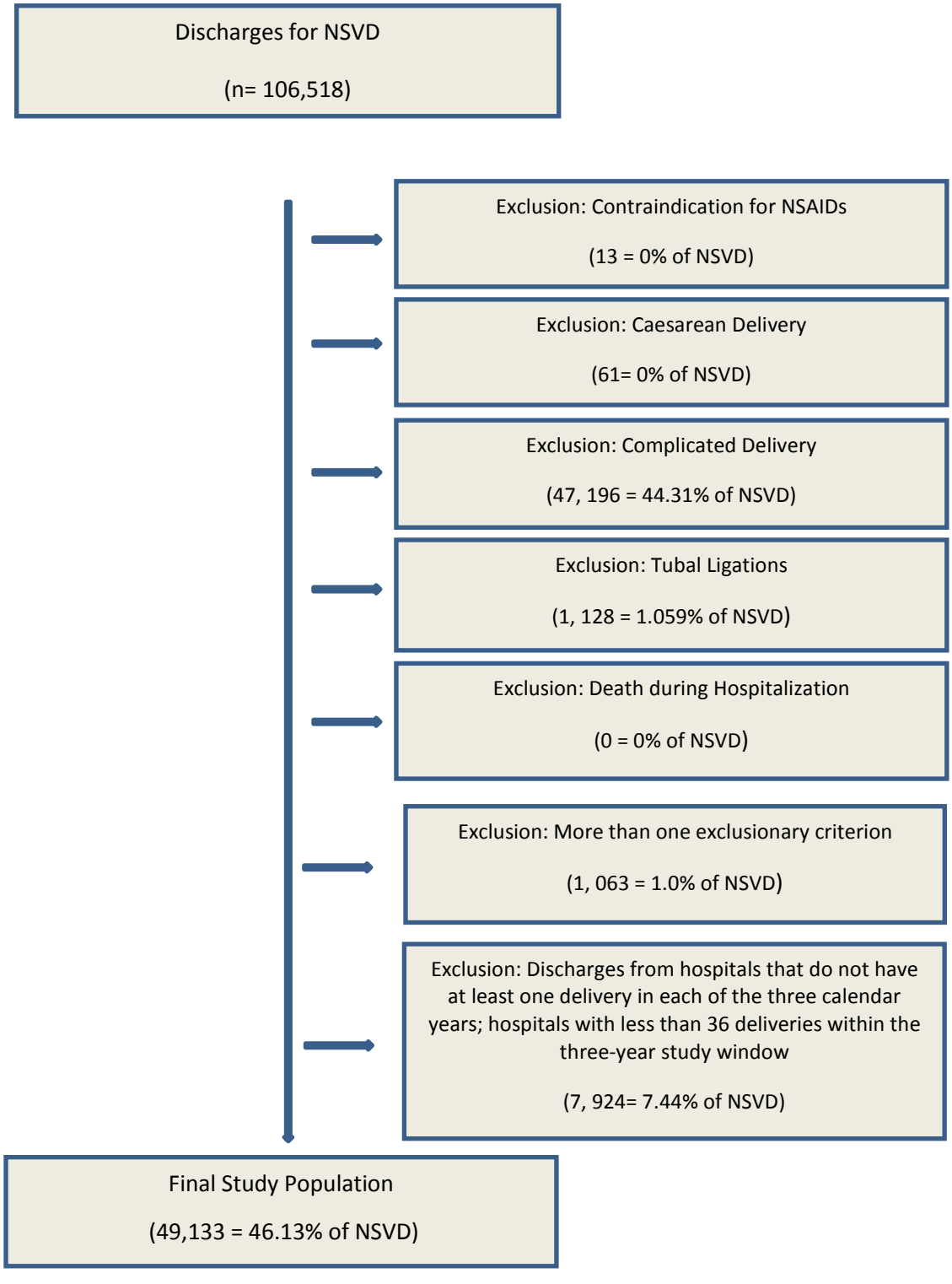
5. LIMITATIONS

This study is subject to several limitations. Charge data from the hospital's billing system are assumed to indicate use of opioids. Patients with several potential indications for opioid treatment were excluded from the study, but there may be additional indications for appropriate opioid treatment we did not exclude or evaluate.

Appendix A (continued)

6. LIST OF TABLES AND DATA SUMMARIES

Figure 1. Study population identification



Appendix A (continued)

Table 4a. NSVD Patient Characteristics of Opioid Utilization during Hospitalization: January 1, 2014 to December 31, 2016

Opioid use (any route) by year		Total NSVD Encounters	NSVD Patients with opioid	NSVD Patients w/o opioid	p-value
Number of patients (%)		**49,133**	**38,432**	**10,701**	
Age Group (n, %)	15-18	1, 691 (3.4%)	1, 406 (3.7%)	285 (2.7%)	<.0001
	19-34	46, 723 (95.1%)	36, 519 (95.0 %)	10, 204 (95.4%)	
	35-44	719 (1.5%)	507 (1.3%)	212 (2.0%)	
Marital Status (n, %)	Married	20, 703 (42.1%)	15, 449(40.2 %)	5,254 (49.1%)	<.0001
	Single	23, 427 (47.7%)	19, 456 (50.6%)	3, 971 (37.1%)	
	Unknown	5, 003 (10.2%)	3, 527 (9.2%)	1, 476 (13.8%)	
Race (n, %)	White	27, 894 (56.8%)	21, 859 (56.9%)	6, 035 (56.4%)	<.0001
	Black	8, 007 (16.3%)	6, 839 (17.8%)	1, 168 (10.9%)	
	Other-Unknown	13, 232 (26.9%)	9, 734 (25.3%)	3, 498 (32.7%)	
Ethnicity (n, %)	Hispanic or Latino	12, 175 (24.8%)	9, 459 (24.6%)	2, 716 (25.4%)	0.1034
	Other-Unknown	36, 958 (75.2%)	28, 973 (75.4%)	7, 985 (74.6%)	
Drug dependence (n, %)	Drug Dependence in pregnancy coded	11 (0.0%)	8 (0.0%)	3 (0.0%)	0.6589
	No drug dependence in pregnancy coded	49, 122 (100.0%)	38, 424 (100.0%)	10, 698 (100.0 %)	
Benzodiazepine Use (n, %)	Concomitant utilization of benzo and opioid on same day	203 (0.4%)	203 (0.5%)	0 (0.0%)	<.0001
	No concomitant use of benzo and opioid on same day	48, 930 (99.6%)	38, 229 (99.5%	10, 701 (100.0%)	
Payer	Medicaid	27, 636 (56.2%)	22, 416 (58.3%)	5, 220 (48.8%)	<.0001

Type (n, %)	Managed Care	15, 024 (30.6%)	11, 169 (29.1%)	3, 855 (36.0%)	
	Commercial-Indemnity	2, 815 (5.7%)	2, 033 (5.3%)	782 (7.3%)	
	Other	3, 658 (7.4%)	2, 814 (7.3%)	844 (7.9%)	
Length of Stay	Mean-Std Dev	1.8(±.6)	1.9(±.6)	1.7(±.6)	<.0001
	Median	2.0	2.0	2.0	
	IQR	[1.0, 2.0]	[1.0, 2.0]	[1.0, 2.0]	
	Min-Max	1.0--14.0	1.0--14.0	1.0--14.0	

Table 4b. Hospital Characteristics of Opioid Utilization in NSVD Patients During Hospitalization 2014 to 2016

Opioid use (any route) 329 U.S. Hospitals		**Total NSVD Encounters N=49, 133**	**NSVD Patients with opioid N=38, 432 (78.2%)**	**NSVD Patients without opioid N=10, 701 (21.8%)**	**p-value opioid vs. no opioid use**
Bed Size (n, %)	001-099	1616 (3.3%)	1202 (3.1%)	414 (3.9%)	<.0001
	100-199	6, 915 (14.1%)	5, 580 (14.5%)	1, 335 (12.5%)	
	200-299	10, 621 (21.6%)	8, 783 (22.9%)	1, 838 (17.2%)	
	300-499	16, 710 (34%)	13, 040 (33.9%)	3, 670 (34.3%)	
	500+	13, 271(27%)	9827 (25.6%)	3, 444 (32.2%)	
Region (n, %)	New England	1, 285 (2.6%)	805 (2.1%)	480 (4.5%)	<.0001
	Mid-Atlantic	2, 731 (5.6)	1, 570 (4.1%)	1, 161 (10.8%)	
	East North Central	5, 105 (10.4%)	3, 676 (9.6%)	1, 429 (13.4%)	
	West North Central	1, 668 (3.4%)	1, 363 (3.5%)	305 (2.9%)	
	South Atlantic	13, 582 (27.6%)	11, 250 (29.3%)	2, 332 (21.8%)	
	East South Central	2, 567	2, 187	380	

		(5.2%)	(5.7%)	(3.6%)	
	West South Central	9, 912 (20.2%)	8, 027 (20.9%)	1, 885 (17.6%)	
	Mountain	3,903 (7.9%)	3, 259 (8.5%)	644 (6.0%)	
	Pacific	8,380 (17.1%)	6, 295 (16.4%)	2, 085 (19.5%)	
Teaching Status (n, %)	Teaching	15, 962 (32.5%)	11, 801 (30.7)	4, 161 (38.9%)	<.0001
	Non-teaching	33, 171 (67.5%)	26, 631 (69.3%)	6, 540 (61.1%)	
Urbanicity (n, %)	Urban	43, 145 (87.8%)	33, 861 (88.1%)	9, 284 (86.8%)	.0002
	Rural	5, 988 (12.2%)	4, 571 (11.9%)	1, 417 (13.2%)	

Table 5. Opioid Utilization during Hospitalization: Normal Spontaneous Vaginal Deliveries (NSVD) 2014 to 2016

Discharge Year	**Overall (N= 49, 133)**	**NSVD Encounters with Opioid Use N= 38, 432 (78.2%)**	**NSVD Encounters with No Opioid Use N= 10, 701 (21.8%)**
2014	17, 357	13, 575 (78.2%)	3, 782 (21.8%)
2015	17, 188	13, 532 (78.7%)	3, 656 (21.3%)
2016	14, 588	11, 325 (77.6%)	3, 263 (22.4%)

Appendix A (continued)

Table 6. Route of Opioid and Trending of Opioid Utilization during Hospitalization: Normal Spontaneous Vaginal Deliveries (NSVD) January 1, 2014 to December 31, 2016

Population	Overall	2014	2015	2016
NSVD, n	49, 133	17, 357	17, 188	14, 588
NSVD, without any opioid, n (%)	10, 701 (21.8%)	3, 782 (21.8%)	3, 656 (21.3%)	3, 263 (22.4%)
NSVD with any opioid during hospitalization, n (%)	38, 432 (78.2%)	13, 575 (78.2%)	13, 532 (78.7%)	11, 325 (77.6%)
NSVD with only non-PO opioid during hospitalization, n (%)	14, 673 (29.9%)	4, 957 (28.6%)	5, 078 (29.5%)	4, 638 (31.8%)
NSVD with only PO opioid during hospitalization, n (%)	7, 760 (15.8%)	2, 841 (16.4%)	2, 775 (16.1%)	2, 144 (14.7%)
NSVD with both PO and non-PO opioid during hospitalization, n (%)	15, 999 (32.6%)	5, 777 (33.3%)	5, 679 (33.0%)	4, 543 (31.1%)

Appendix A (continued)

Table 7a. Patient Characteristics of Opioid Utilization on Day of Discharge: Normal Spontaneous Vaginal Deliveries (NSVD) January 1, 2014 to December 31, 2016

		Total NSVD Encounters	**Patients with opioid on day of discharge**	**Patients without opioid on day of discharge**	**p-value**
Number of Patients		**49, 133**	**14, 635**	**34, 498**	
Age Group (n, %)	15-18	1, 691 (3.4%)	412 (2.8%)	1, 279 (3.7%)	<.0001
	19-34	46, 723 (95.1%)	14, 066 (96.1%)	32, 657 (94.7%)	
	35-44	719 (1.5%)	157 (1.1%)	562 (1.6%)	
Marital Status (n, %)	Married	20, 703 (42.1%)	5, 296 (36.2%)	15, 407 (44.7%)	<.0001
	Single	23, 427 (47.7%)	8, 121 (55.5%)	15, 306 (44.4%)	
	Other-Unknown	5, 003 (10.2%)	1,218 (8.3%)	3,785 (11.0%)	
Race (n, %)	White	27, 894 (56.8%)	8, 227 (56.2%)	19, 667 (57.0%)	<.0001
	Black	8,007 (16.3%)	3, 135 (21.4%)	4, 872 (14.1%)	
	Other-Unknown	13, 232 (26.9%)	3,273 (22.4%)	9, 959 (28.9%)	
Ethnicity (n, %)	Hispanic or Latino	12, 175 (24.8%)	3, 110 (21.3%)	9, 065 (26.3%)	<.0001
	Unknown	36, 958 (75.2%)	11,525 (78.7%%)	25, 433 (73.7%)	
Drug dependence (n, %)	Drug dependence in pregnancy coded	11 (0.0%)	4 (0.0%)	7 (0.0%)	0.6333
	No drug dependence in pregnancy coded	49, 122 (100.0%)	14, 631 (100.0%)	34, 491 (100.0%)	
Benzodiazepine use (n, %)	Concomitant benzodiazepine on same day as opioid	203 (0.4%)	142 (1.0%)	61 (0.2%)	<.0001
	No concomitant use of benzodiazepine on same day as opioid	48, 930 (99.6%)	14, 493 (99.0%)	34, 437 (99.8%)	
Payer Type (n, %)	Medicaid	27, 636 (56.2%)	9, 407 (64.3%)	18, 229 (52.8%)	<.0001
	Managed Care	15, 024	3, 603	11, 421	

		(30.6%)	(24.6%)	(33.1%)	
	Commercial-Indemnity	2, 815 (5.7%)	684 (4.7%)	2, 131 (6.2%)	
	Other	3, 658 (7.4%)	941 (6.4%)	2, 717 (7.9%)	
Length of Stay	Mean (Std Dev)	1.8 ± 0.6	1.9 ±0.6	1.8 ±0.6	<.0001
	Median	2.0	2.0	2.0	
	IQR	[1.0, 2.0]	[1.0, 2.0]	[1.0 2.0]	
	Min-Max	1.0-14.0	1.0-14.0	1.0-10.0	

Note: P-values are derived from T-tests for means and Chi-Squared tests for categorical variables.

Table 7b. Hospital Characteristics of Opioid Utilization on Day of Discharge: Normal Spontaneous Vaginal Deliveries (NSVD) January 1, 2014 to December 31, 2016

Opioid use (any route by year)		**Total NSVD Encounters**	**Patients with opioid on day of discharge**	**Patients without opioid on day of discharge**	**p-value**
Number of Hospitals		**330**	**325**	**330**	
Length of Stay	N	49, 133	14, 635	34, 498	<.0001
	Mean (Std Dev)	1.8 ± 0.6	1.9 ±0.6	1.8 ±0.6	
	Median	2.0	2.0	2.0	
	IQR	[1.0, 2.0]	[1.0, 2.0]	[1.0 2.0]	
	Min-Max	1.0-14.0	1.0-14.0	1.0-10.0	
Bed Size (n, %)	001-099	1616 (3.3%)	554 (3.8%)	1, 062 (3.1%)	<.0001
	100-199	6915 (14.1%)	2, 242 (15.3%)	4, 673 (13.5%)	
	200-299	10, 621 (21.6%)	3, 509 (24.0%)	7, 112 (20.6)	
	300-499	16, 710 (34.0%)	4, 915 (33.6%)	11, 795 (34.2%)	
	500+	13, 271 (27%)	3, 415 (23.3%)	9, 856 (28.6%)	
Region (n, %)	New England	1, 285 (2.6%)	160 (1.1%)	1, 125 (3.3%)	<.0001
	Mid-Atlantic	2, 731 (5.6%)	370 (2.5%)	2, 361 (6.8%)	
	East North Central	5, 105 (10.4%)	1, 218 (8.3%)	3, 887 (11.3%)	
	West North	1, 668	574 (3.9%)	1, 094	

	Central	(3.4%)		(3.2%)	
	South Atlantic	13, 582 (27.6%)	4, 361 (29.8%)	9, 221 (26.7%)	
	East South Central	2, 567 (5.2%)	999 (6.8%)	1, 568 (4.5%)	
	West South Central	9, 912 (20.2%)	3, 414 (23.3%)	6, 498 (18.8%)	
	Mountain	3, 903 (7.9%)	1, 264 (8.6%)	2, 639 (7.6%)	
	Pacific	8, 380 (17.1%)	2, 275 (15.5%)	6, 105 (17.7%)	
Teaching Status (n, %)	Teaching	15, 962 (32.5%)	4, 077 (27.9%)	11, 885 (34.5%)	<.0001
	Non-teaching	33, 171 (67.5%)	10, 558 (72.1%)	22, 613 (65.5%)	
Urbanicity (n, %)	Urban	43, 145 (87.8%)	12, 654 (86.5%)	30, 491 (88.4%)	<.0001
	Rural	5, 988 (12.2%)	1, 981 (13.5%)	4, 007 (11.6%)	

P-values derived from T-Tests for means and Chi-Squared for categorical variables

Appendix A (continued)

Table 8. Trends in Opioid on Day of Discharge: Normal Spontaneous Vaginal Deliveries (NSVD) January 1, 2014 to December 31, 2016

Discharge Year	**Overall**	**Patients with opioid on day of discharge (any route) (n, %)**	**Patients without opioid on day of discharge (any route), (n %)**
Number of Patients	N= 49, 133	N= 14, 635	N= 34, 498
2014	17, 357 (100%)	5, 291 (30.5%)	12, 066 (69.5%)
2015	17, 188 (100%)	5, 238 (30.5%)	11, 950 (69.5%)
2016	14, 588 (100%)	4, 106 (28.1%)	10, 482 (71.9%)

Table 9. Route of Opioid Utilization and Trends in Opioid Use on Day of Discharge: Normal Spontaneous Vaginal Deliveries (NSVD) January 1, 2014 to December 31, 2016

Population (N)	Overall N= 49, 133	2014 N= 17, 357	2015 N= 17, 188	2016 N= 14, 588
NSVD without any opioid on day of discharge (n, %)	34, 498 (70.2%)	12, 066 (69.5%)	11, 950 (69.5%)	10, 482 (71.9%)
NSVD with any opioid on day of discharge (n, %)	14, 635 (29.8%)	5, 291 (30.5%)	5, 238 (30.5%)	4, 106 (28.1%)
NSVD with any non-PO opioid on day of discharge (n, %)	132 (0.3%)	57 (0.3%	42 (0.2%)	33 (0.2%)
NSVD with any PO opioid on day of discharge (n, %)	14, 415 (29.3%)	5, 201 (30.0%)	5, 162 (30.0%)	4, 052 (27.8%)
NSVD with both PO and non-PO opioid on day of discharge (n, %)	88 (0.2%)	33 (0.2%)	34 (0.2%)	21 (0.1%)

Appendix A (continued)

Table 10. GLMM Analysis: Normal Spontaneous Vaginal Deliveries (NSVD) who received an Opioid January 1, 2014- December 31, 2016

Any Opioid During Hospitalization REDUCED Model
Adjusted Odds Ratio Estimates

Effects	Description	Odds Ratio	95% Wald Lower Confidence	95% Wald Upper Confidence	P-value
Age	19-34 (ref 15-18)	0.93	0.81	1.07	0.3095
	35-44 (ref 15-18)	0.73	0.59	0.89	0.002
Marital Status	Married (ref Single)	0.68	0.64	0.72	<.0001
	Other-Unknown status (ref Single)	0.79	0.70	0.89	0.0001
Race	Black (ref White)	1.42	1.31	1.54	<.0001
	Other (ref White)	0.92	0.86	0.97	0.0044
Payor	Managed Care (ref Commercial - Indemnity)	1.07	0.96	1.21	0.225
	Medicaid (ref Commercial - Indemnity)	1.36	1.21	1.51	<.0001
	Other Payor (ref Commercial - Indemnity)	1.04	0.91	1.19	0.5895
Hospital Geographic Region	East North Central (ref West South Central)	0.46	0.32	0.66	<.0001
	East South Central (ref West South Central)	1.10	0.71	1.71	0.6709
	Middle Atlantic (ref West South Central)	0.30	0.20	0.46	<.0001
	Mountain (ref West South Central)	0.80	0.51	1.24	0.317
	New England (ref West South Central)	0.34	0.19	0.62	0.0004
	Pacific (ref West South Central)	0.52	0.38	0.73	0.0001
	South Atlantic (ref West South Central)	0.78	0.58	1.05	0.1013
	West North Central (ref West South Central)	1.06	0.63	1.78	0.8244
Hospital Teaching Status	Teaching (ref Non-Teaching)	0.80	0.65	0.99	0.0397

Appendix A (continued)

Any Opioid on Day of Discharge REDUCED Model
Adjusted Odds Ratio Estimates

Effects	Description	Odds Ratio	95% Wald Lower Confidence	95% Wald Upper Confidence	P-value
age	19-34 (ref 15-18)	1.65	1.46	1.86	<.0001
	35-44 (ref 15-18)	1.27	1.04	1.54	0.0180
Marital Status	Married (ref Single)	0.77	0.73	0.81	<.0001
	Other-Unknown status (ref single)	0.90	0.80	1.00	0.0549
Race	Black (ref White)	1.27	1.19	1.36	<.0001
	Other (ref White)	0.86	0.81	0.92	<.0001
Ethnicity	Hispanic (ref non-Hispanic)	0.86	0.81	0.92	<.0001
Payor	Managed Care (ref Commercial - Indemnity)	1.10	0.98	1.23	0.1097
	Medicaid (ref Commercial - Indemnity)	1.71	1.53	1.90	<.0001
	Other Payor (ref Commercial - Indemnity)	1.22	1.07	1.40	0.0027
Hospital Geographic Region	East North Central (ref West South Central)	0.44	0.32	0.60	<.0001
	East South Central (ref West South Central)	0.83	0.57	1.21	0.3327
	Middle Atlantic (ref West South Central)	0.24	0.17	0.36	<.0001
	Mountain (ref West South Central)	0.65	0.44	0.96	0.0289
	New England (ref West South Central)	0.19	0.11	0.33	<.0001
	Pacific (ref West South Central)	0.57	0.43	0.77	0.0002
	South Atlantic (ref West South Central)	0.62	0.48	0.80	0.0003
	West North Central (ref West South Central)	0.94	0.60	1.46	0.7736
Hospital Teaching Status	Teaching (ref non-teaching)	0.79	0.65	0.95	0.0123

Appendix A (continued)

SAP APPENDIX A: DATA SOURCE AS DEFINED BY PREMIER, INC.

Data for the extract described in this document are derived from the Premier Healthcare Database, which currently contains data from more than 681 million patient encounters, or one in every five discharges in the nation. Hospital discharge data in Premier's dynamic database are updated on a regular basis and are currently available from January 2000 through the September 2016. The Premier database contains data from standard hospital discharge files, including a patient's demographic and disease state, and information on billed services, including medications, laboratory tests performed, diagnostics and therapeutic services in de-identified patient daily service records. In addition, information on hospital characteristics, including geographic location, bed size and teaching status, is also available.

The Premier database is a comprehensive view of inpatient and hospital-based outpatient visits from geographically diverse hospitals. It is not a random sample; patient-related data are collected from all payers and therapeutic areas. Patients can be tracked across the inpatient and hospital-based outpatient settings, as well as across visits with a unique identifier within a single hospital. In addition to the data elements available in most of the standard hospital discharge files, the Premier database also contains a date-stamped log of billed items, including procedures, medications, laboratory test performed, and diagnostic and therapeutic services at the individual patient level. All procedures and diagnoses are captured for each patient, as well as all drugs and devices received. Drug utilization information is available by day of stay and includes quantity, strength used, charge, and hospital reported cost. Billing reconciliation occurs at the encounter level; variation at the line item level is to be expected.

Comparisons between patient and hospital characteristics for the hospitals submitting data to Premier and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) suggest the patient populations are similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups. It should be noted that the number of participating hospitals within the Premier database may change over time during the study period, and a random hospital identifier assigned by Premier will be used to identify the various hospitals.

Appendix A (continued)

SAP APPENDIX B. OPIOID MEDICATIONS (POSSIBLE ROUTES OF ADMINISTRATION: IV, PO, IM OR TOPICAL)

GENERIC	**Brands**
Opioids and Combinations	
CODEINE + ACETAMENOPHEN	Tylenol #3, Tylenol #4, multiple combinations
FENTANYL TRANSDERMAL	Duragesic, Ionsys
FENTANYL INJECTION	Sublimaze
FENTANYL ORAL, SUBLINGUAL, BUCCAL, NASAL	Abstral, Actiq, Fentora, Lazanda, Subsys
HYDROCODONE	Hysingla ER, Zohydro ER
HYDROCODONE + ACETAMINOPHEN	Norco, Vicodin, Lortab, Lorcet
HYDROCODONE + ASPIRIN	Lortab ASA, Azdone, Alor, Panasal
HYDROMORPHONE	Dilaudid
MEPERIDINE	Demerol
MEPERIDINE + PROMETHAZINE	Mepergan
MORPHINE	MS Contin, Roxanol, Astramorph, Avinza, Kadian, Ora-Morph SR
MORPHINE + NALTREXONE	Embeda
OXYCODONE	Oxycontin
OXYCODONE + ACETAMINOPHEN	Percocet, Tylox, Oxycocet, Roxicet
OXYCODONE + ASPIRIN	Endodan, Oxycodan, Percodan, Roxiprin
OXYCODONE + NALOXONE	Targiniq ER
OXYMORPHONE	Numorphan, Numorphone, Opana
PENTAZOCINE + NALOXONE	Talwin NX
TAPENTADOL	Nucynta
TRAMADOL	Ultram
TRAMADOL/ACETAMINOPHEN	Ultracet, Tramapap
ALFENTANIL	Alfenta
BUPRENORPHINE	Subutex
BUTORPHANOL	Stadol
LEVORPHANOL	Levo-Dromoran
NALBUPHINE	Nubain, Manfine
REMIFENTANIL	Ultiva
SUFENTANIL	Sufenta

SAP APPENDIX C. BENZODIAZEPINE MEDICATIONS

Generic name	Common brand names*
ALPRAZOLAM	Xanax, Helex, Xanor, Trankimazin, Onax, Alprox, Restyl, Solanax, Tafil, Neurol
CHLORDIAZEPOXIDE	Librium, Risolid, Elenium
CLOBAZAM	Onfi, Frisium, Urbanol
CLONAZEPAM	Rivatril, Rivotril, Klonopin, Iktorivil, Paxam
CLORAZEPATE	Tranxene, Tranxilium
DIAZEPAM	Antenex, Apaurin, Apzepam, Apozepam, Diazepan, Hexalid, Pax, Stesolid, Stedon, Valium, Vival, Valaxona
ESTAZOLAM	ProSom, Nuctalon
FLURAZEPAM	Dalmadorm, Dalmane
HALAZEPAM	Paxipam
LORAZEPAM	Ativan, Orfidal, Lorenin, Lorsilan, Temesta, Tavor, Lorabenz
MIDAZOLAM	Dormicum, Versed, Hypnovel, Dormonid
NITRAZOPAM	Mogadon, Alodorm, Pacisyn, Dumolid, Nitrazadon
OXAZEPAM	Seresta, Serax, Serenid, Serepax, Sobril, Oxabenz, Oxapax, Opamox
QUAZEPAM	Doral
TEMAZEPAM	Restoril, Normison, Euhypnos, Temaze, Tenox
TRIAZOLAM	Halcion, Rilamir

Appendix B: IRB and Premier Approval, Part I (Epidemiological Study)

-IRB Approval

-Premier approval letter

Approval Notice
Initial Review (Response To Modifications)

October 3, 2017

Jennie (Becca) Mills, DrPHc, MSM, BA
Health Policy and Administration
14995 Wetterhorn Pk Tr
Phone: (913) 707-1661

RE: Protocol # 2017-0781
"A National Analysis of Opioid Prescribing in NSVD to Inform Leaders in Maternal Health Practice & Policy"

Dear Ms. Mills:

Please note that UIC OPRS will no longer send approved and stamped document(s) via email correspondence. Effective 7/24/2017, newly approved, stamped recruitment and informed consent document(s) can be accessed via OPRS Live. Documents will be located in the specific protocol workspace under the "Approved Documents" tab. (Note that documents approved and stamped prior to 7/24/2017 may not be accessible through OPRS Live; these would have been sent as email attachments at the time of approval.)

Your Initial Review (Response To Modifications) was reviewed and approved by the Expedited review process on October 3, 2017. You may now begin your research

Please note the following information about your approved research protocol:

Protocol Approval Period: October 3, 2017 - October 3, 2018
Approved Subject Enrollment #: 20 (Delphi Panel physicians)
Additional Determinations for Research Involving Minors: These determinations have not been made for this study since it has not been approved for enrollment of minors.
Performance Sites: UIC, Premier, Inc.
Sponsor: None

Research Protocol(s):

a) Delphi Protocol, Version 2, August 30

Recruitment Material(s):

a) No recruitment materials will be used

Informed Consent(s):

a) Informed Consent and Non-Disclosure; Version 2
b) Alteration of informed consent [45CFR46.116(d)] granted for online consent.

RESEARCH TITLE: A National Analysis of Opioid Prescribing in Normal, Spontaneous, Vaginal Delivery Patients (NSVD) to Inform leaders in Maternal Health Practice & Policy

OBJECTIVE(S)

Provide Recommendations to Clinical, Administrative and Policy Leadership for Opioid Prescribing during NSVD.

Characterize U.S. Opioid Prescribing Practices During the Hospital Stay and on the Day of Discharge for NSVD patients with and without a documented history of OUD.

PROJECT DESIGN

Methods being utilized (which involve Premier): *Observational retrospective study using the Premier Data otherwise known as PHD...*

- *descriptive analysis only*
- *modeled analysis included*

OTHER CONSIDERATIONS

The CHIO serves on the dissertation committee for which this research will be presented for approval. The committee has approved the dissertation proposal.

The other method employed is the Delphi Method for surveying health care providers. Premier will not be involved in this work.

DATA SOURCE

Data for the analyses described in this document are derived from the Premier Healthcare Database, which currently contains data from more than 690 million patient encounters, or one in every five discharges in the nation. Hospital discharge data in Premier's dynamic database are updated on a regular basis, and are currently available from January 2000 through December 2016. The Premier database contains data from standard hospital discharge files, including a patient's demographic and disease state, and information on billed services, including medications, laboratory tests performed, diagnostics and therapeutic services in de-identified patient daily service records. In addition, information on hospital characteristics, including geographic location, bed size and teaching status, is also available.

The Premier database is a comprehensive view of inpatient and hospital-based outpatient visits from geographically diverse hospitals. It is not a random sample; patient-related data are collected from all payers and therapeutic areas. Patients can be tracked across the inpatient and hospital-based outpatient settings, as well as across visits with a unique identifier within a single hospital. In addition to the data elements available in most of the standard hospital discharge files, the Premier database also contains a date-stamped log of billed items, including

procedures, medications, laboratory test performed, and diagnostic and therapeutic services at the individual patient level. All procedures and diagnoses are captured for each patient, as well as all drugs and devices received. Drug utilization information is available by day of stay and includes quantity, strength used, charge, and hospital reported cost. Billing reconciliation occurs at the encounter level; variation at the line item level is to be expected.

Comparisons between patient and hospital characteristics for the hospitals that submit data to Premier and those of the probability sample of hospitals and patients selected for the National Hospital Discharge Survey (NHDS) suggest that the patient populations are similar with regard to patient age, gender, length of stay, mortality, primary discharge diagnosis and primary procedure groups. It should be noted that the number of participating hospitals within the Premier database may change over time during the study period, and a random hospital identifier assigned by Premier will be used to identify the various hospitals.

I, Mimi Huizinga, give permission for the PI of this study, Jennie Rebecca Mills, to use data from the Premier database (PHD) to pursue the research work associated with the national prescribing patterns associated with the NSVD population. I approve Premier to be considered a non-UIC performance site.

Printed Name and Title:

Mary Margaret (Mimi) Huizinga, MD MPH FACP

Signature:

Date:

June 29, 2017

Appendix C: CDC Guidelines for Opioid Prescribing for Chronic Pain

-Fact Sheet

-Full Guidelines

-Fact Sheet

***LEARN MORE** | www.cdc.gov/drugoverdose/prescribing/guideline.html*

IMPROVING PRACTICE THROUGH RECOMMENDATIONS

CDC's Guideline for Prescribing Opioids for Chronic Pain *is intended to improve communication between providers and patients about the risks and benefits of opioid therapy for chronic pain, improve the safety and effectiveness of pain treatment, and reduce the risks associated with long-term opioid therapy, including opioid use disorder and overdose. The Guideline is not intended for patients who are in active cancer treatment, palliative care, or end-of-life care.*

DETERMINING WHEN TO INITIATE OR CONTINUE OPIOIDS FOR CHRONIC PAIN

Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.

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

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.

CLINICAL REMINDERS

- **Opioids are not first-line or routine therapy for chronic pain**
- **Establish and measure goals for pain and function**
- **Discuss benefits and risks and availability of nonopioid therapies with *patient***

OPIOID SELECTION, DOSAGE, DURATION, FOLLOW-UP, AND DISCONTINUATION

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

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

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

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.

CLINICAL REMINDERS

- **Use immediate-release opioids when starting**
- **Start low and go slow**
- **When opioids are needed for acute pain, prescribe no more *than needed***
- **Do not prescribe ER/LA opioids for acute pain**
- **Follow-up and re-evaluate risk of harm; reduce dose or taper *and discontinue if needed***

ASSESSING RISK AND ADDRESSING HARMS OF OPIOID USE

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.

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.

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.

Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.

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.

CLINICAL REMINDERS

- **Evaluate risk factors for opioid-related harms**

- **Check PDMP for high dosages and prescriptions from other *providers***

- **Use urine drug testing to identify prescribed substances and *undisclosed use***

- **Avoid concurrent benzodiazepine and opioid prescribing**

- **Arrange treatment for opioid use disorder if needed**

LEARN MORE | *www.cdc.gov/drugoverdose/prescribing/guideline.html*

-Full Guidelines

For Full CDC Opioid Prescribing Guidelines for Chronic Pain please visit:

https://www.cdc.gov/mmwr/volumes/65/rr/pdfs/rr6501e1.pdf

or, see below:

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

Prepared by [1] Deborah Dowell, MD [1]

Tamara M. Haegerich, PhD [1] Roger Chou, MD[1]

Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC, Atlanta, Georgia

Summary

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

Introduction Background

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

Prevention, assessment, and treatment of chronic pain are challenges for health providers and systems. Pain might go unrecognized, and patients, particularly members of racial and ethnic minority groups, women, the elderly, persons with

cognitive impairment, and those with cancer and at the end of life, can be at risk for inadequate pain treatment (*4*). Patients can experience persistent pain that is not well controlled. There are clinical, psychological, and social consequences associated with chronic pain including limitations in complex activities, lost work productivity, reduced quality of life, and stigma, emphasizing the importance of appropriate and compassionate patient care (*4*). Patients should receive appropriate pain treatment based on a careful consideration of the benefits and risks of treatment options.

Chronic pain has been variably defined but is defined within this guideline as pain that typically lasts >3 months or past the time of normal tissue healing (*5*). Chronic pain can be the result of an underlying medical disease or condition, injury, medical treatment, inflammation, or an unknown cause (*4*). Estimates of the prevalence of chronic pain vary, but it is clear that the number of persons experiencing chronic pain in the United States is substantial. The 1999–2002 National Health and Nutrition Examination Survey estimated that 14.6% of adults have current widespread or localized pain lasting at least 3 months (*6*). Based on a survey conducted during 2001–2003 (*7*), the overall prevalence of common, predominantly musculoskeletal pain conditions (e.g., arthritis, rheumatism, chronic back or neck problems, and frequent severe headaches) was estimated at 43% among adults in the United States, although minimum duration of symptoms was not specified. Most recently, analysis of data from the 2012 National Health Interview Study showed that 11.2% of adults report having daily pain (*8*). Clinicians should consider the full range of therapeutic options for the treatment of chronic pain. However, it is hard to estimate the number of persons who could potentially benefit from opioid pain medication long term. Evidence supports short-term efficacy of opioids for reducing pain and improving function in noncancer nociceptive and neuropathic pain in randomized clinical trials lasting primarily ≤12 weeks (*9*,*10*), and patients receiving opioid therapy for chronic pain report some pain relief when surveyed (*11*–*13*). However, few studies have been conducted to rigorously assess the long-term benefits of opioids for chronic pain (pain lasting >3 months) with outcomes examined at least 1 year later (*14*). On the basis of data available from health systems, researchers estimate that 9.6–11.5 million adults, or approximately 3%–4% of the adult U.S. population, were prescribed long-term opioid therapy in 2005 (*15*).

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

receiving opioids for chronic noncancer pain and followed for up to 13 years revealed that one in 550 patients died from opioid-related overdose at a median of 2.6 years from their first opioid prescription, and one in 32 patients who escalated to opioid dosages >200 morphine milligram equivalents (MME) died from opioid-related overdose (*25*).

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

Rationale

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

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

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

Scope and Audience

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

and identify, the guideline is intended to inform clinicians who are considering prescribing opioid pain medication for painful conditions that can or have become chronic.

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

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

and encouraged, to inform development of future guidelines for this critical population.

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

Guideline Development Methods

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

CDC developed this guideline using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method (http://www.gradeworkinggroup.org). This method specifies the systematic review of scientific evidence and offers a transparent approach to grading quality of evidence and strength of recommendations. The method has been adapted by the CDC Advisory Committee on Immunization Practices (ACIP) (*47*). CDC has applied the ACIP translation of the GRADE framework in this guideline. Within the ACIP GRADE framework, the body of evidence is categorized in a hierarchy. This hierarchy reflects degree of confidence in the effect of a clinical action on health outcomes. The categories include type 1 evidence (randomized clinical trials or overwhelming evidence from observational studies), type 2 evidence (randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies), type 3 evidence (observational studies or randomized clinical trials with notable limitations), and type 4 evidence (clinical

experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations). Type of evidence is categorized by study design as well as limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of treatment effects, dose-response gradient, and a constellation of plausible biases that could change observations of effects. Type 1 evidence indicates that one can be very confident that the true effect lies close to that of the estimate of the effect; type 2 evidence means that the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; type 3 evidence means that confidence in the effect estimate is limited and the true effect might be substantially different from the estimate of the effect; and type 4 evidence indicates that one has very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of the effect (*47*,*48*). When no studies are present, evidence is considered to be insufficient. The ACIP GRADE framework places recommendations in two categories, Category A and Category B. Four major factors determine the category of the recommendation: the quality of evidence, the balance between desirable and undesirable effects, values and preferences, and resource allocation (cost). Category A recommendations apply to all persons in a specified group and indicate that most patients should receive the recommended course of action. Category B recommendations indicate that there should be individual decision making; different choices will be appropriate for different patients, so clinicians must help patients arrive at a decision consistent with patient values and preferences, and specific clinical situations (*47*). According to the GRADE methodology, a particular quality of evidence does not necessarily imply a particular strength of recommendation (*48*–*50*). Category A recommendations can be made based on type 3 or type 4 evidence when the advantages of a clinical action greatly outweigh the disadvantages based on a consideration of benefits and harms, values and preferences, and costs. Category B recommendations are made when the

advantages and disadvantages of a clinical action are more balanced. GRADE methodology is discussed extensively elsewhere (*47*,*51*). The U.S. Preventive Services Task Force (USPSTF) follows different methods for developing and categorizing recommendations (http://www. uspreventiveservicestaskforce.org). USPSTF recommendations focus on preventive services and are categorized as A, B, C, D, and I. Under the Affordable Care Act, all "nongrandfathered" health plans (that is, those health plans not in existence prior to March 23, 2010 or those with significant changes to their coverage) and expanded Medicaid plans are required to cover

preventive services recommended by USPSTF with a category A or B rating with no cost sharing. The coverage requirements went into effect September 23, 2010. Similar requirements are in place for vaccinations recommended by ACIP, but do not exist for other recommendations made by CDC, including recommendations within this guideline.

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

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

stratification/mitigation approaches, and effectiveness of treatments for addressing potential harms of opioid therapy); clinician and patient values and preferences; and resource allocation. CDC constructed narrative summaries of this contextual evidence and used the information to support the clinical recommendations. More details on methods for the contextual evidence review are provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/cdc/38027).

On the basis of a review of the clinical and contextual evidence (review methods are described in more detail in subsequent sections of this report), CDC drafted recommendation statements focused on determining when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and

discontinuation; and assessing risk and addressing harms of opioid use. To help assure the draft guideline's integrity and credibility, CDC then began a multistep review process to obtain input from experts, stakeholders, and the public to help refine the recommendations.

Solicitation of Expert Opinion

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

Prior to their participation, CDC asked potential experts to reveal possible conflicts of interest such as financial relationships with industry, intellectual preconceptions, or previously stated public positions. Experts could not serve if they had conflicts that might have a direct and predictable effect on the recommendations. CDC excluded experts who had a financial or promotional relationship with a company

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

that makes a product that might be affected by the guideline. CDC reviewed potential nonfinancial conflicts carefully (e.g., intellectual property, travel, public statements or positions such as congressional testimony) to determine if the activities would have a direct and predictable effect on the recommendations. CDC determined the risk of these types of activities to be minimal for the identified experts. All experts completed a statement certifying that there was no potential or actual conflict of interest. Activities that did not pose a conflict (e.g., participation in Food and Drug Administration [FDA] activities or other guideline efforts) are disclosed.

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

Federal Partner Engagement

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

the U.S. Department of Defense, the Office of the National Coordinator for Health Information Technology, the Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, AHRQ, and the Office of National Drug Control Policy.

Stakeholder Comment

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

Constituent Engagement

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

Peer Review

Per the final information quality bulletin for peer review (https://www.whitehouse.gov/sites/default/files/omb/ memoranda/fy2005/m05-03.pdf), peer review requirements applied to this guideline because it provides influential

scientific information that could have a clear and substantial impact on public- and private-sector decisions. Three experts independently reviewed the guideline to determine the reasonableness and strength of recommendations; the clarity with which scientific uncertainties were clearly identified; and the rationale, importance, clarity, and ease of implementation of the recommendations.* CDC selected peer reviewers based on expertise, diversity of scientific viewpoints, and independence from the guideline development process. CDC assessed and managed potential conflicts of interest using a process similar to the one as described for solicitation of expert opinion. No financial interests were identified in the disclosure and review process, and nonfinancial activities were determined to be of minimal risk; thus, no significant conflict of interest concerns were identified. CDC placed the names of peer reviewers on the CDC and the National Center for Injury Prevention and Control Peer Review Agenda websites that are used to provide information about the peer review of influential documents. CDC reviewed peer review comments and revised the draft guideline accordingly.

Public Comment

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

Federal Advisory Committee Review and Recommendation

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

to disclose relevant interests. BSC members also reported on their disclosures during meetings. Disclosures for the BSC are reported in the guideline.

To assist in guideline review, on December 14, 2015, via Federal Register notice, CDC announced the intent to form an Opioid Guideline Workgroup (OGW) to provide observations on the draft guideline to the BSC. CDC provided the BSC with the draft guideline as well as summaries of comments provided to CDC by stakeholders, constituents, and peer reviewers, and edits made to the draft guideline in response. During an open meeting held on January 7, 2016, the BSC recommendedtheformationoftheOGW.TheOGWincluded a balance of perspectives from audiences directly affected by the guideline, audiences that would be directly involved with implementing the recommendations, and audiences qualified to provide representation. The OGW comprised clinicians, subject matter experts, and a patient representative, with the following perspectives represented: primary care, pain medicine, public health, behavioral health, substance abuse treatment, pharmacy, patients, and research.* Additional sought-after attributes were appropriate academic and clinical training and relevant clinical experience; high scientific standing; and knowledge of the patient, clinician, and caregiver perspectives. In accordance with CDC policy, two BSC committee members also served as OGW members, with one serving as the OGW Chair. The professional credentials and interests of OGW members were carefully reviewed to identify possible conflicts of interest such as financial relationships with industry, intellectual preconceptions, or previously stated public positions. Only OGW members whose interests were determined to be minimal were selected. When an activity was perceived as

having the potential to affect a specific aspect of the recommendations, the activity was disclosed, and the OGW member was recused from discussions related to that specific aspect of the recommendations (e.g., urine drug testing and abuse-deterrent formulations). Disclosures for the OGW are reported. CDC and the OGW identified ad-hoc consultants to supplement the workgroup expertise, when needed, in the areas of pediatrics, occupational medicine, obstetrics and gynecology, medical ethics, addiction psychiatry, physical medicine and rehabilitation, guideline development methodology, and the perspective of a family member who lost a loved one to opioid use disorder or overdose.

The BSC charged the OGW with reviewing the quality of the clinical and contextual evidence reviews and reviewing each of the recommendation statements and accompanying rationales. For each recommendation statement, the OGW considered the quality of the evidence, the balance of benefits and risks, the values and preferences of clinicians and patients, the cost feasibility, and the category designation

of the recommendation (A or B). The OGW also reviewed supplementary documents, including input provided by the CEG, SRG, peer reviewers, and the public. OGW members discussed the guideline accordingly during virtual meetings and drafted a summary report of members' observations, including points of agreement and disagreement, and delivered the report to the BSC.

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

Summary of the Clinical Evidence Review

Primary Clinical Questions

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

- The effectiveness of long-term opioid therapy versus placebo, no opioid therapy, or nonopioid therapy for long term (≥1 year) outcomes related to pain, function, and quality of life, and how effectiveness varies according to

the type/cause of pain, patient demographics, and patient

comorbidities (Key Question [KQ] 1).
• The risks of opioids versus placebo or no opioids on abuse,

addiction, overdose, and other harms, and how harms vary according to the type/cause of pain, patient demographics, patient comorbidities, and dose (KQ2).

• The comparative effectiveness of opioid dosing strategies (different methods for initiating and titrating opioids; immediate-release versus ER/LA opioids; different ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled, continuous versus as-needed dosing; dose escalation versus dose maintenance; opioid rotation versus maintenance; different strategies for treating acute exacerbations of chronic pain; decreasing opioid doses or tapering off versus continuation; and different tapering protocols and strategies) (KQ3).

• The accuracy of instruments for predicting risk for opioid overdose, addiction, abuse, or misuse; the effectiveness of risk mitigation strategies (use of risk prediction instruments); effectiveness of risk mitigation strategies including opioid management plans, patient education, urine drug testing, prescription drug monitoring program (PDMP) data, monitoring instruments, monitoring intervals, pill counts, and abuse-deterrent formulations for reducing risk for opioid overdose, addiction, abuse, or misuse; and the comparative effectiveness of treatment strategies for managing patients with addiction (KQ4).

• The effects of prescribing opioid therapy versus not prescribing opioid therapy for acute pain on long-term use (KQ5).

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

Clinical Evidence Systematic Review Methods

Complete methods and data for the 2014 AHRQ report, upon which this updated systematic review is based, have been published previously (*14*,*52*). Study authors developed the protocol using a standardized process (*53*) with input from experts and the public and registered the protocol in the PROSPERO database (*54*). For the 2014 AHRQ report, a research librarian searched MEDLINE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, PsycINFO, and CINAHL for English-language articles published January 2008 through August 2014, using search terms for opioid therapy, specific opioids, chronic pain, and comparative study designs. Also included were relevant studies from an earlier review (*10*) in which searches were conducted without a date restriction, reference lists were reviewed, and

ClinicalTrials.gov was searched. CDC updated the AHRQ literature search using the same search strategies as in the original review including studies published before April, 2015. Seven additional studies met inclusion criteria and were added to the review. CDC used the GRADE approach outlined in the ACIP Handbook for Developing Evidence-Based Recommendations (*47*) to rate the quality of evidence for the full body of evidence (evidence from the 2014 AHRQ review plus the update) for each clinical question. Evidence was categorized into the following types: type 1 (randomized clinical trials or overwhelming evidence from observational studies), type 2 (randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies), type 3 (observational studies, or randomized clinical trials with notable limitations), or type 4 (clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations). When no studies were present, evidence was considered to be insufficient. Per GRADE methods, type of evidence was categorized by study design as well as a function of limitations in study design or implementation, imprecision of estimates, variability in findings, indirectness of evidence, publication bias, magnitude of treatment effects, dose-response gradient, and constellation of plausible biases that could change effects. Results were synthesized qualitatively, highlighting new evidence identified during the update process. Meta-analysis was not attempted due to the small numbers of studies, variability in study designs and clinical heterogeneity, and methodological shortcomings of the studies. More detailed information about data sources and searches, study selection, data extraction and quality assessment, data synthesis, and update search yield and new evidence for the current review is provided in the Clinical Evidence Review (http://stacks.cdc.gov/view/cdc/38026).

Summary of Findings for Clinical Questions

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

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

Effectiveness

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

Harms

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

(using DSM-IV criteria) ranged from 3% to 26% (*55*,*56*,*59*). In pain clinic settings, prevalence of addiction ranged from 2% to 14% (*57*,*58*,*60*,*61*,*63*–*65*).

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

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

Opioid Dosing Strategies

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

For comparative effectiveness and harms of ER/LA opioids, the 2014 AHRQ report included three randomized, head- to-head trials of various ER/LA opioids that found no clear differences in 1-year outcomes related to pain or function (*78–80*) but had methodological shortcomings. A fair-quality retrospective cohort study based on national Veterans Health

Administration system pharmacy data found that methadone was associated with lower overall risk for all-cause mortality versus morphine (*81*), and a fair-quality retrospective cohort study based on Oregon Medicaid data found no statistically significant differences between methadone and long-acting morphine in risk for death or overdose symptoms (*82*). However, a new observational study (*83*) found methadone associated with increased risk for overdose versus sustained- release morphine among Tennessee Medicaid patients. The observed inconsistency in study findings suggests that risks of methadone might vary in different settings as a function of different monitoring and management protocols, though more research is needed to understand factors associated with safer methadone prescribing.

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

Risk Assessment and Mitigation

For KQ4, the body of evidence is rated as type 3 for the accuracy of risk assessment tools and insufficient for the effectiveness of use of risk assessment tools and mitigation strategies in reducing harms (six studies contributing; four from the original review plus two new studies). The 2014 AHRQ report included four studies (*88–91*) on the accuracy of risk assessment instruments, administered prior to opioid therapy initiation, for predicting opioid abuse or misuse. Results for the Opioid Risk Tool (ORT) (*89–91*) were extremely inconsistent; evidence for other risk assessment instruments was very sparse, and studies had serious methodological shortcomings. One additional fair-quality (*92*) and one poor-quality (*93*) study identified for this update compared the predictive accuracy of the ORT, the Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R), and the Brief Risk Interview.

For the ORT, sensitivity was 0.58 and 0.75 and specificity 0.54 and 0.86; for the SOAPP-R, sensitivity was 0.53 and 0.25 and specificity 0.62 and 0.73; and for the Brief Risk Interview, sensitivity was 0.73 and 0.83 and specificity 0.43 and 0.88. For the ORT, positive likelihood ratios ranged from noninformative (positive likelihood ratio close to 1) to moderately useful (positive likelihood ratio >5). The SOAPP-R was associated with noninformative likelihood ratios (estimates close to 1) in both studies.

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

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

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

Summary of the Contextual Evidence Review

Primary Areas of Focus

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

• Effectiveness of nonpharmacologic (e.g., cognitive behavioral therapy [CBT], exercise therapy, interventional treatments, and multimodal pain treatment) and nonopioid pharmacologic treatments (e.g., acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs], antidepressants, and anticonvulsants), including studies of any duration.

• Benefits and harms of opioid therapy (including additional studies not included in the clinical evidence review, such as studies that were not restricted to patients with chronic pain, evaluated outcomes at any duration, performed ecological analyses, or used observational study designs other than cohort and case-cohort control studies) related to specific opioids, high-dose therapy, co-prescription with other controlled substances, duration of use, special populations, and potential usefulness of risk stratification/ mitigation approaches, in addition to effectiveness of treatments associated with addressing potential harms of opioid therapy (opioid use disorder).

• Clinician and patient values and preferences related to opioids and medication risks, benefits, and use.

• Resource allocation including costs and economic efficiency of opioid therapy and risk mitigation strategies. CDC also reviewed clinical guidelines that were relevant to opioid prescribing and could inform or complement the CDC recommendations under development (e.g., guidelines on nonpharmacologic and nonopioid pharmacologic treatments and guidelines with recommendations related to specific clinician actions such as urine drug testing or opioid tapering protocols).

Contextual Evidence Review Methods

CDC conducted a contextual evidence review to assist in developing the recommendations by providing an assessment of the balance of benefits and harms, values and preferences, and cost, consistent with the

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

Detailed information about contextual evidence data sources and searches, inclusion criteria, study selection, and

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

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

Summary of Findings for Contextual Areas

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

Effectiveness of Nonpharmacologic and Nonopioid Pharmacologic Treatments

Several nonpharmacologic and nonopioid pharmacologic treatments have been shown to be effective in managing chronic pain in studies ranging in duration from 2 weeks to 6 months. For example, CBT that trains patients in behavioral techniques

and helps patients modify situational factors and cognitive processes that exacerbate pain has small positive effects on disability and catastrophic thinking (*97*). Exercise therapy can help reduce pain and improve

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

Benefits and Harms of Opioid Therapy

Balance between benefits and harms is a critical factor influencing the strength of clinical recommendations. In particular, CDC considered what is known from the epidemiology research about benefits and harms related to specific opioids and formulations, high dose therapy, co-prescription with other controlled substances, duration of use, special populations, and risk stratification and mitigation approaches. Additional information on benefits and harms of long-term opioid therapy from studies meeting rigorous selection criteria is provided in the clinical evidence review (e.g., see KQ2). CDC also considered the number of persons experiencing chronic pain, numbers potentially benefiting

from opioids, and numbers affected by opioid-related harms. A review of these data is presented in the background section of this document, with detailed information provided in the Contextual Evidence Review (http://stacks.cdc.gov/view/ cdc/38027). Finally, CDC considered the effectiveness of treatments that addressed potential harms of opioid therapy (opioid use disorder).

Regarding specific opioids and formulations, as noted by FDA, there are serious risks of ER/LA opioids, and the indication for this class of medications is for management of pain severe enough to require daily, around-the-clock, long- term opioid treatment in patients for whom other treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain (*121*). Time-scheduled opioid use was associated with substantially higher average daily opioid dosage than as-needed opioid use in one study (*122*). Methadone has been associated with disproportionate numbers of overdose deaths relative to the frequency with which it is prescribed for pain. Methadone has been found to account for as much as a third of opioid- related overdose deaths involving single or multiple drugs in states that participated in the Drug Abuse Warning Network, which was more than any opioid other than oxycodone, despite representing <2% of opioid prescriptions outside of opioid treatment programs in the United States; further, methadone was involved in twice as many single-drug deaths as any other prescription opioid (*123*).

Regarding high-dose therapy, several epidemiologic studies that were excluded from the clinical evidence review because patient samples were not restricted to patients with chronic pain also examined the association between opioid dosage and overdose risk (*23*,*24*,*124–126*). Consistent with the clinical evidence review, the contextual review found that opioid-related overdose risk is dose- dependent, with higher opioid dosages associated with increased overdose risk. Two of these studies (*23*,*24*), as well as the two studies in the clinical evidence review (*66*,*67*), evaluated similar MME/day dose ranges for association with overdose risk. In these four studies, compared with opioids prescribed at <20 MME/ day, the odds of overdose among patients prescribed opioids for chronic nonmalignant pain were between 1.3 (*67*) and 1.9 (*24*) for dosages of 20 to <50 MME/day, between 1.9 (*67*) and 4.6 (*24*) for dosages of 50 to <100 MME/day, and between 2.0 (*67*) and 8.9 (*66*) for dosages of ≥100 MME/day. Compared with dosages of 1–<20 MME/day, absolute risk difference approximation for 50–<100 MME/day was 0.15% for fatal overdose (*24*) and 1.40% for any overdose (*66*), and for ≥100 MME/day was 0.25% for fatal overdose (*24*) and 4.04% for any overdose (*66*). A recent study of Veterans Health Administration patients with chronic pain found that patients who died of overdoses related to opioids were

prescribed higher opioid dosages (mean: 98 MME/day; median: 60 MME/day) than controls (mean: 48 MME/day, median: 25 MME/day) (*127*). Finally, another recent study of overdose deaths among state residents with and without opioid prescriptions revealed that prescription opioid-related overdose mortality rates rose rapidly up to prescribed doses of 200 MME/day, after which the mortality rates continued to increase but grew more gradually (*128*). A listing of common opioid medications and their MME equivalents is provided (Table 2).

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

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

Regarding populations potentially at greater risk for harm, risk is greater for patients with sleep apnea or other causes of sleep-disordered breathing, patients with renal or hepatic insufficiency, older adults, pregnant women, patients with depression or other mental health conditions, and patients with alcohol or other substance use disorders. Interpretation of clinical data on the effects of opioids on sleep-disordered breathing is difficult because of the types of study designs and methods employed, and there is no clear consensus regarding association with risk for developing obstructive sleep apnea syndrome (*132*). However, opioid therapy can decrease respiratory drive, a high percentage of patients on long-term opioid therapy have been reported to have an abnormal apnea- hypopnea index (*133*), opioid therapy can worsen central sleep apnea in obstructive sleep apnea patients, and it can cause further desaturation in obstructive sleep apnea patients not on continuous positive airway pressure (CPAP) (*31*). Reduced renal or hepatic function can result in greater peak effect and longer duration of action and reduce the dose at which respiratory depression and overdose occurs (*134*). Age-related changes in patients aged ≥65 years, such as reduced renal function and medication clearance, even in the absence of renal disease (*135*), result in a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose. Older adults might also be at increased risk for falls and fractures related to opioids (*136–138*). Opioids used

in pregnancy can be associated with additional risks to both mother and fetus. Some studies have shown an association of opioid use in pregnancy with birth defects, including neural tube defects (*139*,*140*), congenital heart defects (*140*), and gastroschisis (*140*); preterm delivery (*141*), poor fetal growth (*141*), and stillbirth (*141*). Importantly, in some cases, opioid use during pregnancy leads to neonatal opioid withdrawal syndrome (*142*). Patients with mental health comorbidities and patients with histories of substance use disorders might be at higher risk than other patients for opioid use disorder (*62*,*143*,*144*). Recent analyses found that depressed patients were at higher risk for drug overdose than patients without depression, particularly at higher opioid dosages, although investigators were unable to distinguish unintentional overdose from suicide attempts (*145*). In case-control and case-cohort studies, substance abuse/dependence was more prevalent among patients experiencing overdose than among patients not experiencing overdose (12% versus 6% [*66*], 40% versus 10% [*24*], and 26% versus 9% [*23*]).

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

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

Concerns have been raised that prescribing changes such as dose reduction might be associated with unintended negative consequences, such as patients seeking heroin or other illicitly obtained opioids (*148*) or interference with appropriate pain treatment (*149*). With the exception of a study noting

an association between an abuse-deterrent formulation of OxyContin and heroin use, showing that some patients in qualitative interviews reported switching to another opioid, including heroin, for many reasons, including cost and availability as well as ease of use (*150*), CDC did not identify studies evaluating these potential outcomes.

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

Clinician and Patient Values and Preferences

Clinician and patient values and preferences can inform how benefits and harms of long-term opioid therapy are weighted and estimate the effort and resources required to effectively provide implementation support. Many physicians lack confidence in their ability to prescribe opioids safely (*156*), to predict (*157*) or detect

(*158*) prescription drug abuse, and to discuss abuse with their patients (*158*). Although clinicians have reported favorable beliefs and attitudes about improvements in pain and quality of life attributed to opioids (*159*), most consider prescription drug abuse to be a "moderate" or "big" problem in their community, and large proportions are "very" concerned about opioid addiction (55%) and death (48%) (*160*). Clinicians do not consistently use practices intended to decrease the risk for misuse, such as PDMPs (*161*,*162*), urine drug testing (*163*), and opioid treatment agreements (*164*). This is likely due in part to challenges related to registering for PDMP access and logging into the PDMP (which can interrupt normal clinical workflow if data are not integrated into electronic health record systems) (*165*), competing clinical demands, perceived inadequate time to discuss the rationale for urine drug testing and to order confirmatory testing, and feeling unprepared to interpret and address results (*166*).

Many patients do not have an opinion about "opioids" or know what this term means (*167*). Most are familiar with the term "narcotics." About a third associated "narcotics" with addiction or abuse, and about half feared "addiction" from long-term "narcotic" use (*168*). Most patients taking opioids experience side effects (73% of patients taking hydrocodone for noncancer pain [*11*], 96% of patients taking opioids for chronic pain [*12*]), and side effects, rather than pain relief,

have been found to explain most of the variation in patients' preferences related to taking opioids (*12*). For example, patients taking hydrocodone for noncancer pain commonly reported side effects including dizziness, headache, fatigue, drowsiness, nausea, vomiting, and constipation (*11*). Patients with chronic pain in focus groups emphasized effectiveness of goal setting for increasing motivation and functioning (*168*). Patients taking high dosages report reliance on opioids despite ambivalence about their benefits (*169*) and regardless of pain reduction, reported problems, concerns, side effects, or perceived helpfulness (*13*).

Resource Allocation

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

Recommendations

The recommendations are grouped into three areas for consideration:

• Determining when to initiate or continue opioids for chronic pain.

• Opioid selection, dosage, duration, follow-up, and discontinuation.

• Assessing risk and addressing harms of opioid use.

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

Category A recommendations indicate that most patients should receive the recommended course of action; category B recommendations indicate that different choices will be appropriate for different patients, requiring clinicians to help patients arrive at a decision consistent with patient values and preferences and specific clinical situations. Consistent with the ACIP (*47*) and GRADE process (*48*), category A recommendations were made, even with type 3 and 4 evidence, when there was broad agreement that the advantages of a clinical action greatly outweighed the disadvantages based on a consideration of benefits and harms, values and preferences, and resource allocation. Category B recommendations were made when there was broad agreement that the advantages and disadvantages of a clinical action were more balanced, but advantages were significant enough to warrant a recommendation. All recommendations are category A recommendations, with the exception of recommendation 10, which is rated as category B. Recommendations were associated with a range of evidence types, from type 2 to type 4.

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

• No evidence shows a long-term benefit of opioids in pain and function versus no opioids for chronic pain with outcomes examined at least 1 year later (with most placebo- controlled randomized trials ≤6 weeks in duration).

• Extensive evidence shows the possible harms of opioids (including opioid use disorder, overdose, and motor vehicle injury).

• Extensive evidence suggests some benefits of nonpharmacologic and nonopioid pharmacologic treatments compared with long-term opioid therapy, with less harm.

US Department of Health and Human Services/Centers for Disease Control and Prevention MMWR / March 18, 2016 / Vol. 65 / No. 1 15

Recommendations and Reports

BOX 1. CDC recommendations for prescribing opioids for chronic pain outside of active cancer, palliative, and end-of-life care

Determining When to Initiate or Continue Opioids for Chronic Pain

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

2. Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety.
3. Beforestartingandperiodicallyduringopioidtherapy, 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. Whenstartingopioidtherapyforchronicpain,clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids.

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

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

Assessing Risk and Addressing Harms of Opioid Use

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

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

10. When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs.

11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible.

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

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

BOX 2. Interpretation of recommendation categories and evidence type

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

Several nonopioid pharmacologic therapies (including acetaminophen, NSAIDs, and selected antidepressants and anticonvulsants) are effective for chronic pain. In particular, acetaminophen and NSAIDs can be useful for arthritis and low back pain. Selected anticonvulsants such as pregabalin and gabapentin can improve pain in diabetic neuropathy and post-herpetic neuralgia (contextual evidence review). Pregabalin, gabapentin, and carbamazepine are FDA-approved for treatment of certain neuropathic pain conditions, and pregabalin is FDA approved for fibromyalgia management. In patients with or without depression, tricyclic antidepressants and SNRIs provide effective analgesia for neuropathic pain conditions including diabetic neuropathy and post-herpetic neuralgia, often at lower dosages and with a shorter time to onset of effect than for treatment of depression (see contextual evidence review). Tricyclics and SNRIs can also relieve fibromyalgia symptoms. The SNRI duloxetine is FDA-approved for the treatment of diabetic neuropathy and fibromyalgia. Because patients with chronic pain often suffer from concurrent depression (*144*), and depression can exacerbate physical symptoms including pain (*177*), patients with co-occurring pain and depression are especially likely to benefit from antidepressant medication (see Recommendation 8). Nonopioid pharmacologic therapies

Recommendation Categories

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

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

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

Evidence Type

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

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

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

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

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

Determining When to Initiate or Continue Opioids for Chronic Pain

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

Patients with pain should receive treatment that provides the greatest benefits relative to risks. The contextual evidence review found that many nonpharmacologic therapies, including physical therapy, weight loss for knee osteoarthritis, psychological therapies such as CBT, and certain interventional procedures can ameliorate chronic pain. There is high-quality

are not generally associated with substance use disorder, and the numbers of fatal overdoses associated with nonopioid medications are a fraction of those associated with opioid medications (contextual evidence review). For example, acetaminophen, NSAIDs, and opioid pain medication were involved in 881, 228, and 16,651 pharmaceutical overdose deaths in the United States in 2010 (*178*). However, nonopioid pharmacologic therapies are associated with certain risks, particularly in older patients, pregnant patients, and patients with certain co-morbidities such as cardiovascular, renal, gastrointestinal, and liver disease (see contextual evidence review). For example, acetaminophen can be hepatotoxic at dosages of >3–4 grams/day and at lower dosages in patients with chronic alcohol use or liver disease (*109*). NSAID use has been associated with gastritis, peptic ulcer disease, cardiovascular events (*111*,*112*), and fluid retention, and most NSAIDs (choline magnesium trilisate and selective COX-2 inhibitors are exceptions) interfere with platelet

aggregation (*179*). Clinicians should review FDA-approved labeling including boxed warnings before initiating treatment with any pharmacologic therapy.

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

Integrated pain management requires coordination of medical, psychological, and social aspects of health care and includes primary care, mental health care, and specialist services when needed (*180*). Nonpharmacologic physical and psychological treatments such as exercise and CBT are approaches that encourage active patient participation in the care plan, address the effects of pain in the patient's life, and can result in sustained improvements in pain and function without apparent risks. Despite this, these therapies are not always or fully covered by insurance, and access and cost can be barriers for patients. For many patients, aspects of these approaches can be used even when there is limited access to specialty care. For example, previous guidelines have strongly recommended aerobic, aquatic, and/or resistance exercises for patients with osteoarthritis of the knee or hip (*176*) and maintenance of

activity for patients with low back pain (*110*). A randomized trial found no difference in reduced chronic low back pain intensity, frequency or disability between patients assigned to relatively low-cost group aerobics and individual physiotherapy or muscle reconditioning sessions (*181*). Low-cost options to integrate exercise include brisk walking in public spaces or use of public recreation facilities for group exercise. CBT addresses psychosocial contributors to pain and improves function (*97*). Primary care clinicians can integrate elements of a cognitive behavioral approach into their practice by encouraging patients to take an active role in the care plan, by supporting patients in engaging in beneficial but potentially anxiety-provoking activities, such as exercise (*179*), or by providing education in relaxation techniques and coping strategies. In many locations, there are free or low-cost patient support, self-help, and educational community-based programs that can provide stress reduction and other mental health benefits. Patients with more entrenched anxiety or fear related to pain, or other significant psychological distress, can be referred for formal therapy with a mental health specialist (e.g., psychologist, psychiatrist, clinical social worker). Multimodal therapies should be considered for patients not responding to single-modality therapy, and combinations should be tailored depending on patient needs, cost, and convenience.

To guide patient-specific selection of therapy, clinicians should evaluate patients and establish or confirm the diagnosis. Detailed recommendations on diagnosis are provided in other guidelines (*110*,*179*), but evaluation should generally include a focused history, including history and characteristics of pain and potentially contributing factors (e.g., function, psychosocial stressors, sleep) and physical exam, with imaging or other diagnostic testing only if indicated (e.g., if severe or progressive neurologic deficits are present or if serious underlying conditions are suspected) (*110*,*179*). For complex pain syndromes, pain specialty consultation can be considered to assist with diagnosis as well as management. Diagnosis can help identify disease-specific interventions to reverse or ameliorate pain; for example, improving glucose control to prevent progression of diabetic neuropathy; immune-modulating agents for rheumatoid arthritis; physical or occupational therapy to address posture, muscle weakness, or repetitive occupational motions that contribute to musculoskeletal pain; or surgical intervention to relieve mechanical/compressive pain (*179*). The underlying mechanism for most pain syndromes can be categorized as neuropathic (e.g., diabetic neuropathy, postherpetic neuralgia, fibromyalgia), or nociceptive (e.g., osteoarthritis, muscular back pain). The diagnosis and pathophysiologic mechanism of pain have implications for symptomatic pain treatment with medication. For example, evidence is limited or insufficient

for improved pain or function with long-term use of opioids for several chronic pain conditions for which opioids are commonly prescribed, such as low back pain (*182*), headache (*183*), and fibromyalgia (*184*). Although NSAIDs can be used for exacerbations of nociceptive pain, other medications (e.g., tricyclics, selected anticonvulsants, or transdermal lidocaine) generally are recommended for neuropathic pain. In addition, improvement of neuropathic pain can begin weeks or longer after symptomatic treatment is initiated (*179*). Medications should be used only after assessment and determination that expected benefits outweigh risks given patient-specific factors. For example, clinicians should consider falls risk when selecting and dosing potentially sedating medications such as tricyclics, anticonvulsants, or opioids, and should weigh risks and benefits of use, dose, and duration of NSAIDs when treating older adults as well as patients with hypertension, renal insufficiency, or heart failure, or those with risk for peptic ulcer disease or cardiovascular disease. Some guidelines recommend topical NSAIDs for localized osteoarthritis (e.g., knee osteoarthritis) over oral NSAIDs in patients aged ≥75 years to minimize systemic effects (*176*).

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

combined with nonpharmacologic therapy to reduce pain and improve function. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate, to provide greater benefits to patients in improving pain and function.

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

The clinical evidence review found insufficient evidence to determine long-term benefits of opioid therapy for chronic pain and found an increased risk for serious harms related to long-term opioid therapy that appears to be dose-dependent. In addition, studies on currently available

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

Experts agreed that before opioid therapy is initiated for chronic pain outside of active cancer, palliative, and end-of- life care, clinicians should determine how effectiveness will be evaluated and should establish treatment goals with patients. Because the line between acute pain and initial chronic pain is not always clear, it might be difficult for clinicians to determine when they are initiating opioids for chronic pain rather than treating acute pain. Pain lasting longer than 3 months or past the time of normal tissue healing (which could be substantially shorter than 3 months, depending on the condition) is generally no longer considered acute. However, establishing treatment goals with a patient who has already received opioid therapy for 3 months would defer this discussion well past the point of

initiation of opioid therapy for chronic pain. Clinicians often write prescriptions for long-term use in 30-day increments, and opioid prescriptions written for ≥30 days are likely to represent initiation or continuation of long-term opioid therapy. Before writing an opioid prescription for ≥30 days, clinicians should establish treatment goals with patients. Clinicians seeing new patients already receiving opioids should establish treatment goals for continued opioid therapy. Although the clinical evidence review did not find studies evaluating the effectiveness of written agreements or treatment plans (KQ4), clinicians and patients who set a plan in advance will clarify expectations regarding how opioids will be prescribed and monitored, as well as situations in which opioids will be discontinued or doses tapered (e.g., if treatment goals are not met, opioids are no longer needed, or adverse events put the patient at risk) to improve patient safety.

Experts thought that goals should include improvement in both pain relief and function (and therefore in quality of life). However, there are some clinical circumstances under which reductions in pain without improvement in physical function might be a more realistic goal (e.g., diseases typically associated with progressive functional impairment or catastrophic injuries such as spinal cord trauma). Experts noted that function can include emotional and social as well as physical dimensions. In addition, experts emphasized that mood has important interactions with pain and function. Experts agreed that clinicians may use validated instruments such as the three- item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (*186*) to track patient outcomes. Clinically meaningful

improvement has been defined as a 30% improvement in scores for both pain and function (*187*). Monitoring progress toward patient-centered functional goals (e.g., walking the dog or walking around the block, returning to part-time work, attending family sports or recreational activities) can also contribute to the assessment of functional improvement. Clinicians should use these goals in assessing benefits of opioid therapy for individual patients and in weighing benefits against risks of continued opioid therapy (see Recommendation 7, including recommended intervals for follow-up). Because depression, anxiety, and other psychological co-morbidities often coexist with and can interfere with resolution of pain, clinicians should use validated instruments to assess for these conditions (see Recommendation 8) and ensure that treatment for these conditions is optimized. If patients receiving opioid therapy for chronic pain do not experience meaningful improvements in both pain and function compared with prior to initiation of opioid therapy, clinicians should consider working with patients to taper and discontinue opioids (see Recommendation 7) and should use nonpharmacologic and

nonopioid pharmacologic approaches to pain management (see Recommendation 1).

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

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

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

• Be explicit and realistic about expected benefits of opioids, explaining that while opioids can reduce pain during short- term use, there is no good evidence that opioids improve pain or function with long-term use, and that complete relief of pain is unlikely (clinical evidence review, KQ1).

- Emphasizeimprovementinfunctionasaprimarygoaland that function can improve even when pain is still present.
- Advise patients about serious adverse effects of opioids, including potentially fatal respiratory depression and development of a potentially serious lifelong opioid use disorder that can cause distress and inability to fulfill major role obligations.
- Advise patients about common effects of opioids, such as constipation, dry mouth, nausea, vomiting, drowsiness, confusion, tolerance, physical dependence, and withdrawal symptoms when stopping opioids. To prevent constipation associated with opioid use, advise patients to increase

hydration and fiber intake and to maintain or increase

physical activity. Stool softeners or laxatives might be needed.

- Discuss effects that opioids might have on ability to safely operate a vehicle, particularly when opioids are initiated, when dosages are increased, or when other central nervous system depressants, such as benzodiazepines or alcohol,

  are used concurrently.

- Discuss increased risks for opioid use disorder, respiratory

  depression, and death at higher dosages, along with the importance of taking only the amount of opioids prescribed, i.e., not taking more opioids or taking them more often.

- Review increased risks for respiratory depression when opioids are taken with benzodiazepines, other sedatives, alcohol, illicit drugs such as heroin, or other opioids.
- Discussriskstohouseholdmembersandotherindividuals if opioids are intentionally or unintentionally shared with others for whom they are not prescribed, including the possibility that others might experience overdose at the same or at lower dosage than prescribed for the patient, and that young children are susceptible to unintentional ingestion. Discuss storage of opioids in a secure, preferably locked location and options for safe disposal of unused opioids (*188*).
- Discusstheimportanceofperiodicreassessmenttoensure that opioids are helping to meet patient goals and to allow opportunities for opioid discontinuation and consideration of additional nonpharmacologic or nonopioid pharmacologic treatment options if opioids are not effective or are harmful.
- Discuss planned use of precautions to reduce risks, including use of prescription drug monitoring program information (see Recommendation 9) and urine drug testing (see Recommendation 10). Consider including discussion of naloxone use for overdose reversal (see Recommendation 8).
- Consider whether cognitive limitations might interfere with management of opioid therapy (for older adults in particular) and, if so, determine whether a caregiver can responsibly co-manage medication therapy. Discuss the importance of reassessing safer medication use with both the patient and caregiver.

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

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

4. Whenstartingopioidtherapyforchronicpain,clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids (recommendation category: A, evidence type: 4).

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

In 2014, the FDA modified the labeling for ER/LA opioid pain medications, noting serious risks and recommending that ER/LA opioids be reserved for "management of pain severe enough to require daily,

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

Abuse-deterrent technologies have been employed to prevent manipulation intended to defeat extended-release properties of ER/LA opioids and to prevent opioid use by unintended routes of administration, such as injection of oral opioids. As indicated in FDA guidance for industry on evaluation and labeling of abuse-deterrent opioids (*190*), although abuse- deterrent technologies are expected to make manipulation of opioids more difficult or less rewarding, they do not prevent

opioid abuse through oral intake, the most common route of opioid abuse, and can still be abused by nonoral routes. The "abuse-deterrent" label does not indicate that there is no risk for abuse. No studies were found in the clinical evidence review assessing the effectiveness of abuse-deterrent technologies as a risk mitigation strategy for deterring or preventing abuse. In addition, abuse-deterrent technologies do not prevent unintentional overdose through oral intake. Experts agreed that recommendations could not be offered at this time related to use of abuse-deterrent formulations.

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

Experts agreed that for patients not already receiving opioids, clinicians should not initiate opioid treatment with ER/LA opioids and should not prescribe ER/LA opioids for intermittent use. ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received immediate-release opioids daily for at least 1 week. When changing to an ER/LA opioid for a patient previously receiving a different immediate-release opioid, clinicians should consult product labeling and reduce total daily dosage to account for incomplete opioid cross-tolerance. Clinicians should use additional caution with ER/LA opioids and consider a longer dosing interval when prescribing to patients with renal or

hepatic dysfunction because decreased clearance of drugs among these patients can lead to accumulation of drugs to toxic levels and persistence in the

body for longer durations. Although there might be situations in which clinicians need to prescribe immediate-release and ER/LA opioids together (e.g., transitioning patients from ER/LA opioids to immediate-release opioids by temporarily using lower dosages of both), in general, avoiding the use of immediate-release opioids in combination with ER/LA opioids is preferable, given potentially increased risk and diminishing returns of such an approach for chronic pain.

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

• Methadone should not be the first choice for an ER/LA opioid. Only clinicians who are familiar with methadone's unique risk profile and who are prepared to educate and closely monitor their patients, including risk assessment for QT prolongation and consideration of electrocardiographic monitoring, should consider prescribing methadone for pain. A clinical practice guideline that contains further guidance regarding methadone prescribing for pain has been published previously (*191*).

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

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

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

related to opioid therapy increase at higher opioid dosage. The clinical evidence review found that higher opioid dosages are associated with increased risks for motor vehicle injury, opioid use disorder, and overdose (KQ2). The clinical and contextual evidence reviews found that opioid overdose risk increases in a dose–response manner, that dosages of 50–<100 MME/day have been found to increase risks for opioid overdose by factors of 1.9 to 4.6 compared with dosages of 1–<20 MME/day, and that dosages ≥100 MME/day are associated with increased risks of overdose 2.0–8.9 times the risk at 1–<20 MME/day. In a national sample of Veterans Health

Administration patients with chronic pain who were prescribed opioids, mean prescribed opioid dosage among patients who died from opioid overdose was 98 MME (median 60 MME) compared with mean prescribed opioid dosage of 48 MME (median 25 MME) among patients not experiencing fatal overdose (*127*).

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

When opioids are used for chronic pain outside of active cancer, palliative, and end-of-life care, clinicians should start opioids at the lowest possible effective dosage (the lowest starting dosage on product labeling for patients not already taking opioids and according to product labeling guidance regarding tolerance for patients already taking opioids). Clinicians should use additional caution when initiating opioids for patients aged ≥65 years and for patients with renal or hepatic insufficiency because decreased clearance of drugs in these patients can result in accumulation of drugs to toxic levels. Clinicians should use caution when increasing opioid dosages and increase dosage by the smallest practical amount because overdose risk increases with increases in opioid dosage. Although there is limited evidence to recommend specific intervals for dosage titration, a previous guideline recommended waiting at least five half-lives before increasing dosage and waiting at least a week before increasing dosage of methadone to make sure that full effects of the previous dosage are evident (*31*). Clinicians should re-evaluate patients after increasing dosage for changes in pain, function, and risk for harm (see Recommendation 7). Before increasing total opioid dosage to ≥50 MME/day, clinicians should reassess whether opioid treatment is meeting the patient's treatment goals (see Recommendation 2). If a patient's opioid dosage for all sources of opioids combined reaches or exceeds 50 MME/day, clinicians should implement additional precautions, including increased

frequency of follow-up (see Recommendation 7) and considering offering naloxone and overdose prevention education to both patients and the patients' household members (see Recommendation 8). Clinicians should avoid increasing opioid dosages to ≥90 MME/day or should carefully justify a decision to increase dosage to ≥90 MME/day based on individualized assessment of benefits and risks and weighing factors such as diagnosis, incremental benefits for pain and function relative to harms as dosages approach 90 MME/day, other treatments and effectiveness, and recommendations based on consultation with pain specialists. If patients do not experience improvement in pain and function at ≥90 MME/day, or if there are escalating dosage requirements, clinicians should discuss other approaches to pain management with the patient, consider working with patients to taper opioids to a lower dosage or to taper and discontinue opioids (see Recommendation 7), and consider consulting a pain specialist. Some states require clinicians to implement clinical protocols at specific dosage levels. For example, before increasing long-term opioid therapy dosage to >120 MME/day, clinicians in Washington state must obtain consultation from a pain specialist who agrees that this is indicated and appropriate (*30*). Clinicians should be aware of rules related to MME thresholds and associated clinical protocols established by their states.

Established patients already taking high dosages of opioids, as well as patients transferring from other clinicians, might consider the possibility of opioid dosage reduction to be anxiety-provoking, and tapering opioids can be especially challenging after years on high dosages because of physical and psychological dependence. However, these patients should be offered the opportunity to re-evaluate their continued use of opioids at high dosages in light of recent evidence regarding the association of opioid dosage and overdose risk. Clinicians should explain in a nonjudgmental manner to patients already taking high opioid dosages (≥90 MME/day) that there is

now an established body of scientific evidence showing that overdose risk is increased at higher opioid dosages. Clinicians should empathically review benefits and risks of continued high-dosage opioid therapy and should offer to work with the patient to taper opioids to safer dosages. For patients who agree to taper opioids to lower dosages, clinicians should collaborate with the patient on a tapering plan (see Recommendation 7). Experts noted that patients tapering opioids after taking them for years might require very slow opioid tapers as well as pauses in the taper to allow gradual accommodation to lower opioid dosages. Clinicians should remain alert to signs of anxiety, depression, and opioid use disorder (see Recommendations 8 and 12) that might be unmasked by an opioid taper and arrange for management of these co-morbidities. For patients agreeing to taper to lower opioid dosages as well as for those remaining on high opioid dosages, clinicians should establish goals with the patient for continued opioid therapy (see Recommendation 2), maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 1), and consider consulting a pain specialist as needed to assist with pain management.

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

The clinical evidence review found that opioid use for acute pain (i.e., pain with abrupt onset and caused by an injury or other process that is not ongoing) is associated with long-term opioid use, and that a greater amount of early opioid exposure is associated with greater risk for long-term use (KQ5). Several guidelines on opioid prescribing for acute pain from emergency departments (*192–194*) and other settings (*195*,*196*) have recommended prescribing ≤3 days of opioids in most cases, whereas others have recommended ≤7 days (*197*) or <14 days (*30*). Because physical dependence on opioids is an expected physiologic response in patients exposed to opioids for more than a few days (contextual evidence review), limiting days of opioids prescribed also should minimize the need to taper opioids to prevent distressing or unpleasant withdrawal symptoms. Experts noted that more than a few days of exposure to opioids significantly increases hazards, that each day of unnecessary opioid use increases likelihood of physical dependence without adding benefit, and that prescriptions

with fewer days' supply will minimize the number of pills available for unintentional or intentional diversion.

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

Acute pain can often be managed without opioids. It is important to evaluate the patient for reversible causes of pain, for underlying etiologies with potentially serious sequelae, and to determine appropriate treatment. When the diagnosis and severity of nontraumatic, nonsurgical acute pain are reasonably assumed to warrant the use of opioids, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids, often 3 days or less, unless circumstances clearly warrant additional opioid therapy. More than 7 days will rarely be needed. Opioid treatment for post-surgical pain is outside the scope of this guideline but has been addressed elsewhere (*30*). Clinicians should not prescribe additional opioids to patients "just in case" pain continues longer than expected. Clinicians should re-evaluate the subset of patients who experience severe acute pain that continues longer than the expected duration to confirm or

revise the initial diagnosis and to adjust management accordingly. Given longer half-lives and longer duration of effects (e.g., respiratory depression) with ER/LA opioids such as methadone, fentanyl patches, or extended release versions of opioids such as oxycodone, oxymorphone, or morphine, clinicians should not prescribe ER/LA opioids for the treatment of acute pain.

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

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

Clinicians should evaluate patients to assess benefits and harms of opioids within 1 to 4 weeks of starting long-term opioid therapy or of dose escalation. Clinicians should consider follow-up intervals within the lower end of this range when ER/LA opioids are started or increased or when total daily opioid dosage is ≥50 MME/day. Shorter follow-up intervals (within 3 days) should be strongly considered when starting or increasing the dosage of methadone. At follow up, clinicians should assess benefits in function, pain control, and quality of life using tools such as the three-item "Pain average, interference with Enjoyment of life, and interference with General activity" (PEG) Assessment Scale (*186*) and/or asking patients about progress toward functional goals that have meaning for them (see Recommendation 2). Clinicians should also ask patients about common adverse effects such as

constipation and drowsiness (see Recommendation 3), as well as asking about and assessing for effects that might be early warning signs for more serious problems such as overdose (e.g., sedation or slurred speech) or opioid use disorder (e.g., craving, wanting to take opioids in greater quantities or more frequently than prescribed, or difficulty controlling use). Clinicians should ask patients about their preferences for continuing opioids, given their effects on pain and function relative to any adverse effects experienced.

Because of potential changes in the balance of benefits and risks of opioid therapy over time, clinicians should regularly reassess all patients receiving long-term opioid therapy, including patients who are new to the clinician but on long- term opioid therapy, at least every 3 months. At reassessment, clinicians should determine whether opioids continue to meet treatment goals, including sustained improvement in pain and function, whether the patient has experienced common or serious adverse events or early warning signs of serious adverse events, signs of opioid use disorder (e.g., difficulty controlling use, work or family problems related to opioid use), whether benefits of opioids continue to outweigh risks, and whether opioid dosage can be reduced or opioids can be discontinued. Ideally, these reassessments would take place in person and be conducted by the prescribing clinician. In practice contexts where virtual visits are part of standard care (e.g., in remote areas where distance or other issues make follow-up visits challenging), follow-up assessments that allow the clinician to communicate with and observe the patient through video and audio could be conducted, with in-person visits occurring at least once per year. Clinicians should re-evaluate patients who are exposed to greater risk of opioid use disorder or overdose (e.g., patients with depression or other mental health conditions, a history of substance use disorder, a history of overdose, taking ≥50 MME/day, or taking other central nervous system depressants with opioids) more frequently than every 3 months. If clinically meaningful improvements in pain and function are not sustained, if patients are taking high-risk regimens (e.g., dosages ≥50 MME/day or opioids combined with benzodiazepines) without evidence of benefit, if patients believe benefits no longer outweigh risks or if they request dosage reduction or discontinuation, or if patients experience overdose or other serious adverse events (e.g., an event leading to hospitalization or disability) or warning signs of serious adverse events, clinicians should work with patients to reduce opioid dosage or to discontinue opioids when possible. Clinicians should maximize pain treatment with nonpharmacologic and nonopioid pharmacologic treatments as appropriate (see Recommendation 1) and consider consulting a pain specialist as needed to assist with pain management.

US Department of Health and Human Services/Centers for Disease Control and Prevention MMWR / March 18, 2016 / Vol. 65 / No. 1 25

Considerations for Tapering Opioids

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

opioids for longer durations (e.g., for years). Opioid withdrawal during pregnancy has been associated with spontaneous abortion and premature labor.

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

Assessing Risk and Addressing Harms of Opioid Use

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

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

Patients with Sleep-Disordered Breathing, Including Sleep Apnea

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

Pregnant Women

Opioids used in pregnancy might be associated with additional risks to both mother and fetus. Some studies have shown an association of opioid use in pregnancy with stillbirth, poor fetal growth, pre-term delivery, and birth defects (contextual evidence review). Importantly, in some cases, opioid use during pregnancy leads to neonatal opioid withdrawal syndrome. Clinicians and patients together should carefully weigh risks and benefits when making decisions

26 MMWR / March 18, 2016 / Vol. 65 / No. 1 US Department of Health and Human Services/Centers for Disease Control and Prevention

about whether to initiate opioid therapy for chronic pain during pregnancy. In addition, before initiating opioid therapy for chronic pain for reproductive-age women, clinicians should discuss family planning and how long-term opioid use might affect any future pregnancy. For pregnant women already receiving opioids, clinicians should access appropriate expertise if considering tapering opioids because of possible risk to the pregnant patient and to the fetus if the patient goes into withdrawal (see Recommendation 7). For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine or methadone has been associated with improved maternal outcomes and should be offered (*202*) (see Recommendation 12). Clinicians caring for pregnant women receiving opioids for pain or receiving buprenorphine or methadone for opioid use disorder should arrange for delivery at a facility prepared to monitor, evaluate for, and treat neonatal opioid withdrawal syndrome. In instances when travel to such a facility would present an undue burden on the pregnant woman, it is appropriate to deliver locally, monitor and evaluate the newborn for neonatal opioid withdrawal syndrome, and transfer the newborn for additional treatment if needed. Neonatal toxicity and death have been reported in breast- feeding infants whose mothers are taking codeine (contextual evidence review); previous guidelines have recommended that codeine be avoided whenever possible among mothers who are breast feeding and, if used, should be limited to the lowest possible dose and to a 4-day supply (*203*).

Patients with Renal or Hepatic Insufficiency

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

Patients Aged ≥65 Years

Inadequate pain treatment among persons aged ≥65 years has been documented (*204*). Pain management for older patients can be challenging given increased risks of both nonopioid pharmacologic therapies (see Recommendation 1) and opioid therapy in this population. Given reduced

renal function and medication clearance even in the absence of renal disease, patients aged ≥65 years might have increased susceptibility to accumulation of opioids and a smaller therapeutic window between safe dosages and dosages associated with respiratory depression and overdose (contextual evidence review). Some older adults suffer from cognitive impairment, which can

increase risk for medication errors and make opioid–related confusion more dangerous. In addition, older adults are more likely than younger adults to experience co–morbid medical conditions and more likely to receive multiple medications, some of which might interact with opioids (such as benzodiazepines). Clinicians should use additional caution and increased monitoring (see Recommendations 4, 5, and 7) to minimize risks of opioids prescribed for patients aged ≥65 years. Experts suggested that clinicians educate older adults receiving opioids to avoid risky medication–related behaviors such as obtaining controlled medications from multiple prescribers and saving unused medications. Clinicians should also implement interventions to mitigate common risks of opioid therapy among older adults, such as exercise or bowel regimens to prevent constipation, risk assessment for falls, and patient monitoring for cognitive impairment.

Patients with Mental Health Conditions

Because psychological distress frequently interferes with improvement of pain and function in patients with chronic pain, using validated instruments such as the Generalized Anxiety Disorder (GAD)-7 and the Patient Health Questionnaire (PHQ)-9 or the PHQ-4 to assess for anxiety, post-traumatic stress disorder, and/or depression (*205*), might help clinicians improve overall pain treatment outcomes. Experts noted that clinicians should use additional caution and increased monitoring (see Recommendation 7) to lessen the increased risk for opioid use disorder among patients with mental health conditions (including depression, anxiety disorders, and PTSD), as well as increased risk for drug overdose among patients with depression. Previous guidelines have noted that opioid therapy should not be initiated during acute psychiatric instability or uncontrolled suicide risk, and that clinicians should consider behavioral health specialist consultation for any patient with a history of suicide attempt or psychiatric disorder (*31*). In addition, patients with anxiety disorders and other mental health conditions are more likely to receive benzodiazepines, which can exacerbate opioid-induced respiratory depression and increase risk for overdose (see Recommendation 11). Clinicians should ensure that treatment for depression and other mental health conditions is optimized, consulting with behavioral health specialists when needed. Treatment for depression can improve pain symptoms as well as depression and might decrease overdose risk (contextual evidence review). For treatment of chronic pain in patients with depression, clinicians should strongly consider using tricyclic or SNRI antidepressants for analgesic as well as antidepressant effects if these medications are not otherwise contraindicated (see Recommendation 1).

Patients with Substance Use Disorder

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

Clinicians should ask patients about their drug and alcohol use. Single screening questions can be used (*206*). For example, the question "How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?" (with an answer of one or more considered positive) was found in a primary care setting to be 100% sensitive and 73.5% specific for the detection of a drug use disorder compared with a standardized diagnostic interview (*207*). Validated screening tools such as the Drug Abuse Screening Test (DAST) (*208*) and the Alcohol Use Disorders Identification Test (AUDIT) (*209*) can also be used. Clinicians should use PDMP data (see Recommendation 9) and drug testing (see Recommendation 10) as appropriate to assess for concurrent substance use that might place patients at higher risk for opioid use disorder and overdose. Clinicians should also provide specific counseling on increased risks for overdose when opioids are combined with other drugs or alcohol (see Recommendation 3) and ensure that patients receive effective treatment for substance use disorders when needed (see Recommendation 12).

The clinical evidence review found insufficient evidence to determine how harms of opioids differ depending on past or current substance use disorder (KQ2), although a history of substance use disorder was associated with misuse. Similarly, based on contextual evidence, patients with drug or alcohol use disorders are likely to experience greater risks for opioid use disorder and overdose than persons without these conditions. If clinicians consider opioid therapy for chronic pain outside of active cancer, palliative, and end-of-life care for patients with drug or alcohol use disorders, they should discuss increased risks for opioid use disorder and overdose with patients, carefully consider whether benefits of opioids outweigh increased risks, and incorporate strategies to mitigate risk into

the management plan, such as considering offering naloxone (see Offering Naloxone to Patients When Factors That Increase Risk for Opioid-Related Harms Are Present) and increasing frequency of monitoring (see Recommendation 7) when opioids are prescribed. Because pain management in patients with substance use disorder can be complex, clinicians should consider consulting substance use disorder specialists and pain specialists regarding pain management for persons with active or recent past history of substance abuse. Experts also noted that clinicians should communicate with patients' substance use disorder treatment providers if opioids are prescribed.

Patients with Prior Nonfatal Overdose

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

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

Naloxone is an opioid antagonist that can reverse severe respiratory depression; its administration by lay persons, such as friends and family of persons who experience opioid overdose, can save lives. Naloxone precipitates acute withdrawal among patients physically dependent on opioids. Serious adverse effects, such as pulmonary edema, cardiovascular instability, and seizures, have been reported but are rare at doses consistent with labeled use for opioid overdose (*210*). The contextual evidence review did not find any studies on effectiveness of prescribing naloxone for overdose prevention among patients prescribed opioids for chronic pain. However, there is evidence for effectiveness of naloxone provision in preventing opioid-related overdose death at the community level through community-based distribution (e.g., through overdose education and naloxone distribution programs in community service agencies) to persons at risk for overdose

28 MMWR / March 18, 2016 / Vol. 65 / No. 1 US Department of Health and Human Services/Centers for Disease Control and Prevention

(mostly due to illicit opiate use), and it is plausible that effectiveness would be observed when naloxone is provided in the clinical setting as well. Experts agreed that it is preferable not to initiate opioid treatment when factors that increase risk for opioid–related harms are present. Opinions diverged about the likelihood of naloxone being useful to patients and the circumstances under which it should be offered. However, most experts agreed that clinicians should consider offering naloxone when prescribing opioids to patients at increased risk for overdose, including patients with a history of overdose, patients with a history of substance use disorder, patients taking benzodiazepines with opioids (see Recommendation 11), patients at risk for returning to a high dose to which they are no longer tolerant (e.g., patients recently released from prison), and patients taking higher dosages of opioids (≥50 MME/day). Practices should provide education on overdose prevention and naloxone use to patients receiving naloxone prescriptions and to members of their households. Experts noted that naloxone co–prescribing can be facilitated by clinics or practices with resources to provide naloxone training and by collaborative practice models with pharmacists. Resources for prescribing naloxone in primary care settings can be found through Prescribe to Prevent at http://prescribetoprevent.org.

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

PDMPs are state-based databases that collect information on controlled prescription drugs dispensed by pharmacies in most states and, in select states, by dispensing physicians as well. In addition, some clinicians employed by the federal government, including some clinicians in the Indian Health Care Delivery System, are not licensed in the states where they practice, and do not have access to PDMP data. Certain states require clinicians to review PDMP data prior to writing each opioid prescription (see state-level PDMP-

related policies on the National Alliance for Model State Drug Laws website at http://www.namsdl.org/prescription-monitoring-programs. cfm). The clinical evidence review did not find studies evaluating the effectiveness of PDMPs on outcomes related to overdose, addiction, abuse, or misuse (KQ4). However, even though evidence is limited on the effectiveness of PDMP implementation at the state level on prescribing and mortality

outcomes (*28*), the contextual evidence review found that most fatal overdoses were associated with patients receiving opioids from multiple prescribers and/or with patients receiving high total daily opioid dosages; information on both of these risk factors for overdose are available to prescribers in the PDMP. PDMP data also can be helpful when patient medication history is not otherwise available (e.g., for patients from other locales) and when patients transition care to a new clinician. The contextual evidence review also found that PDMP information could be used in a way that is harmful to patients. For example, it has been used to dismiss patients from clinician practices (*211*), which might adversely affect patient safety.

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

Clinicians should review PDMP data for opioids and other controlled medications patients might have received from additional prescribers to determine whether a patient is receiving high total opioid dosages or dangerous combinations (e.g., opioids combined with benzodiazepines) that put him or her at high risk for overdose. Ideally, PDMP data should be reviewed before every opioid prescription. This is recommended in all states with well-functioning PDMPs and where PDMP access policies make this practicable (e.g., clinician and delegate access permitted), but it is not currently possible in states without functional PDMPs or in those that do not permit certain prescribers to access them. As vendors and practices facilitate integration of PDMP information into regular clinical workflow (e.g., data made available in electronic health records), clinicians' ease of access in reviewing PDMP data is expected to improve.

US Department of Health and Human Services/Centers for Disease Control and Prevention MMWR / March 18, 2016 / Vol. 65 / No. 1 29

In addition, improved timeliness of PDMP data will improve their value in identifying patient risks.

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

• Clinicians should discuss information from the PDMP with their patient and confirm that the patient is aware of the additional prescriptions. Occasionally, PDMP information can be incorrect (e.g., if the wrong name or birthdate has been entered, the patient uses a nickname or maiden name, or another person has used the patient's identity to obtain prescriptions).

consider other possible reasons for this test result (see

Recommendation 10).
Experts agreed that clinicians should not dismiss patients

from their practice on the basis of PDMP information. Doing so can adversely affect patient safety, could represent patient abandonment, and could result in missed opportunities to provide potentially lifesaving information (e.g., about risks of opioids and overdose prevention) and interventions (e.g., safer prescriptions, nonopioid pain treatment [see Recommendation 1], naloxone [see Recommendation 8], and effective treatment for substance use disorder [see Recommendation 12]).

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

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

Experts agreed that prior to starting opioids for chronic pain and periodically during opioid therapy, clinicians should

Clinicians should discuss safety concerns, including increased risk for respiratory depression and overdose, with patients found to be receiving opioids from more than one prescriber or receiving medications that increase risk when combined with opioids (e.g., benzodiazepines) and consider offering naloxone (see Recommendation 8). Clinicians should avoid prescribing opioids and benzodiazepines concurrently whenever possible. Clinicians should communicate with others managing the patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care (see Recommendation 11). Clinicians should calculate the total MME/day for concurrent opioid prescriptions to help assess the patient's overdose risk (see Recommendation 5). If patients are found to be receiving high total daily dosages of opioids, clinicians should discuss their safety concerns with the patient, consider tapering to a safer dosage (see Recommendations 5 and 7), and consider offering naloxone (see Recommendation 8).

Clinicians should discuss safety concerns with other clinicians who are prescribing controlled substances for their patient. Ideally clinicians should first discuss concerns with their patient and inform him or her that they plan to coordinate care with the patient's other prescribers to improve the patient's safety.

Clinicians should consider the possibility of a substance use disorder and discuss concerns with their patient (see Recommendation 12).
If clinicians suspect their patient might be sharing or selling opioids and not taking them, clinicians should consider urine drug testing to assist in determining whether opioids can be discontinued without causing withdrawal (see Recommendations 7 and 10). A negative drug test for prescribed opioids might indicate the patient is not taking prescribed opioids, although clinicians should

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

In most situations, initial urine drug testing can be performed with a relatively inexpensive immunoassay panel for commonly prescribed opioids and illicit drugs. Patients prescribed less commonly used opioids might require specific testing for those agents. The use of confirmatory testing adds substantial costs and should be based on the need to detect specific opioids that cannot be identified on standard immunoassays or on the presence of unexpected urine drug test results. Clinicians should be familiar with the drugs included in urine drug testing panels used in their practice and should understand how to interpret results for these drugs. For example, a positive "opiates" immunoassay detects morphine, which might reflect patient use of morphine, codeine, or heroin, but this immunoassay does not detect synthetic opioids (e.g., fentanyl or methadone) and might not detect semisynthetic opioids (e.g., oxycodone). However, many laboratories use an oxycodone immunoassay that detects oxycodone and oxymorphone. In some cases, positive results for specific opioids might reflect metabolites from opioids the patient is taking and might not mean the patient is taking the specific opioid for which the test was positive. For example, hydromorphone is a metabolite of hydrocodone, and oxymorphone is a metabolite of oxycodone. Detailed guidance on interpretation of urine drug test results, including which tests to order and expected results, drug detection time in urine, drug metabolism, and other considerations has been published previously (*30*). Clinicians should not test for substances

for which results would not affect patient management or for which implications for patient management are unclear. For example, experts noted that there might be uncertainty about the clinical implications of a positive urine drug test for tetrahyrdocannabinol (THC). In addition, restricting confirmatory testing to situations and substances for which results can reasonably be expected to affect patient management can reduce costs of urine drug testing, given the substantial costs associated with confirmatory testing methods. Before ordering urine drug testing, clinicians should have a plan for responding to unexpected results. Clinicians should explain to patients that urine drug testing is intended to improve their safety and should also explain expected results (e.g., presence of prescribed medication and absence of drugs, including illicit drugs, not reported by the patient). Clinicians should ask patients about use of prescribed and other drugs and ask whether there might be unexpected results. This will provide an opportunity for patients to provide information about changes in their use of prescribed opioids or other drugs. Clinicians should discuss unexpected results with the local laboratory or toxicologist and with the patient. Discussion with patients

prior to specific confirmatory testing can sometimes yield a candid explanation of why a particular substance is present or absent and obviate the need for expensive confirmatory testing on that visit. For example, a patient might explain that the test is negative for prescribed opioids because she felt opioids were no longer helping and discontinued them. If unexpected results are not explained, a confirmatory test using a method selective enough to differentiate specific opioids and metabolites (e.g., gas or liquid chromatography/mass spectrometry) might be warranted to clarify the situation.

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

11. Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently

whenever possible (recommendation category: A,

evidence type: 3).

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

specific anti-depressants or other nonbenzodiazepine medications approved for anxiety should be offered. Experts emphasized that clinicians should communicate with mental health professionals managing the

patient to discuss the patient's needs, prioritize patient goals, weigh risks of concurrent benzodiazepine and opioid exposure, and coordinate care.

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

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

The clinical evidence review found prevalence of opioid dependence (using DSM-IV diagnosis criteria) in primary care settings among patients with chronic pain on opioid therapy to be 3%–26% (KQ2). As found in the contextual evidence review and supported by moderate quality evidence, opioid agonist or partial agonist treatment with methadone maintenance therapy or buprenorphine has been shown to be more effective in preventing relapse among patients with opioid use disorder (*151–153*). Some studies suggest that using behavioral therapies in combination with these treatments can reduce opioid misuse and increase retention during maintenance therapy and improve compliance after detoxification (*154*,*155*); behavioral therapies are also recommended by clinical practice guidelines (*215*). The cited studies primarily evaluated patients with a history of illicit opioid use, rather than prescription opioid use for chronic pain. Recent studies among patients with prescription opioid dependence (based on DSM-IV criteria) have found maintenance therapy with buprenorphine and buprenorphine- naloxone effective in preventing relapse (*216*,*217*). Treatment need in a community is often not met by capacity to provide buprenorphine or methadone maintenance therapy (*218*), and patient cost can be a barrier to buprenorphine treatment because insurance coverage of buprenorphine for opioid use disorder is often limited (*219*). Oral or long-acting injectable formulations of naltrexone can also be used as medication- assisted treatment for opioid use disorder in nonpregnant adults, particularly for highly motivated persons (*220*,*221*). Experts agreed that clinicians prescribing opioids should identify treatment resources for opioid use disorder in the community and should work together to ensure sufficient treatment capacity for opioid use disorder at the practice level.

If clinicians suspect opioid use disorder based on patient concerns or behaviors or on findings in prescription drug monitoring program data (see Recommendation 9) or from urine drug testing (see Recommendation 10), they should discuss their concern with their patient and provide an opportunity for the patient to disclose related concerns or problems. Clinicians should assess for the presence of opioid use disorder using DSM-5 criteria (*20*). Alternatively, clinicians can arrange for a substance use disorder treatment specialist to assess for the presence of opioid use disorder. For patients meeting criteria for opioid use disorder, clinicians should offer or arrange for patients to receive evidence-based treatment, usually medication-assisted treatment with buprenorphine or methadone maintenance therapy in combination with behavioral therapies. Oral or long-acting injectable naltrexone, a long-acting opioid antagonist, can also be used in non- pregnant adults. Naltrexone blocks the effects of opioids if they are used but requires adherence to daily oral therapy or monthly injections. For pregnant women with opioid use disorder, medication-assisted therapy with buprenorphine (without naloxone) or methadone has been associated with improved maternal outcomes and should be offered (see Recommendation 8). Clinicians should also consider offering naloxone for overdose prevention to patients with opioid use disorder (see Recommendation 8). For patients with problematic

opioid use that does not meet criteria for opioid use disorder, experts noted that clinicians can offer to taper and discontinue opioids (see Recommendation 7). For patients who choose to but are unable to taper, clinicians may reassess for opioid use disorder and offer opioid agonist therapy if criteria are met.

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

Additional guidance has been published previously (*215*) on induction, use, and monitoring of buprenorphine treatment (see Part 5) and naltrexone treatment (see Part 6) for opioid use disorder and on goals, components of, and types of effective psychosocial treatment that are recommended in conjunction with pharmacological treatment of opioid use disorder (see Part 7). Clinicians unable to provide treatment themselves should arrange for patients with opioid use disorder to receive

care from a substance use disorder treatment specialist, such as an office-based buprenorphine or naltrexone treatment provider, or from an opioid treatment program certified by SAMHSA to provide supervised medication-assisted treatment for patients with opioid use disorder. Clinicians should assist patients in finding qualified treatment providers and should arrange for patients to follow up with these providers, as well as arranging for ongoing coordination of care. Clinicians should not dismiss patients from their practice because of a substance use disorder because this can adversely affect patient safety and could represent patient abandonment. Identification of substance use disorder represents an opportunity for a clinician to initiate potentially life-saving interventions, and it is important for the clinician to collaborate with the patient regarding their safety to increase the likelihood of successful treatment. In addition, although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should continue to use nonpharmacologic and nonopioid pharmacologic pain treatments as appropriate (see Recommendation 1) and consider consulting a pain specialist as needed to provide optimal pain management.

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

Conclusions and Future Directions

Clinical guidelines represent one strategy for improving prescribing practices and health outcomes. Efforts are required to disseminate the guideline and achieve widespread adoption and implementation of the recommendations in clinical settings. CDC will translate this guideline into user-friendly materials for distribution and use by health systems, medical professional societies, insurers, public health departments, health information technology developers, and clinicians and engage in dissemination efforts. CDC has provided a

checklist for prescribing opioids for chronic pain (http:// stacks.cdc.gov/view/cdc/38025), additional resources such as fact sheets (http://www.cdc.gov/drugoverdose/prescribing/ resources.html), and will provide a mobile application to guide clinicians in implementing the recommendations. CDC will also work with partners to support clinician education on pain management options, opioid therapy, and risk mitigation strategies (e.g., urine drug testing). Activities such as development of clinical decision support in electronic health records to assist clinicians' treatment decisions at the point of care; identification of mechanisms that insurers and pharmacy benefit plan managers can use to promote safer prescribing within plans; and development of clinical quality improvement measures and initiatives to improve prescribing and patient care within health systems have promise for increasing guideline adoption and improving practice. In addition, policy initiatives that address barriers to implementation of the guidelines, such as increasing accessibility of PDMP data within and across states, e-prescribing, and availability of clinicians who can offer medication-assisted treatment for opioid use disorder, are strategies to consider to enhance implementation of the recommended practices. CDC will work with federal partners and payers to evaluate strategies such as payment reform and health care delivery models that could improve patient health and safety. For example, strategies might include strengthened coverage for nonpharmacologic treatments, appropriate urine drug testing, and medication-assisted treatment; reimbursable time for patient counseling; and payment models that improve access to interdisciplinary, coordinated care.

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

monitoring program improvements, and support for community coalitions and state prevention programs.

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

identify the highest priority research areas to build the evidence base. Yet, given that chronic pain is recognized as a significant public health problem, the risks associated with long-term opioid therapy, the availability of effective nonpharmacological and nonopioid pharmacologic treatment options for pain, and the potential for improvement in the quality of health care with the implementation of recommended practices, a guideline for prescribing is warranted with the evidence that is currently available. The balance between the benefits and the risks of long-term opioid therapy for chronic pain based on both clinical and contextual evidence is strong enough to support the issuance of category A recommendations in most cases.

34 MMWR / March 18, 2016 / Vol. 65 / No. 1 US Department of Health and Human Services/Centers for Disease Control and Prevention

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

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Type of Outcome Studies Limitations Inconsistency Imprecision evidence

Effectiveness and comparative effectiveness (KQ1)

Effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (≥1 year) outcomes

Pain, function, and None —† — — Insufficient quality of life

Other factors

—

Estimates of effect/findings

No evidence

One retrospective cohort study found long-term use of prescribed opioids associated with an increased risk of abuse or dependence diagnosis versus no opioid use (adjusted OR ranged from 14.9 to 122.5, depending on dose).

In primary care settings, prevalence of opioid abuse ranged from 0.6% to 8% and prevalence of dependence from 3% to 26%. In pain clinic settings, prevalence of misuse ranged from 8% to 16% and addiction from 2% to 14%. Prevalence of aberrant drug-related behaviors ranged from 6% to 37%.

Current opioid use associated with increased risk of any overdose events (adjusted HR 5.2, 95% CI = 2.1–12) and serious overdose events (adjusted HR 8.4, 95% CI = 2.5–28) versus current nonuse.

Opioid use associated with increased risk of fracture in 1 cohort study (adjusted HR 1.28, 95% CI = 0.99–1.64) and 1 case-control study (adjusted OR 1.27,

95% CI = 1.21–1.33).
Current opioid use associated with

increased risk of myocardial infarction versus nonuse (adjusted OR 1.28,
95% CI = 1.19–1.37 and incidence rate ratio 2.66, 95% CI = 2.30–3.08).

Long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement versus nonuse (adjusted OR 1.5, 95% CI = 1.1–1.9).

One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared to no opioid prescription, the adjusted odds ratios were 15 (95% CI = 10–21) for 1 to 36 MME/day, 29 (95 % CI = 20–41) for 36 to120 MME/day, and 122 (95 % CI = 73–205) for ≥120 MME/day.

Versus 1 to <20 MME/day, one cohort study found an adjusted HR for an overdose event of 1.44 (95% CI = 0.57–3.62) for 20 to <50 MME/day that increased to 8.87 (95% CI = 3.99–19.72) at ≥100 MME/day; one case-control study found an adjusted OR for an opioid-related death of 1.32 (95% CI = 0.94–1.84) for 20 to 49 MME/day that increased to 2.88 (95% CI = 1.79–4.63) at ≥200 MME/day.

Risk of fracture increased from an adjusted HR of 1.20 (95% CI = 0.92–1.56) at 1 to <20 MME/day to 2.00 (95% CI = 1.24–3.24) at ≥50 MME/day; the trend was of borderline statistical significance.

Abuse or addiction

Abuse or addiction

Overdose

Fractures

Myocardial infarction

Endocrinologic harms

1 cohort study (n = 568,640)

10 uncontrolled studies (n = 3,780)

1 cohort study (n = 9,940)

1 cohort study
(n = 2,341) and
1 case–control study (n = 21,739 case patients)

1 cohort study
(n = 426,124) and
1 case–control study (n = 11,693 case patients)

1 cross-sectional study (n = 11,327)

Serious limitations

Very serious limitations

Serious limitations

Serious limitations

No limitations

Serious limitations

Unknown (1 study)

Very serious inconsistency

Unknown (1 study)

No inconsistency

No inconsistency

Unknown (1 study)

Unknown (1 study)

No inconsistency

Unknown (1 study)

No imprecision

No imprecision

Serious imprecision

No imprecision

No imprecision

No imprecision

No imprecision

No imprecision

Serious imprecision

3 None identified

4 None identified

3 None identified

3 None identified

3 None identified

3 None identified

3 None identified

3 Magnitude of effect, dose

response relationship

3 None identified

How do harms vary depending on the opioid dose used?

Abuse or addiction

Overdose

Fractures

1 cohort study (n = 568,640)

1 cohort study
(n = 9,940) and
1 case–control study (n = 593 case patients in primary analysis)

1 cohort study (n = 2,341)

Serious limitations

Serious limitations

Serious limitations

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

Harms and adverse events (KQ2)
Risks of opioids versus placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms

See table footnotes on page 47.

Outcome

Myocardial infarction

Motor vehicle crash injuries

Endocrinologic harms

Studies

1 cohort study (n = 426,124)

1 case–control study (n = 5,300 case patients)

1 cross-sectional study (n = 11,327) New for update: 1 additional cross-sectional study (n=1,585)

Limitations

Serious limitations

No limitations

Serious limitations

Inconsistency

Unknown (1 study)

Unknown (1 study)

Consistent

Imprecision

No imprecision

No imprecision

No imprecision

Type of evidence

3

3

3

Other factors

None identified

None identified

None identified

Estimates of effect/findings

Relative to a cumulative dose of 0 to 1,350 MME during a 90-day period, the incidence rate ratio for myocardial infarction for 1350 to <2700 MME was 1.21 (95% CI = 1.02–1.45), for 2,700 to <8,100 MME was 1.42 (95% CI = 1.21–1.67), for 8,100 to <18,000 MME was 1.89

(95% CI = 1.54–2.33), and for ≥18,000 MME

was 1.73 (95% CI = 1.32–2.26).
No association between opioid dose and risk of motor vehicle crash injuries even

though opioid doses >20 MME/day were associated with increased odds of road trauma among drivers.

Relative to 0 to <20 MME/day, the adjusted OR for ≥120 MME/day for use of medications for erectile dysfunction or testosterone replacement was 1.6

(95% CI = 1.0–2.4).
One new cross-sectional study found

higher-dose long-term opioid therapy associated with increased risk of androgen deficiency among men receiving immediate-release opioids (adjusted OR per 10 MME/day 1.16, 95% CI = 1.09–1.23), but the dose response was very weak among men receiving ER/LA opioids.

Trials on effects of titration with immediate- release versus ER/LA opioids reported inconsistent results and had additional differences between treatment arms in dosing protocols (titrated versus fixed dosing) and doses of opioids used.

One new cross-sectional study found initiation of therapy with an ER/LA opioid associated with increased risk of overdose versus initiation with an immediate-release opioid (adjusted HR 2.33,
95% CI = 1.26–4.32).

No differences

One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity-adjusted analysis (adjusted HR 0.56, 95% CI = 0.51–0.62) and one cohort study among Tennessee Medicaid patients found methadone to be associated with higher risk of all-cause mortality than sustained-release morphine (adjusted HR 1.46, 95% CI = 1.17–1.73).

One cohort study found some differences between ER/LA opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions.

One cross-sectional study found ER/LA opioids associated with increased risk of androgen deficiency versus immediate- release opioids (adjusted OR 3.39,

95% CI = 2.39–4.77).

Pain 3 randomized trials (n = 93)

Overdose New for update: 1 cohort study

(n = 840,606)

Serious limitations

Serious limitations

Serious inconsistency

Unknown (1 study)

No inconsistency

Serious inconsistency

Unknown (1 study)

Unknown (1 study)

Very serious imprecision

No imprecision

No imprecision No imprecision

Serious imprecision

No imprecision

4

4

3 4

4

4

None identified

None identified

None identified None identified

None identified

None identified

Comparative effectiveness of different ER/LA opioids

Pain and function All-cause mortality

Abuse and related outcomes

3 randomized trials (n = 1,850)

1 cohort study (n = 108,492)

New for update: 1 cohort study (n = 38,756)

1 cohort study (n = 5,684)

Serious limitations

Serious limitations

Serious limitations

Serious limitations

ER/LA versus immediate-release opioids

Endocrinologic harms New for update:
1 cross-sectional study (n = 1,585)

See table footnotes on page 47.

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

Dosing strategies (KQ3)
Comparative effectiveness of different methods for initiating opioid therapy and titrating doses

Outcome Studies Limitations

Dose escalation versus dose maintenance or use of dose thresholds

Inconsistency

Unknown (1 study)

Imprecision

Very serious imprecision

Type of evidence Other factors

3 None identified

Estimates of effect/findings

No difference between more liberal dose escalation versus maintenance of current doses in pain, function, or risk of withdrawal due to opioid misuse, but there was limited separation in opioid doses between groups (52 versus 40 MME/day at the end of the trial).

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

Pain, function, or withdrawal due to opioid misuse

1 randomized trial (n = 140)

Serious limitations

Immediate-release versus ER/LA opioids; immediate-release plus ER/LA opioids versus ER/LA opioids alone; scheduled and continuous versus as-needed dosing of opioids; or opioid rotation versus maintenance of current therapy

Pain, function, quality of None — — life, and outcomes related to abuse

Effects of decreasing or tapering opioid doses versus continuation of opioid therapy

Pain and function 1 randomized trial Very serious Unknown (n = 10) limitations (1 study)

Comparative effectiveness of different tapering protocols and strategies

Opioid abstinence 2 nonrandomized trials Very serious No inconsistency (n = 150) limitations

Risk assessment and risk mitigation strategies (KQ4)

—

Very serious imprecision

Very serious imprecision

Insufficient —

4 None identified

4 None identified

No evidence

Abrupt cessation of morphine was associated with increased pain and decreased function compared with continuation of morphine.

No clear differences between different methods for opioid discontinuation or tapering in likelihood of opioid abstinence after 3–6 months

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

Opioid risk tool

Screener and Opioid Assessment for Patients with Pain, Version 1

Screener and Opioid Assessment for Patients with Pain-Revised

Brief Risk Interview

3 studies of diagnostic accuracy (n = 496)

New for update:
2 studies of diagnostic accuracy (n = 320)

2 studies of diagnostic accuracy (n = 203)

New for update:
2 studies of diagnostic accuracy (n = 320)

New for update:
2 studies of diagnostic accuracy (n = 320)

Serious limitations

Very serious limitations

Very serious limitations

Very serious limitations

Very serious inconsistency

No inconsistency

No inconsistency No inconsistency

Serious imprecision

Serious imprecision

Serious imprecision

Serious imprecision

4 None identified

3 None identified

3 None identified 3 None identified

Based on a cutoff score of >4 (or unspecified), five studies (two fair-quality, three poor-quality) reported sensitivity that ranged from 0.20 to 0.99 and specificity that ranged from 0.16 to 0.88.

Based on a cutoff score of ≥8, sensitivity was 0.68 and specificity was 0.38 in one study, for a positive likelihood ratio of 1.11 and a negative likelihood ratio of 0.83. Based on a cutoff score of >6, sensitivity was 0.73 in one study.

Based on a cutoff score of >3 or unspecified, sensitivity was 0.25 and 0.53 and specificity was 0.62 and 0.73 in two studies, for likelihood ratios close to 1.

Based on a "high risk" assessment, sensitivity was 0.73 and 0.83 and specificity was 0.43 and 0.88 in two studies, for positive likelihood ratios of 1.28 and 7.18 and negative likelihood ratios of 0.63 and 0.19.

See table footnotes on page 47.

Comparative effectiveness of treatment strategies for managing patients with addiction to prescription opioids

Outcomes related to None — abuse

Effects of opioid therapy for acute pain on long-term use (KQ5)

—
No inconsistency

—
No imprecision

Long-term opioid use

New for update: 2 cohort studies (n = 399,852)

Serious limitations

3 None identified

Recommendations and Reports

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

Type of
Outcome Studies Limitations Inconsistency Imprecision evidence Other factors Estimates of effect/findings

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

Outcomes related to None — — — Insufficient — No evidence abuse

Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse

Outcomes related to None — — — Insufficient — No evidence abuse

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

Outcomes related to None — — — Insufficient — No evidence abuse

Effectiveness of risk mitigation strategies, including opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, and use of abuse-deterrent formulations, on outcomes related to overdose, addiction, abuse, or misuse

No evidence

No evidence

One study found use of opioids within
7 days of low-risk surgery associated with increased likelihood of opioid use at 1 year (adjusted OR 1.44, 95% CI = 1.39–1.50), and one study found use of opioids within 15 days of onset of low back pain among workers with a compensation claim associated with increased risk of late opioid use (adjusted OR 2.08,
95% CI = 1.55–2.78 for 1 to 140 MME/day and OR 6.14, 95% CI = 4.92–7.66 for
≥450 MME/day).

Outcomes related to None — — — Insufficient abuse

— Insufficient —

Abbreviations: CI = confidence interval; ER/LA = extended release/long-acting; HR = hazard ratio; MME = morphine milligram equivalents; OR = odds ratio.
* Ratings were made per GRADE quality assessment criteria; "no limitations" indicates that limitations assessed through the GRADE method were not identified. † Not applicable as no evidence was available for rating.

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

Recommendations and Reports

Opioid

Codeine
Fentanyl transdermal (in mcg/hr) Hydrocodone
Hydromorphone
Methadone

1–20 mg/day 21–40 mg/day 41–60 mg/day ≥61–80 mg/day

Morphine Oxycodone Oxymorphone Tapentadol†

Conversion factor*

0.15 2.4 1
4

4

8 10 12 1

1.5 3 0.4

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

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

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

Steering Committee and Core Expert Group Members

Steering Committee: *Deborah Dowell, MD, Tamara M. Haegerich, PhD; Division of Unintentional Injury Prevention, National Center for Injury Prevention and Control, CDC; Roger Chou, MD; on detail to CDC under contract.*
Core Expert Group Members: *Pam Archer, MPH, Oklahoma State Department of Health; Jane Ballantyne, MD; University of Washington (retired); Amy Bohnert, PhD; University of Michigan; Bonnie Burman, ScD; Ohio Department on Aging; Roger Chou, MD; on detail to CDC under contract; Phillip Coffin, MD, San Francisco Department of Public Health; Gary Franklin, MD, MPH; Washington State Department of Labor and Industries/University of Washington; Erin Krebs, MDH; Minneapolis VA Health Care System/University of Minnesota; Mitchel Mutter, MD, Tennessee Department of Health; Lewis Nelson, MD; New York University School of Medicine; Trupti Patel, MD, Arizona Department of Health Services; Christina A. Porucznik, PhD, University of Utah; Robert "Chuck" Rich, MD, FAAFP, American Academy of Family Physicians; Joanna Starrels, MD, Albert Einstein College of Medicine of Yeshiva University; Michael Steinman, MD, Society of General Internal Medicine; Thomas Tape, MD, American College of Physicians; Judith Turner, PhD, University of Washington.*

Stakeholder Review Group

John Markman, MD, American Academy of Neurology; Bob Twillman, PhD, American Academy of Pain Management; Edward C. Covington, MD, American Academy of Pain Medicine; Roger F. Suchyta, MD, FAAP, American Academy of Pediatrics; Kavitha V. Neerukonda, JD, American Academy of Physical Medicine and Rehabilitation; Mark Fleury, PhD, American Cancer Society Cancer Action Network; Penney Cowan, American Chronic Pain Association; David Juurlink, BPharm, MD, PhD, American College of Medical Toxicology; Gerald "Jerry" F. Joseph, Jr, MD, American College of Obstetrics and Gynecology; Bruce Ferrell, MD, AGSF, M. Carrington Reid, MD, PhD, American Geriatrics Society; Ashley Thompson, American Hospital Association; Barry D. Dickinson, PhD, American Medical Association; Gregory Terman MD, PhD, American Pain Society; Beth Haynes, MPPA, American Society of Addiction Medicine; Asokumar Buvanendran, MD, American Society of Anesthesiologists; Robert M. Plovnick; MD, American Society of Hematology; Sanford M. Silverman, MD, American Society of Interventional Pain Physicians; Andrew Kolodny, MD, Physicians for Responsible Opioid Prescribing.

Opioid Guideline Workgroup

Chair: *Christina Porucznik, PhD, MSPH*
Workgroup Members: *Anne Burns, RPh; Penney Cowan; Chinazo Cunningham, MD, MS; Katherine Galluzzi, DO; Traci Green, PhD, MSC; Mitchell Katz, MD;*

Erin Krebs, MD, MPH; Gregory Terman, MD, PhD; Mark Wallace, MD. Workgroup Consultants: Roger Chou, MD; Edward Covington, MD; Diana Eppolito; Michael Greene, MD; Steven Stanos, DO.

Peer Reviewers

Jeanmarie Perrone, MD, University of Pennsylvania; Matthew Bair, MD, Indiana University School of Medicine;, David Tauben, MD, University of Washington.

NCIPC Board of Scienti c Counselors

US Department of Health and Human Services/Centers for Disease Control and Prevention MMWR / March 18, 2016 / Vol. 65 / No. 1 49

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Appendix D: e-Delphi Protocol and Panel Documents

-e-Delphi Protocol

-Physician Letter

-Physician Intake Form

-e-Delphi Protocol

A National Analysis of Opioid Prescribing in NSVD to Inform Leaders in Maternal Health Practice & Policy

Principal Investigator:
Jennie “Rebecca” Mills, DrPH(c), MSM
Jmills3@uic.edu

Protocol for Delphi Panel Recommendations

Note: This protocol is only for the Delphi portion of the Study. The Epi portion of the Study is in a separate protocol.

Version 1

Date: June 29, 2017

TABLE OF CONTENTS

Page

LIST OF ABBREVIATIONS

ACOG American College of Obstetricians and Gynecologists
CDC Centers for Disease Prevention and Control
COI Conflict of Interest
HHS Department of Health and Human Services
HIPAA Health Insurance Portability and Accountability Act
IRB Institutional Review Board
NSVD Normal, Spontaneous, Vaginal Delivery
OBGYN An Obstetrician and/or Gynecologist
OP Opioid Prescribing
OUD Opioid Use Disorder
PI Principal Investigator
SME Subject Matter Expert

1.0 Project Summary/Abstract

There is a prescription opioid overdose epidemic in the United States. Drug overdose deaths are the leading cause of injury death in the United States. Local, state and federal agencies are looking for opportunities to employ primary, secondary, and tertiary prevention strategies. In 2013, there were 259, 000, 000 prescriptions written for opioids, enough for every adult in the U.S. to have their own script; prescription opioids are involved in almost half of opioid overdose deaths (Paulozzi et al., 2014; CDC, 2016). According to the US Centers for Disease Control:

• "Women are more likely to have chronic pain, be prescribed prescription painkillers, be given higher doses, and use them for longer time periods than men.
• Women may become dependent on prescription painkillers more quickly than men.
• Women may be more likely than men to engage in "doctor shopping" (obtaining prescriptions from multiple prescribers).
• Abuse of prescription painkillers by pregnant women can put an infant at risk. Cases of neonatal abstinence syndrome (NAS)—which is a group of problems that can occur in newborns exposed to prescription painkillers or other drugs while in the womb—grew by almost 300% in the US between 2000 and 2009 (CDC, 2013)."

There are data on opioid prescriptions for women during reproductive years, pregnancy and postpartum. There are no such data for labor and delivery or on the day of discharge, though labor and delivery is the number one reason for hospitalization in the United States, and an especially vulnerable time for women. As agencies like the CDC, and not for profits such as the American College of Obstetricians and Gynecologists, continue to look for ways to prevent unnecessary opioid use, abuse, addiction and death, the maternal population in labor and delivery presents a relevant and important population to consider. A descriptive

epidemiological study will be employed to illuminate possible patterns of aberrant prescribing behavior. Further, this data analysis in conjunction with recommendations from subject matter experts in the obstetric community, can serve as a foundation for clinical and administrative leadership to develop guidelines for low risk maternal populations undergoing normal spontaneous vaginal delivery in the United States.

2.0 Background/Scientific Rationale

Labor and delivery is a time of acute pain, and while some opioid use may be appropriate, other pharmacologic approaches would be expected in low risk, straightforward procedures such as normal, spontaneous, vaginal delivery (NSVD). The CDC and local, state and federal stakeholders have emphasized that responsible pain management includes avoiding writing a prescription for opioids when less risky modalities are available and efficacious. The American College of Obstetrics and Gynecology (ACOG) has stated that pain management at delivery is appropriate, and prescribers should consider both pharmacologic and non-pharmacologic interventions. But, there has been no direct guidance in this population, nor is there any national data for benchmarking inpatient opioid orders in this population. The closest direction provided comes from a 2017 ACOG committee opinion based on thirteen-year-old data and states that in the "hospital setting, pharmacologic analgesia should be available for all women in labor who desire medication" (ACOG, 2017). ACOG's most recent recommendation and guidance related to NSVD are general allowing for divergent opinions in pain management. But with the U.S. opioid epidemic and the escalating numbers of women who have overdosed or died, this may be the time to reevaluate guidance in the most straightforward of labor and delivery procedures, NVSD without

complications. There has been some data published regarding opioid prescribing practices before and after delivery, and recent data regarding opioid prescribing post CSection reported that most patients "are prescribed in excess of the amount needed (Osmundson, et al., 2017)." But to date there are no national descriptive epidemiological

data to illuminate prescribing patterns during normal spontaneous vaginal delivery. Expert opinion based on experience and epidemiological data could help form this guidance.

The CDC reported approximately 2.7 million vaginal deliveries for the final birth data for the U.S. in 2015 (Martin, 2017). The very size of this population warrants consideration as to how narcotics are deployed, but an additional and important factor is that this population will be discharged to care for an infant. Further, because of the opioid epidemic, it is incumbent on clinicians, and administrative and policy leadership to consider their respective formulary, protocol and prescribing disciplines where this drug class is concerned. "While actions to address prescription opioid abuse must target both prescribers and high-risk patients, prescribers are the gatekeepers for preventing inappropriate access and providing appropriate pain treatment (HHS, 2017)."

It is hypothesized that understanding the overall patterns of opioid prescribing will elucidate variations by hospital factors (e.g., geography and academic status) and patient factors (e.g., payer, documented substance abuse). A description of the route and type of opioids administered in a given hospitalization and on the day of discharge will provide detailed information which can then be used to set benchmarks for healthcare professionals to use in the future.

Completing a descriptive epidemiological study to better understand the factors associated with opioid prescribing practices in NSVD, may well serve as a foundation for

providing recommendations to improve opioid prescribing patterns in the maternal health arena in the United States. These data may then be deployed along with expert opinion for initial recommendations as to appropriate prescribing practice at delivery.

3.0 Objectives/Aims

RESEARCH QUESTION:

How might clinicians in administrative and policy leadership roles contribute to opioid abuse prevention efforts by addressing opioid prescribing patterns in low-risk procedures such as normal, spontaneous, vaginal delivery patients?

STUDY AIMS:

The study aims are to:

- Provide Recommendations to Clinical, Administrative and Policy Leadership for Opioid Prescribing during NSVD through:
  - Retrospective, observational study and the CDC chronic pain guidelines for opioid prescribing to architect questions for a Delphi Panel;
  - Delphi panel consensus recommendations for opioid prescribing in NSVD.

Subject matter expert (SME) input will be obtained through a modified Delphi process to offer opioid prescribing recommendations for NSVD patients. The SMEs will be selected to participate on the Delphi Panel based on clinical expertise in labor and delivery, as well as demonstrated leadership roles in maternal/child health (MCH). The Delphi panel will be asked

to participate in 2-3 rounds of questions for the purpose of arriving at a consensus on recommendations for pain management during labor and delivery in NSVD patients.

To assist the Panel in the formation of recommendations, the following analyses will be performed and reported:

• Patterns of opioid prescribing in US hospitals for patients discharged with normal, spontaneous, vaginal delivery (NSVD);
• Factors associated with opioid prescribing on the day of discharge;
• Patient and hospital level factors associated with the prescribing of opioids in normal, spontaneous, vaginal deliveries.

As a secondary analysis, an exploration of patient and hospital factors associated with opioid administration to mothers who have a documented history of OUD will also be performed. The protocol for these analyses is under separate cover.

4.0 Participation on the Delphi Panel

A convenience sample will be used by identifying experts that have published in the literature, served on national committees, or are known to the PI from other contacts. The PI will select the Delphi panel. All Delphi participants will hold a current MD or DO license. Selection will be based on the participants' ability to bring knowledge and experience to bear on the research question.

5.0 Subject Enrollment

The panel will comprise of no fewer than ten and no more than twenty subject matter experts (SMEs) as the subject matter experts will be more vs. less homogenous in their expertise. (Akins et al., 2005; Keeney et al., 2005; McMillan et al., 2016). The SMEs will be selected by the PI based on the following criteria:

• Informed consent and willingness to participate in two to three rounds of consensus building over the span of 2-3 months;
• Currently or previously served as a leader and/or practitioner in obstetrics and gynecology. Leader is defined in this setting as having influence in academic institutions, medical societies or policy groups and serving in a role to use said influence to affect change in the healthcare system. Examples include:
o OGGYN physicians who have served on ACOG committees to influence guidelines and provide expert opinion;
o OBGYN Practitioners who have served in editorial roles or as reviewers for peerreviewed publications;
• Have an interest in opioid prescribing and substance abuse or OUD, which has been verified in the form of committee volunteering, public speaking or other professional endeavors;
• Those "willing to revise their initial or previous judgments for the purpose of reaching or attaining consensus (Hsu and Sandford, 2007)";

The SMEs must complete a basic intake form which will reflect the above experience. The SMEs will also be required to sign an informed consent document, non-disclosure agreement, and be willing to allow their names to be cited as part of the process, although all responses will be de-identified, unless the SME releases permission to be quoted directly in the final dissertation or manuscript. The non-disclosure agreement will remain on file until after publication as unpublished data will be shared. PI work products related to Part 1 of the study

will be kept on a password protected PC and will remain in possession of the PI. Managing any SME attrition during the active Delphi process will be managed by the PI and the Committee

Chair. There is minimal risk with this subject population given they are licensed physicians. There will be no remuneration for participation.

6.0 Study Design and Procedures

The Delphi Technique will be employed to build consensus regarding recommendations for opioid orders during labor and delivery and discharge of NSVD patients. The goal of Part 1 will be twofold: 1) to gain SME input on the findings of Part 2 and; 2) to use those findings (if any), as well as expert consensus to offer guidance for opioid prescribing during labor and delivery. The purpose of Part 1 is to provide initial recommendations to ACOG, the CDC and OWH and other stakeholders on appropriate opioid prescribing orders for NSVD patients. As previously noted, there are no national guidelines on opioid prescribing during labor and delivery. Providing recommendations formulated by experts, and informed by national data on current prescribing patterns, would prove useful in assisting in opioid prescribing prevention efforts in the maternal population.

The Delphi technique was chosen as the consensus building technique because it has a fifty plus year history and is an “accepted method for achieving convergence of opinion concerning realworld
knowledge solicited from experts within certain topic areas (Hsu and Sandford, 2007).” The advantages of the technique include anonymity of the panelists, an iterative process, controlled feedback, and statistical “group response” (von der Gracht, 2012).

• The Delphi process is iterative and typically takes two to three iterations; two rounds are optimal as additional rounds may cause panelist attrition. (Hsu and Sandford, 2007; McMillan et al., 2016). For the purposes of this study, questions will be submitted to the

Panel electronically. The electronic “platform” has been referred to in the literature as e-Delphi and notes the advantages of using technology in this approach. “The conduct of Delphi studies is amenable to the Internet platform where iterative collection of data can be made more efficient (Donohoe et al., 2012).” Question composition will be primarily quantitative in nature with an opportunity for qualitative input and the quantitative answers will be expressed via a Likert scale with measures of central tendency reported and (Hsu and Sandford, 2007). There is no standard guideline for defining consensus and researchers have used multiple approaches for measuring consensus including IQRs and median scores (Hasson et al., 2000; Bentley et al., 2016). Using a four point Likert scale, consensus will be met if the majority of Delphi participants rate a three or higher, with a median of 3.25 or higher, and the Interquartile range (IQR) is 1 or less (Hsu and Sandford, 2007; von der Gracht, 2012). If consensus cannot be obtained in the initial two rounds, a third round will be added. At the end of the third round, those recommendations achieving consensus will be included in the final report. Prior to each round of questions being submitted to the Panel, an amendment will be submitted to the UIC IRB for approval of the questions being submitted.

The cadence of questioning and feedback will be as follows:

• The first round of questions will be formulated by the PI after Part 2 of the research has been conducted and analyzed. Questions will be based on the Part 2 study data and the CDC guidelines currently recommended for

providers prescribing opioids for chronic pain patients. The purpose of this round is twofold: To identify priority areas for formulating recommendations on opioid prescribing practices during labor and

delivery for NSVD patients; to respond to the PIs suggested adaptation of the CDC guidelines for NSVD opioid prescribing.

o Feedback will be returned to the panel reporting the median and IQR for the responses in the first round. A summation of qualitative comments (removing any identifiable details which would forfeit the anonymity of the participant providing comment) will also be provided.

o The second round of questions will be formulated and sent for IRB approval.

o Once approved, the questions will be sent to the Delphi panel.

• The second round of question will be based on responses from the first round and the purpose of the second round is to resolve any outstanding questions/priorities from the epidemiological data and to further refine the adaptation of the CDC guidelines for the NSVD population. The questions will be formulated by the PI with appropriate input from the Dissertation Committee as needed.

o Feedback will be returned to the panel reporting the median and IQR for the responses in the second round. A summation of qualitative comments (removing any identifiable details which would forfeit the anonymity of the participant providing comment) will also be provided.

o If consensus is not achieved, a third round of questions will be formulated and sent for IRB approval.

o Once approved, the third round of questions will be sent to the Delphi panel.

• The third round of questions, will provide a summation and give panelists a conduit for further refinement of responses to reach consensus.

Each round of questions will be reviewed by a member the committee and will be emailed to participants with instructions for completion and return. All respondents will have a code that only the PI, committee, and respondent will know and all data will be password protected and stored electronically. The informed consent and non-disclosure agreement can be found in Appendix C.

7.0 Expected Risks/Benefits

There are no anticipated risks with the study. Benefits would include participating in a consensus building project to inform prescribing guidelines.

8.0 Data Collection, Analysis and Management Procedures

The PI only will have access to the intake form of the physician participants which will give age-range, gender, years and type of experience and licensure information. When data is shared with the panel in aggregate, codes will be assigned to each panelist.

Surveys will be distributed electronically via Survey Monkey. Security regarding Survey Monkey is outlined below:

Authentication: User data is logically segregated by account-based access rules. User accounts have unique usernames and passwords that must be entered each time a user logs on. SurveyMonkey issues a session cookie only to record encrypted authentication information for the duration of a specific session. The session cookie does not include the password of the user.

•Passwords: User application passwords have minimum complexity requirements. Passwords are individually salted and hashed.

•Data Encryption: Certain sensitive user data, such as credit card details and account passwords, are stored in encrypted format.

•Data Residency: All SurveyMonkey user data is stored on servers located in the United States.

Physical Security--All SurveyMonkey information systems and infrastructure are hosted in worldclass data centers. These data centers include all the necessary physical security controls you would expect in a data center these days (e.g., 24Å~7 monitoring, cameras, visitor logs, entry requirements). SurveyMonkey has dedicated cages to separate our equipment from other tenants. In addition, these data centers are SOC 2 accredited. •Connectivity: Fully redundant IP network connections with multiple independent connections to a range of Tier 1 Internet access providers.

•Power: Servers have redundant internal and external power supplies. Data centers have backup power supplies, and are able to draw power from the multiple substations on the grid, several diesel generators, and backup batteries.

••Failover: Database is replicated in real-time and can failover in less than an hour.

•Backup Frequency: Backups occur daily at multiple geographically disparate sites.

Network Security

•Testing: System functionality and design changes are verified in an isolated test “sandbox” environment and subject to functional and security testing prior to deployment to active production systems.

•Firewalls: Firewalls restrict access to all ports except 80 (http) and 443 (https).

•Access Control: Secure VPN, 2FA (two-factor authentication), and role-based access is enforced for systems management by authorized engineering staff.

•Logging and Auditing: Central logging systems capture and archive all internal systems access including any failed authentication attempts.

•Encryption in Transit: By default, our survey collectors have Transport Layer Security (TLS) enabled to encrypt respondent traffic. All other communications with the surveymonkey.com website are sent over TLS connections, which protects communications by using both server authentication and data encryption. This ensures that user data in transit is safe, secure, and available only to intended recipients. Our application endpoints are TLS only and score an “A” rating on SSL Labs‘ tests. We also employ Forward Secrecy and only support strong ciphers for added privacy and security.

Vulnerability Management

•Patching: Latest security patches are applied to all operating systems, applications, and network infrastructure to mitigate exposure to vulnerabilities.

•Third Party Scans: Our environments are continuously scanned using best of breed security tools. These tools are configured to perform application and network vulnerability assessments, which test for patch status and basic misconfigurations of systems and sites.

•Penetration Testing: External organizations perform penetration tests at least annually.

•Organizational & Administrative Security

•Information Security Policies: We maintain internal information security policies, including incident response plans, and regularly review and update them.

•Access: Access controls to sensitive data in our databases, systems, and environments are set on a need-to-know / least privilege necessary basis.

•Audit Logging: We maintain and monitor audit logs on our services and systems.

•PCI: SurveyMonkey is currently PCI 3.1 compliant.SSL creates a secure connection between a client and a server, encrypting sensitive information being transmitted through the web page.

Questions will be quantitative in nature employing a four point Likert scale. Any qualitative commentary will be aggregated and any identifiable information removed. Examples of identifiable information are employer of the participant, publications they have authored and cited. Consensus will be achieved by the majority of the Delphi participants rating a three or higher, with a median of 3.25 or higher and IQR of 1 or less.

9.0 Regulatory Requirements

9.1 Informed Consent

Informed consent will be obtained by the PI only. The informed consent document will be stored on a password protected computer and only the PI will have access to the documents.

9.2 Subject Confidentiality

Confidentiality of each panel member/subject will be maintained by assigning a code to their name. The study will be single blinded in that the PI will know the participant's individual responses but the panel will only see de-identified responses.

10.0 References

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Dear Dr. XXXXXXX:

My name is Rebecca Mills and I am a doctoral student in the School of Public Health at the University of Illinois, Chicago. I received your name from XXXXX and understand you have an extensive leadership background in maternal health. I am searching for a small group of approximately fifteen experts who would be willing to provide expertise in providing opioid prescribing recommendations during Normal Spontaneous Vaginal Delivery or NSVD.

There are data on opioid prescriptions for women during reproductive years, pregnancy and postpartum. There have been no such data for labor and delivery or on the day of discharge, though labor and delivery is the number one reason for hospitalization in the United States, and an especially vulnerable time for women. Agencies like the CDC, and not for profits such as the American College of Obstetricians and Gynecologists, continue to look for ways to prevent unnecessary opioid use, abuse, addiction and death. The maternal population in labor and delivery presents a relevant and important population to consider.

As baseline input for your policy recommendations, I will be providing a statistical summary from data derived from the first national epidemiological study on opioid prescribing for NSVD patients from 2014-2016. This data was derived from the Premier Healthcare Database with participation from Premier analysts and statisticians. Premier has the largest inpatient database in the country and the derived data will include approximately 300+ hospitals. My intent as part of my dissertation work is to publish both the epidemiological study and the recommendations from the group of subject matter experts-- of which I hope you will be a part.

Please respond to this email at your earliest convenience as to your interest in participating by signing the attached IRB informed consent and the intake form. You may return these to me electronically.

After I have the participants' signatures I will be sending you a link to the first round of surveys via Survey Monkey, an online survey tool. I will also be providing a background document that provides context for the survey questions. In the first round, each survey question asks for your level of agreement or disagreement to eight recommendations. All of the recommendations have been adapted for NSVD patients from the CDC's current opioid prescribing guidelines for chronic pain patients.

There will be at least one and no more than three surveys with the purpose of each round refining the last round of recommendations. Each survey will take approximately 10-20 minutes. The recommendations that reach consensus will be submitted for publication and shared with both ACOG and the CDC. The estimated timeframe is December 15-January 30th. Your responses to the survey will be aggregated but de-identified, including any commentary. All participants who participate in each round of surveys will be included in the acknowledgements segment of the publication. I will also include individual quotes of experts as needed if the expert provides written permission.

Please contact me directly with any questions and if possible return these forms

PHYSICIAN INTAKE FORM FOR NSVD SURVEY

Please print or type the following:

Name:

Email:

Phone:

Please answer the following questions, sign and return electronically:

1) Do you currently hold an MD or DO license? Yes No
2) Are you willing to participate in a minimum of one but no more than three rounds of surveys for the purpose of consensus building regarding the prescribing/ordering of opioids for NSVD patients? Yes No
3) Are you "willing to revise your initial or previous judgments for the purpose of reaching or attaining consensus (Hsu and Sandford, 2007)" during the course of the surveys? This is important as the goal is to reach consensus on draft recommendations to ACOG and the CDC. Yes No
4) Have you in the past or do you currently serve as a leader and/or practitioner in obstetrics and gynecology? If so, please given ONE or more examples. (Leader is defined in this setting as having influence in academic institutions, medical societies or policy groups and serving in a role to use said influence to affect change in the healthcare system. Examples include OGGYN physicians who have served on ACOG committees to influence guidelines and provide expert opinion, practitioners who have served in editorial roles or as reviewers for peer-reviewed publications). Yes (please provide example below) No

   Example: _____

5) Do you have an interest in opioid prescribing and substance abuse or Opioid Use Disorder (OUD), which has been demonstrated in the form of committee volunteering, organizational leadership, public speaking or other professional endeavors in this area? Yes No

To the best of my knowledge this information is true and correct.

_____

Signature Date

-Informed Consent & NDA

Informed Consent and Non-Disclosure vs. 2 1

INFORMED CONSENT and NON-DISCLOSURE for Doctoral Research A National Analysis of Opioid Prescribing in NORMAL SPONTANEOUS VAGINAL DELIVERY to Inform Leaders in Maternal Health Practice & Policy

I volunteer to participate in a research project conducted by the Principal Investigator, J. Rebecca Mills from the University of Illinois, Chicago. I understand that the intent of the research is designed to use a modified Delphi approach with a group of healthcare providers to gain consensus on recommendations for opioid prescribing for NSVD patients during labor and delivery. I will be one of a group of 10-20 physicians being surveyed for this research. The survey will be delivered via the internet via Survey Monkey to the email address I provide on this form. I also acknowledge that a summary of an analysis of de-identified, unpublished, aggregate patient data will be shared with me and that this data is confidential and cannot be used in any form or shared with others until it is published.

1. My participation in this project is voluntary. I understand that I will not be paid for my participation. I may withdraw and discontinue participation at any time without penalty.
2. I have the right to decline to answer any question.
3. Participation involves being electronically surveyed by the PI. Each participant will be given a code so that responses are de-identified to the group. Responses will be identifiable to the PI. There will be 2-3 surveys, each round building on the responses of the last, for the purpose of achieving consensus. If consensus is not achieved after the third round, the surveying will terminate and the results will still be reported. Each survey will take approximately 20 minutes. Survey responses will be shared with the group after each round; and a summary report will be shared at the end of the research and before publication submission. Quantitative questions will be aggregated. Qualitative comments, though not required, will be shared with identifiable information removed. I will be asked to return my questionnaire within 2 weeks of receiving it.
4. I understand that the researcher will not identify me by name in any reports using information obtained from the surveys, unless I provide written permission directly to the PI.
5. I understand the intent of this research is to publish the findings as a part of the requirements for the Principal Investigator’s doctoral dissertation work and the research will be submitted for publication. The data from this study will be kept on file for three years or until the time of publication, whichever comes first.
6. I understand that a possible risk to this study is the identification of my responses to others.
7. I understand that a possible harm is that this study may take longer than

expected and that consensus may not be achieved.
8. I understand that my name may be acknowledged in publications related to this work.
9. I understand that the possible benefits of my participation in this study include having access to national de-identified data regarding opioid prescribing in the NSVD population; insight into recommendations that will be made to ACOG and the CDC relative to the findings of this study. I agree that I will not disclose any of the data I see prior to publication.
10. I understand that this research study has been reviewed and approved by the Institutional Review Board (IRB) for Studies Involving Human Subjects: University of Illinois, Chicago.
11. I have read and understand the explanation provided to me. I have had all my questions answered to my satisfaction, and I voluntarily agree to participate in this study.
12. I have been given a copy of this consent form.
13. I attest that my name and credentials provided below are accurate and current.

_____ My Signature
_____ My Printed Name & Credentials
_____ My Phone Number
_____ My Email Address

Informed Consent and Non-Disclosure vs. 2 3

For further information, please contact:

J. Rebecca Mills, DrPH(c), MSM
Jmills3@uic.edu
913.707.1661

_____ Date
_____ Signature of the Investigator

Appendix E: IRB Approval, Part II

Appendix E: IRB Approval, Part II (e-Delphi Study)

Appendix D2 Storage of Data

IRB Amend 1 Approved

IRB Amend 2 Approved

IRB Amend 3(4) Approved

FORM - Appendix D-2: Storage of Data for Databases

Version: 1.0
Date: 05/9/2012
Office for the Protection of Research Subjects (OPRS)
Institutional Review Board
FWA# 00000083
203 AOB (MC 672)
1737 West Polk Street
Chicago, IL 60612-7227
Phone: 312 996-1711 Fax: 312 413-2929
www.research.uic.edu/protocolreview/irb

To Be Completed By the Investigator For OPRS Use Only
Date Application Completed: 06/29/2017 UIC Protocol #:
Application Document Version #:1 Assigned IRB:

Research Title: A National Analysis of Opioid Prescribing in NSVD to Inform Leaders in Maternal Health Practice & Policy

If your research proposes to store or bank data for the current research protocol or future research, please answer the questions below. As it pertains to each question, please differentiate between short term storage (i.e., storage until an analysis can be performed) versus longer term storage (i.e., banking).

1. Describe the data. Where will the investigator obtain the data?

Survey data will be obtained from 10-20 physicians regarding their recommendations for opioid prescribing practices. Each provider will be assigned a code so that when results are reported back to the group, anonymity is maintained.

2. Will the information collected and stored with the data include individually identifiable health information subject to the HIPAA Privacy Rule requirements (45 CFR Parts 160 and 164)?
No Yes
a. If YES, please describe:

3. Describe the purpose of taking/receiving the data?

To gain consensus on recommendations for opioid prescribing.

4. Will any information/results of this research be shared with the subjects during or after the current research is completed?

No Yes

a. If YES, please explain: In between and after the final Delphi rounds the data will be shared in aggregate but identifiers will be removed.

5. Describe the manner by which the data will be stored/banked and whether this will allow for identification of the data (relating it back to individual persons). Please clarify whether the data will be stored without identifiers, with indirect identifier "links" or "codes" (i.e., study I.D. #), or with direct identifiers (i.e., name, social security number).

The data will be stored with identifiers--each panelist will have a code the PI uses when reporting out to the group.

a. If the data will be stored with either direct or indirect identifiers/codes, please describe the protections in place to maintain confidentiality and prevent an inadvertent breach of confidentiality. Additionally, if you are maintaining identifiers, you may be asked to obtain a federal Certificate of Confidentiality to exclude your research data from subpoena from third parties (i.e. insurance companies).

The data will be stored on a password protected PC on a password protected network

6. Where and for how long will the data be stored?

On a PC for 3 years after the conclusion of the study or after publication, whichever comes first.

7. Will the data be destroyed after the research purpose is served?

No Yes

a. If NO, how will the data be stored after its use in the current research is completed (i.e., no identifiers, indirect identifiers, or direct identifiers)?

8. Will the principal investigator "own"/be custodian of the data?

No Yes

a. If NO, please explain who will "own"/be custodian of the data:

9. Will data be shared with other UIC investigators?

No Yes

a. If YES, explain how and with whom data will be shared, and if the data will include codes or identifiers(i.e., describe the mechanism for sharing):

Possibly if the dissertation committee has questions, but the data will be coded.

10. Will data be shared with investigators outside UIC?

No Yes

a. If YES, explain how and with whom data will be shared, and if the data will include codes or identifiers(i.e., describe the mechanism for sharing):

11. Has all of the above information been included in the consent document (i.e. purpose, type of information stored, identifiability, for how long, share information back, re-consent for future research uses, confidentiality safeguards, risks related to potential breach of confidentiality, etc.)?

No Yes

Filename: Appendix D2.doc

Approval Notice

Amendment to Research Protocol – Expedited Review

UIC Amendment #1

November 30, 2017

Jennie (Becca) Mills, DrPHc, MSM, BA

Health Policy and Administration

14995 Wetterhorn Pk Tr

Phone: (913) 707-1661

RE: **Protocol # 2017-0781**
"A National Analysis of Opioid Prescribing in NSVD to Inform Leaders in Maternal Health Practice & Policy"

Dear Dr. Mills:

Members of Institutional Review Board (IRB) #1 have reviewed this amendment to your research under expedited procedures for minor changes to previously approved research allowed by Federal regulations [45 CFR 46.110(b)(2)]. The amendment to your research was determined to be acceptable and may now be implemented.

Please note the following information about your approved amendment:

Amendment Approval Date: November 30, 2017

Amendment:

Summary: UIC Amendment #1, dated November 20, 2017 and received on November 21, 2017, is an investigator initiated amendment submitting the questionnaire document for the part 2 of the study which is a Delphi Panel surveying 10-20 physicians (NSVD Opioid Prescribing Survey).

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
11/21/2017	Amendment	Expedited	11/30/2017	Approved

Please be sure to:

❼ Use your research protocol number (2017-0781) on any documents or correspondence with the IRB concerning your research protocol.

❼ Review and comply with all requirements on the enclosure,
"**UIC Investigator Responsibilities, Protection of Human Research Subjects**"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB #1 has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS at (312) 996-1711 or me at (312) 413-9680. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Jovana Ljuboje

Assistant Director, IRB # 1

Office for the Protection of Research Subjects

cc: Kee Chan, Faculty Sponsor
Lisa Powell, Health Policy and Administration, M/C 923

Approval Notice

Amendment to Research – Expedited Review

UIC Amendment #2

January 18, 2018

Jennie (Becca) Mills, DrPHc, MSM, BA

Health Policy and Administration

14995 Wetterhorn Pk Tr

Phone: (913) 707-1661

RE: Protocol # 2017-0781
"A National Analysis of Opioid Prescribing in NSVD to Inform Leaders in Maternal Health Practice & Policy"

Dear Ms. Mills:

Members of Institutional Review Board (IRB) #1 have reviewed this amendment to your research under expedited procedures for minor changes to previously approved research allowed by Federal regulations [45 CFR 46.110(b)(2)]. The amendment to your research was determined to be acceptable and may now be implemented.

Please note the following information about your approved amendment:

Amendment Approval Date: January 18, 2018

Amendment:

Summary: UIC Amendment #2, dated and received by OPRS on January 11, 2018, is an investigator initiated amendment providing the Round 2 survey questions for the Delphi part of the research study. The Questions were developed from the Round 1 survey answers (Survey Questions Round 2).

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
01/11/2018	Amendment	Expedited	01/18/2018	Approved

Please be sure to:

❼ Use your research protocol number (2017-0781) on any documents or correspondence with the IRB concerning your research protocol.

❼ Review and comply with all requirements on the enclosure,
"**UIC Investigator Responsibilities, Protection of Human Research Subjects**"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB #1 has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS at (312) 996-1711 or me at (312) 996-1711. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Jovana Ljuboje

Assistant Director, IRB # 1

Office for the Protection of Research Subjects

cc: Kee Chan, Faculty Sponsor
Lisa Powell, Health Policy and Administration, M/C 923

Note: Amendment 4 is sequential to Amendment 2 and replaces Amendment 3.

Approval Notice

Amendment to Research Protocol – Expedited Review

UIC Amendment #4

February 1, 2018

Jennie (Becca) Mills, DrPHc, MSM, BA

Health Policy and Administration

14995 Wetterhorn Pk Tr

Phone: (913) 707-1661

RE: Protocol # 2017-0781
"A National Analysis of Opioid Prescribing in NSVD to Inform Leaders in Maternal Health Practice & Policy"

Dear Ms. Mills:

Members of Institutional Review Board (IRB) #1 have reviewed this amendment to your research under expedited procedures for minor changes to previously approved research allowed by Federal regulations [45 CFR 46.110(b)(2)]. The amendment to your research was determined to be acceptable and may now be implemented.

Please note the following information about your approved amendment:

Amendment Approval Date: February 1, 2018

Amendment:

Summary: UIC Amendment #4, dated January 29, 2018 and received by OPRS on January 31, 2018, is an investigator initiated amendment providing the round 2 results and instructions for the final survey (survey round 3) round for the Delphi Panel members.

Please note the Review History of this submission:

Receipt Date	Submission Type	Review Process	Review Date	Review Action
01/31/2018	Amendment	Expedited	02/01/2018	Approved

Please be sure to:

❼ Use your research protocol number (2017-0781) on any documents or correspondence with the IRB concerning your research protocol.

❼ Review and comply with all requirements on the enclosure,
"**UIC Investigator Responsibilities, Protection of Human Research Subjects**"
(http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB #1 has the right to ask further questions, seek additional information, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact the OPRS at (312) 996-1711 or me at (312) 413-9680.

Sincerely,

Jovana Ljuboje

Assistant Director, IRB # 1

cc: Kee Chan, Faculty Sponsor
Lisa Powell, Health Policy and Administration, M/C 923

Appendix F: Survey Instructions for e-Delphi Panel and Results

Survey Instructions Round 1

Survey Instructions Round 2 with Round 1 results

Survey Instructions Round 3 with Round 2 results

Survey Results Round 3

Instructions Round 1:

Please read the information below prior to taking the survey. The survey itself should take no more than 10 minutes. The link is at the bottom of this email. Please complete the survey by 12/31 as the survey tool is undergoing maintenance the first week of January. Thank you again for your participation and being willing to contribute to this important body of research.

Background:

There is a prescription opioid overdose epidemic in the United States that has been declared a national public emergency. Drug overdose deaths are the leading cause of injury death in the US. In 2013, there were 259, 000, 000 prescriptions written for opioids, enough for every adult in the U.S. to have their own script; prescription opioids are involved in almost half of opioid overdose deaths (Paulozzi et al., 2014; CDC, 2016).

There are data on opioid prescriptions for women during the reproductive years, including pregnancy and postpartum. However, there have been no such data for the hospitalization period for labor and delivery, though labor and delivery is the number one reason for hospitalization in the US and an especially vulnerable time for women. Organizations like the CDC and the American College of Obstetricians and Gynecologists (ACOG) continue to look for ways to prevent unnecessary opioid use, abuse, addiction and death. The labor and delivery hospitalization present a relevant and important period to consider.

Opioid Prescribing for NSVD Patients:

In November 2017, a study was conducted to illuminate opioid prescribing behavior for patients admitted for labor and delivery in US hospitals. The specific aim of the Study was to characterize prescribing patterns in normal spontaneous vaginal delivery (NSVD) patients. The national study comprised 106, 518 patients admitted for NSVD in US hospitals.

Patients meeting all the following inclusion criteria were eligible for study inclusion:

- Inpatients 15-44 years of age;
- Hospital discharge dates between January 1, 2014 and December 31, 2016;
- At least one service day in the hospital as determined by hospital charge master data;
- At least one ICD-9 or ICD-10 codes for Normal Spontaneous Vaginal Delivery.

Patients with any of the following exclusion criteria were not eligible for study inclusion:

- Patients with a contraindication to NSAIDs.
- Patients undergoing caesarean delivery.
- Patients with selected complicated deliveries (deliveries with codes for fetal distress, episiotomy, use of forceps/assisted delivery, any level of laceration, etc.).
- Patients undergoing tubal ligation during the index hospitalization.
- Death during the index hospitalization.
- Patients from hospitals with volumes below 36 deliveries within the three-year study window.
- Patients from hospitals that do not have at least one delivery in each of the three calendar years (2014-2016).

Findings:

The study population was constructed to enable examination of a well-defined population that is unlikely to need opioids for a separate indication. This resulted in a final study population of 49, 133 NSVD patients from approximately 330 teaching and non-teaching hospitals throughout the U.S.

Among 49, 133 NSVD patients, 78.2 % received an opioid sometime during their hospitalization and 29.8 % received an opioid on the day of discharge. A multilevel multiple logistic regression model was used to ascertain the statistical significance of predictors of opioid prescribing while adjusting for hospital clustering. Being White, Married, not on Medicaid, and a patient in a teaching hospital proved to be protective:

- Other things equal, the odds for a Black patient receiving an opioid during hospitalization were 42% higher than

the odds for a White patient. The odds for a Black patient receiving an opioid on the day of discharge were 27% higher than the odds for a White patient.

- Other things equal, the odds for a Medicaid patient receiving an opioid during hospitalization were 36% higher than the odds for a Commercially insured patient. The odds for a Medicaid patient receiving an opioid on the day of discharge were 71% higher than the odds for a Commercially insured patient.
- Other things equal, the odds for a Married patient receiving an opioid anytime during hospitalization were 32% lower than the odds for a Single patient. The odds for a Married patient receiving an opioid on the day of discharge were 23% lower than the odds for a Single patient.
- Other things equal, the odds for a patient in a teaching hospital receiving an opioid during hospitalization were 20% lower than for a patient in a non-teaching hospital. The odds for a patient in a teaching hospital receiving an opioid on the day of discharge were 21% lower than for a patient in a non-teaching hospital.

Survey:

The timeliness of this data in conjunction with recommendations from subject matter experts in the obstetric community could serve as a foundation for clinical and administrative leadership to develop guidelines for low risk maternity populations undergoing NSVD. The purpose of this survey is to provide the CDC and ACOG with draft guidelines for opioid-prescribing among NSVD patients.

You are not being asked to write final guidelines. You are being asked for your level of agreement or disagreement to draft guidelines adapted from the CDC Guidelines for Prescribing Opioids for Chronic Pain. The draft guidelines are meant to address opioid prescribing for NSVD patients with no complications (e.g., lacerations, episiotomy, assisted birth, tubal ligation) during delivery and to utilize as much of the original CDC chronic pain guideline wording as appropriate for this population.

When filling out the survey, please use code 2017**XX** **Your results cannot be included without this code being entered in Question 1.**

Survey Link: https://www.surveymonkey.com/r/NSVDOPIOID

Respectfully,

J. Rebecca Mills, DrPH(c)

913.707.1661

Instructions for Round 2 with Round 1 Aggregate Results:

Dr. _____:

The three guidelines that did not achieve consensus have been revised. Your code to use in the survey tool and the corresponding survey link are:

Code: **2017001**

Link: https://www.surveymonkey.com/r/NSVDOpioid_Survey2

You are being asked to complete the survey by January 26, 2018. There are three questions and it should take no longer than 3-5 minutes.

For your reference you will find below the results of the first round of surveying. The proposed guidelines are in the same order you answered on the survey, and in red font you will find the consensus determination. Below each consensus determination you will see the qualitative comments each respondent made (all identifiers removed). If no comment was provided you will see "none" notated.

Thank you again for your participation and contributions to this research.

Respectfully,

Rebecca Mills, DrPH(c)
913.707.1661

Delphi Round 1 Survey Results:

1) Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for normal spontaneous vaginal delivery patients with no complications. Clinicians should consider opioid therapy only if

expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
CONSENSUS ACHIEVED: YES
Median: 3.5
IQR: 1
% of Respondents Scoring Guideline as a 3 or higher: 92.9%

2) Well before labor and delivery, clinicians should establish pain treatment goals with all patients, including NSVD patients. Clinicians should discuss with their patients known risks and realistic benefits of opioid therapy as well as the patient and clinician responsibilities for managing pain during labor and delivery. If the benefits do not outweigh the harms of opioid therapy, clinicians should work with their patients to optimize other therapies.
CONSENSUS ACHIEVED: NO
Median: 3.0
IQR: 2.0
% of Respondents Scoring Guideline as a 3 or higher: 64.3%

3) Long-term opioid use often begins with treatment of acute pain. When opioids are started, clinicians should order the lowest effective dosage and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.
CONSENSUS ACHIEVED: YES
Median: 4.0
IQR: .25
% of Respondents Scoring Guideline as a 3 or higher: 100%

4) When starting opioid therapy, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting opioids. This is especially important on the day of discharge.
CONSENSUS ACHIEVED: YES
Median: 4
IQR: 1
% of Respondents Scoring Guideline as a 3 or higher: 92.9%

5) Clinicians should review the patient's history of controlled substance prescriptions before and during pregnancy using the state prescription drug monitoring program (PDMP) data. If the clinician determines that the patient is receiving opioid dosages or dangerous combinations that put her at risk for overdose, the clinician should work with pharmacy or other hospital personnel as appropriate to determine the best course of action during labor and delivery.

CONSENSUS ACHIEVED: NO
Median: 2.5
IQR: 2
% of Respondents Scoring Guideline as a 3 or higher: 50.0%

6) Clinicians should avoid prescribing opioid pain medications and benzodiazepines concurrently whenever possible.
CONSENSUS ACHIEVED: YES
Median: 4
IQR: 1
% of Respondents Scoring Guideline as a 3 or higher: 92.9%

7) Clinicians and hospital administration should consider implementing a protocol for opioid prescribing for NSVD patients during delivery. This could help prevent opioid orders becoming routine in NSVD patients where the benefit may not outweigh the risk for mother and fetus. The protocol should include the utilization of prescription drug monitoring program (PDMP) data for screening purposes and steps for arranging evidence-based treatment for patients with opioid use disorder (OUD). This treatment is usually medication-assisted treatment with buprenorphine or methadone, and is prescribed in combination with behavioral therapies.

CONSENSUS ACHIEVED: NO
Median: 3
IQR: 2

% of Respondents Scoring Guideline as a 3 or higher: 64.3%

8) When clinicians identify a patient with OUD, treatment discussions should be prioritized during hospitalization, upon discharge and at the post-partum appointment.

CONSENSUS ACHIEVED: YES
Median: 3.5
IQR: 1
% of Respondents Scoring Guideline as a 3 or higher: 85.7%

9) What additional opioid prescribing recommendations, if any, do you believe should be established for NSVD labor and delivery patients? Are there any recommendations that you strongly disagreed with that need to be removed?

Instructions for Round 3 with Round 2 Results:

Dear Dr.____:

Below you will find the results of the second round of surveying for draft guidelines 2, 5 and 7. The basis for the consensus determination is in red font. Only Guideline 7 reached consensus so the PI has revised the other two based on your feedback. Below you will find Survey 2 results with the qualitative comments each respondent made (all identifiers removed). If no comment was provided you will see "none" notated.
Guidelines 2 and 5 (these did **not** achieve consensus) have been revised and are included in Survey Round 3 which is the final survey round. Your code to use in the final survey tool and the corresponding survey link are below. You are being asked to complete the survey by 2/8. There are only two guidelines to rank and based on the last survey, it should take no longer than 2-3 minutes to complete.
I appreciate that you took the time to complete the first two rounds and I look forward to your responses for the third and final round. Regardless of the results of the third round, I will send you the summary.
Survey 3 Code: 2017XX
Due Date: 02/8/18
Web link: https://www.surveymonkey.com/r/FinalNSVDSurvey

Respectfully,
Rebecca Mills, DrPH(c)
913.707.1661

Delphi Round 2 Survey Results:

Guideline 2: Options and expectations for intra-and postpartum pain management should be an essential component of every patient's

prenatal care. It is recommended that clinicians discuss these options in the prenatal period, with follow up post-partum if there is reason for concern based on the patient's history prior to pregnancy and behavior during pregnancy. The clinician should document that pain management options were discussed, questions answered, and the patient appeared to understand. To what extent do you agree with the content of this guideline?
CONSENSUS ACHIEVED: NO
Median: 3
IQR: 1
% of Respondents Scoring Guideline as a 3 or higher: 85.7%

Guideline 5: Clinicians should review the patient's history of controlled substance prescriptions before and during pregnancy utilizing feasible and appropriate data sources. If the clinician determines the patient is at risk because of dangerous opioid dosages and/or drug combinations that put her at risk, the clinician should work with available pain management or other appropriate personnel to mitigate risk for the mother and fetus. To what extent do you agree with the content of this guideline?
CONSENSUS ACHIEVED: NO
Median: 3
IQR: 1.25
% of Respondents Scoring Guideline as a 3 or higher: 78.6%

Guideline 7: Clinicians and hospital administration should consider implementing a protocol for opioid prescribing for NSVD patients during and after delivery. This could help prevent opioid orders becoming routine in NSVD patients where the benefit may not outweigh the risk for mother and fetus. To what extent do you agree with the content of this guideline?
CONSENSUS ACHIEVED: YES
Median: 3.5
IQR: 1
% of Respondents Scoring Guideline as a 3 or higher: 85.7%

Round 3 Results:

Dear Delphi Panel Participants:

First, many thanks for taking the time to participate in this research! All fourteen of you participated in every survey round which has served for a much better data set for the draft guidelines. In seven of the eight suggested guidelines, consensus was achieved. The de-identified results from the third and final round are below. My deepest appreciation for your time and expert input.
Second, please email your most current bio so that I may ensure your proper credentials are used in this research, including acknowledgements in the publication submissions.
If you have any questions, please don't hesitate to email or call me.

Respectfully,
Rebecca Mills, DrPH(c), MSM
Jmills3@uic.edu
913.707.1661

Round 3 Results:

Guideline 2: Options and expectations for intra-and postpartum pain management should be an essential component of every patient's prenatal care. It is recommended that clinicians discuss these options in the prenatal period with follow up post-partum if there is reason for concern based on the patient's history prior to pregnancy and behavior during pregnancy. The clinician should document that pain management options were discussed, questions answered, and the patient appeared to understand.

CONSENSUS ACHIEVED: YES
Median: 4.0
IQR: 1.0
% of Respondents Scoring Guideline as a 3 or higher: 85.7%

Guideline 5: Clinicians should review the patient's history of controlled substance use. If the clinician determines that the patient is utilizing opioids (prescribed or unprescribed), the clinician should work with pain management personnel to develop a plan for intra- and post-partum pain medication. A prenatal consult with neonatology or a pediatrician, to counsel the patient about the risk for NAS, should be strongly advised.

CONSENSUS ACHIEVED: NO
Median: 3.0
IQR: 1.0
% of Respondents Scoring Guideline as a 3 or higher: 85.7%

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