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The Association of Prescription Opioid Exposure and Patient Factors with Prolonged Postoperative Opioid Use in Opioid Naive Patients

Jennifer Lanzillotta

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THE ASSOCIATION OF PRESCRIPTION OPIOID EXPOSURE AND
PATIENT FACTORS WITH PROLONGED POSTOPERATIVE OPIOID USE IN OPIOID
NAÏVE PATIENTS

A Dissertation

Submitted to the School of Nursing

Duquesne University

In partial fulfillment of the requirements for
the degree of Doctor of Philosophy

By

Jennifer Lanzillotta

August 2018

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Jennifer Lanzillotta

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By

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ABSTRACT

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By

Jennifer Lanzillotta

August 2018

Dissertation supervised by Melissa Kalarchian, PhD

Background

Research suggests prolonged postoperative opioid use occurs in 4-13% of opioid naïve patients and is related to factors other than surgical pain. However, it is unclear which patient factors and prescribing practices are associated with prolonged use after surgery among opioid naïve patients.

Objectives

To identify factors associated with prolonged postoperative opioid use (refills 90-180 days after surgery) in opioid naïve patients in two domains: specific patient characteristics (demographics, smoking status, comorbidities, etc.) and exposure through postoperative opioid prescriptions (in oral morphine milligram equivalents [OME]).

Methods

An electronic medical record dataset analysis of inpatient and outpatient opioid naïve adult orthopedic surgery patients at the University of Cincinnati Medical Center from January 1, 2012 through December 31, 2017 was conducted. Opioid naïve was defined as no opioid prescription filled in the past twelve months or only a perioperative prescription filled 30 days or less prior to surgery. Patients were excluded if they had a diagnosis of cancer or if they underwent a second surgery within 180 days of the first. A multivariate logistic regression model was used to evaluate the relationship of each domain to opioid refills 90-180 days after surgery.

Results

Of the 7,323 patients met inclusion criteria, 4% continued to refill opioid prescriptions more than 90 days after their surgical procedure. Independent predictors of prolonged postoperative opioid use were alcoholism (O.R. 2.0, C.I. 1.5-2.6), OME > 675 (O.R. 2.3, C.I. 1.5-3.4), female gender (O.R. 1.7, C.I. 1.3-2.1), black race (O.R. 1.6, C.I. 1.2-2.2), Medicaid insurance (O.R. 1.8, C.I. 1.3-2.5), and the following co-morbidities: diabetes (O.R. 1.5, C.I. 1.1-2.0), mood disorders (O.R. 1.4, C.I. 1.1-1.9), hypertension (O.R. 1.4, C.I. 1.1-1.9), and chronic kidney disease (O.R. 1.6, C.I. 1.1-2.4).

Conclusions

Both opioid exposure and patient characteristics increase risk for prolonged opioid use following orthopedic surgery. Since the risk of overdose increases with increased OME, patients with high OME prescriptions should also receive a prescription for naloxone. This study sheds light on the need for postoperative prescribing guidelines for clinicians. To decrease the rate of prolonged postoperative opioid use, clinical changes can be

investigated and implemented including collaborative perioperative pain management strategies utilizing non-opioid pain control methods; perioperative patient screening; education of patients and clinicians; and close postoperative follow-up, especially for the most vulnerable populations.

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1.0 Dissertation Proposal

THE TEMPORAL ASSOCIATION OF PATIENT CHARACTERISTICS AND PRESCRIBING PRACTICES WITH PROLONGED POSTOPERATIVE OPIOID USE

1.1 Specific Aims

The opioid crisis in the United States has reached epidemic proportions. Opioid overdose deaths nearly tripled in the fifteen years between 1999 and 2014 (Rudd, Aleshire, Zibbell, & Gladden, 2016). The rate of drug overdose deaths increased significantly in both males and females and among all adult age groups (Rudd, Akeshire, Zibbell, & Gladden, 2017). There were 52,404 drug overdose deaths in 2015, up from 47,055 in 2014. Of these deaths, 63% (33,091) were attributed to opioids, the highest rate ever recorded. Ohio, the site of the proposed research, is ranked the fourth highest state in opioid overdose deaths (Rudd et al., 2017).

There are many pathways to opioid misuse. Prescribing practices for managing post-surgical pain are important in the development of opioid misuse and the conversion of acute pain to chronic pain (Kehlet, Jensen, & Woolf, 2006). Research suggests that prolonged postoperative opioid abuse is a common complication of elective surgery (Brummett et al., 2017). In fact, when opioid naïve patients (patients who have not taken an opioid for the past 12 months) are prescribed an opioid post-surgery, 6-13% are still taking the medication three months later (Brummett et al., 2017; Carroll et al., 2012; Johnson et al., 2016a; Sun, Darnall, Baker, & Mackey, 2016). The overarching objective of this proposal is to identify risk factors for prolonged opioid use post-surgery, which will directly inform efforts to prevent opioid use disorder (OUD).

Surgery places patients at risk for long term opioid use through exposure to narcotics (Brummett et al., 2017; Carroll et al., 2012; Johnson et al., 2016; Sun et al., 2016). However, research has been inconsistent as to which patient factors and prescribing practices are predictive of prolonged postoperative use (Carroll et al., 2012; Rozet et al., 2014; Sun et al., 2016). The proposed retrospective electronic medical record (EMR) chart review study of orthopedic surgery patients (n=422) aims to utilize the Availability-Proneness Theory of Illicit Drug Abuse framework to identify potential predictive factors of postoperative opioid use in the domains of exposure and patient factors (Smart, 1980). The data will be extracted from the EMR through an honest broker; data will be provided in a secure and HIPPA-compliant format.

Specific Aims are as follows:

Aim 1

Determine if postoperative opioid exposure is related to prolonged postoperative opioid use. Exposure will be based on the initial post-surgery prescription as documented in the EMR, including the medication, milligrams per pill, number of days, and number of pills prescribed.

Hypothesis 1. Exposure (converted to morphine milligram equivalents [MME] per kilogram of body weight and length of prescription in days) will be associated with continued use (prescriptions refills at 30-, 60-, and 90-days post-surgery).

Aim 2

Determine if individual patient factors are related to prolonged postoperative opioid use. Patient factors will include demographics; smoking status; physical and psychological diagnoses via International Classification of Diseases, 9th Revision (ICD-10) codes; pre-surgery medications and history of opioid use; and the American Society of Anesthesiologists (ASA) physical status classification.

Hypothesis 2. Patient factors (e.g., history of opioid use, smoking status, psychological conditions, and increased number of comorbid conditions) will be associated with continued use (prescription refills at 30-, 60-, and 90-days post-surgery).

Exploratory Aim

Evaluate the relative contributions of exposure and patient factors in a multiple logistic regression model predicting opioid refills at 90-days.

This study directly addresses National Institute of Drug Abuse (NIDA) funding priority areas: NIDA Goal #2 is to “*develop new and improved strategies to prevent drug use and its consequences*” (2016-2020 NIDA Strategic Plan Advancing Addiction Science, 2016). By “*determining the mechanisms that underlie drug abuse and its consequences*” this research meets NIDA objective 2.1. Findings will be used to develop screening tools to identify patients at high risk for opioid misuse, develop pain management protocols and prescribing guidelines, increase the use of multi-modal anesthetics targeting different pain pathways, increase regional anesthetic techniques, and develop educational strategies for patients, clinicians, and stakeholders, thus meeting other NIDA objectives. It will support the development of evidenced based best practices for pain management, and will help the nurse scientist applicant launch an independent program of funded research in this high priority area.

Background and Significance

National Opioid Epidemic

It is widely recognized that the United States is experiencing an opioid epidemic. There has been an urgent call to action at the national level by the U.S. Congress, the Centers for Disease Control and Prevention (CDC), the Department of Health and Human Services (*Addressing Prescription Drug Abuse in the United States*, 2013), the U.S. Department of Justice Drug Enforcement Agency (*2016 National Drug Threat Assessment Summary*, 2016), and the National Institutes of Health (*2016-2020 NIDA Strategic Plan Advancing Addiction Science*, 2016). Overdose deaths are increasing in males and females among all age groups; in 2015, 63%, or 33,091 overdose deaths, were attributed to opioids, the highest rate ever recorded (Rudd et al., 2017). Ohio, the state where the proposed retrospective EMR chart review will be conducted, is ranked 4th in the nation in opioid overdose deaths (Rudd et al., 2017). There were 3,050 overdose deaths in Ohio in 2015, up from 2,531 in 2014, a 21% increase (*2015 Ohio Drug Overdose Data: General Findings*, 2015). Ohio ranked first in increased number of emergency department visits related to opioid misuse between 2009 and 2014 and there was a 52% increase in the number of inpatient admissions related to opioid misuse during that same time period (Weiss et al., 2017).

In addition to the human toll, the economic burden of the opioid epidemic is staggering. The CDC's estimated direct costs to insurers in 2011 for nonmedical use of prescription drugs was over \$72 billion per year ("Prescription Painkiller Overdoses in the U.S.," 2011). Although men continue to misuse opioids more than women, this gap is narrowing ("Prescription Painkiller Overdoses," 2013). The CDC reported a 400% increase in the use among women since 1999 compared to a 265% increase among men; the female age groups most affected are women

of childbearing age ("Prescription Painkiller Overdoses," 2013). Thus, a better understanding of risk factors could have a major public health impact.

Postsurgical Pain Management Contributes to the Opioid Epidemic

Prescription opioid abuse is contributing to the heroin epidemic: people often turn to heroin when they are unable to obtain pain pills (Compton, Jones, & Baldwin, 2016). In fact, the strongest predictor of heroin use disorder is previous prescription opioid dependence or opioid use disorder; those who misuse opioids are 40 times more likely to become dependent on heroin ("New research reveals the trends and risk factors behind America's growing heroin epidemic," 2016).

Prescribing practices are an important component in preventing drug substance use disorder ("New research reveals the trends and risk factors behind America's growing heroin epidemic," 2016). In fact, a surgical procedure was the precipitating pain event in 10-50% of chronic pain patients depending upon the procedure (Kehlet et al., 2006). Brummet et al. (2017) found that 6% of patients continued to fill opioid prescriptions whether the surgery was major or minor, suggesting factors other than chronic pain contribute to long term use; Johnson et al. (2016) found 13% of patients continue to fill opioid prescriptions more than 3 months after surgery. Eliminating opioids entirely is not feasible, as this would prevent patients in severe pain from obtaining relief. Therefore, clinicians need to strategically manage acute surgical pain in order to minimize long-term opioid misuse and abuse.

Post-surgery Prescribing Practices may Place Patients at Risk for Prolonged Opioid Use

Surgical exposure to opioids places patients at risk for prolonged use. Previous literature has commonly operationalized ninety days as significant long-term opioid use post-surgery, referred to in this application as "prolonged use" (Manchikanti et al., 2012). Three studies

showed that a surgical procedure places opioid naïve patients at risk for chronic opioid use. Johnson et al. (2016) found that 13% of opioid naïve patients continued to fill prescriptions 90 days post-surgery. Carroll et al. (2012) found that 5% of opioid naïve patients continued to use opioids greater than 150 days after a surgical procedure. Sun et al. (2016) found that seven of the eleven surgical procedures examined placed opioid naïve patients at increased risk for chronic opioid use.

Studies indicate that opioids are overprescribed after surgery and that there is wide variation in prescribing practice. Recent studies indicate opioids are overprescribed after surgery. In a survey of patients, less than 40% of urology patients used all of their opioid pain medication after surgery; only 58% of the prescribed medication was used (Bates, Laciak, Southwick, & Bishoff, 2011). In another survey of patients, less than one third of the prescribed opioid pain medication was used by patients after their elective upper extremity surgical procedure (Rodgers, Cunningham, Fitzgerald, & Finnerty, 2012). A prospective observational study examined patients undergoing dermatology surgery. Only 11% of the patients used all of the prescribed opioids (Harris et al., 2013). Overall, less than 40% of the prescribed pain medication was used. The authors also reported wide variation in opioid prescribing practices among the physicians in this study. In a retrospective chart review, wide variation in prescriber practices occurred not only nationally, but within the same healthcare facility (Harris et al., 2014). These findings indicate inconsistency in postoperative pain management practices, overprescribing of opioids, and prolonged use after surgery that may be related to factors other than pain.

Individual Patient Characteristics Also Confer Risk

Certain patient characteristics may be predictive of postoperative opioid use, but these are inconsistently reported across studies. Demographics such as gender, age, and socioeconomics

were particularly inconsistent. For instance, in one large analysis, the patient demographics predicting prolonged postoperative opioid use were age less than 65, female gender, household income under \$60,000 per year, and private insurance (Johnson et al., 2016). Conversely, in another large database analysis, men and patients over 50 years of age had higher rates of prolonged use (Sun et al., 2016). Another study found no difference in opioid use six months after surgery by age, gender, ethnicity, or type of surgery (Goesling et al., 2016). Rates also varied by geographic location. Statistically significant higher rates of prolonged opioid use were found in the U.S. Census Bureau West South Central (7.02%) and East South Central (7.85%) regions compared to the Middle Atlantic Region (3.78%) (Brummett et al., 2017).

Researchers consistently found that patients who are already on opioids, benzodiazepines, or addicted to alcohol are at increased risk of prolonged postoperative use (Brummett et al., 2017; Goesling et al., 2016; Johnson et al., 2016; Rozet et al., 2014; Sun et al., 2016; Waljee et al., 2016). In fact, mental health disorders, tobacco and alcohol abuse, multiple comorbid conditions, and pre-existing pain conditions were independent predictors of prolonged postoperative opioid use across all surgical procedures (Brummett et al., 2017; Johnson et al., 2016). Preoperative opioid prescriptions, depressive symptoms, and self-perceived risk of addiction predicted prolonged postoperative use more than postoperative intensity and duration of pain (Carroll et al., 2012). One study found that a preoperative opioid prescription greater than 60 morphine milligram equivalents per day was associated with prolonged use after surgery (Goesling et al., 2016). Additionally, patients already on opioids preoperatively were often overprescribed opioids postoperatively (Waljee et al., 2016). Lastly, post-traumatic stress disorder (PTSD) and preoperative opioid use were factors leading to

chronic postoperative opioid use in young veterans having minor elective surgeries (Rozet et al., 2014).

In summary, current evidence suggests that prolonged postoperative opioid use is related to factors other than the duration and severity of surgical pain. Patients already using opioids, benzodiazepines, tobacco, or abusing alcohol were at higher risk for prolonged postoperative opioid use (Brummett et al., 2017; Goesling et al., 2016; Johnson et al., 2016; Rozet et al., 2014; Sun et al., 2016; Waljee et al., 2016). Mental health disorders such as anxiety and depression, a self-perceived risk of addiction, and multiple comorbid conditions independently predicted prolonged use (Brummett et al., 2017; Carroll et al., 2012; Johnson et al., 2016). The contribution of patient demographics is conflicting across studies.

The American Society of Anesthesiologists (ASA) physical status classification system was developed to provide a uniform method for statistical analysis, for communication among colleagues, and for other record keeping purposes. This system classifies patients according to disease morbidity. (Johnson et al., 2016). The system, universally utilized by all anesthesia providers for each surgical procedure, could ultimately assist providers in selecting multi-modal pain management strategies for high risk populations and help guide postoperative acute pain control methods. This system is summarized in Appendix 1.

ASA status was reported in two studies: a retrospective chart review of knee arthroscopies in veterans and a prospective cohort study on the effect of preoperative opioid use in spine surgeries (Armaghani et al., 2014; Rozet et al., 2014). Although neither of the two studies indicated a statistically significant difference in postoperative opioid use related to ASA status, certain studies have shown an increase related to increasing comorbidities.

Proposed Retrospective EMR Chart Review Study

These early studies have begun to lay a foundation of knowledge for future research, but significant gaps remain. The literature does not consistently identify which patients are at risk for prolonged postoperative opioid use, or how prescribing practices influence prolonged postoperative opioid use (Clarke, Soneji, Ko, Yun, & Wijesundera, 2014). Examining opioid use 30 days after surgery is also important because this indicates a high probability of continued long term use at 90 days (Shah, Hayes, & Marting, 2017). Determining how (1) postoperative opioid exposure (measured in morphine milligram equivalents [MME] per kilogram of body weight and length of prescription in days) is related to prolonged postoperative opioid use at 30, 60, and 90 days and (2) determining individual patient factors related to prolonged opioid use, including preoperative drug use, the patient's physical and psychological medical conditions, ASA status, and demographics, will address the gap in knowledge. The MME conversion table is presented in Appendix 2.

The proposed retrospective EMR chart review study will extend previous work in several ways. Current research has mainly focused on patients over age 64 with private insurance (Johnson et al., 2016; Rozet et al., 2014; Sun et al., 2016; Waljee et al., 2016). This research will not exclude adult patients based on age nor type of insurance or lack thereof. Both exposure and patient factors will be examined in tandem. By evaluating the relative contributions of exposure and patient factors, it is anticipated that we can account for some of the variability in prolonged use. Previous literature has commonly described ninety days as significant prolonged use post-surgery (Manchikanti et al., 2012). Recent findings indicate that the risk of prolonged opioid use increases after the first five days of therapy and again after 30 days of therapy regardless of the

reason for the prescription (Shah, Hayes, & Martin, 2017). Because of this evidence, opioid use at 30, 60, and 90 days postoperatively will be analyzed.

Surgery places patients at risk for prolonged opioid use, but the contributions of prescribing practices and patient risk factors is unclear. Findings from the proposed study will be used to develop evidenced based best practices for pain management, including screening tools, perioperative pain management protocols and prescribing guidelines, increased use of multi-modal anesthetics targeting different pain pathways and regional anesthetic techniques, and educational strategies for patients, clinicians, and stakeholders.

Theoretical Framework for the Proposed Dissertation Study

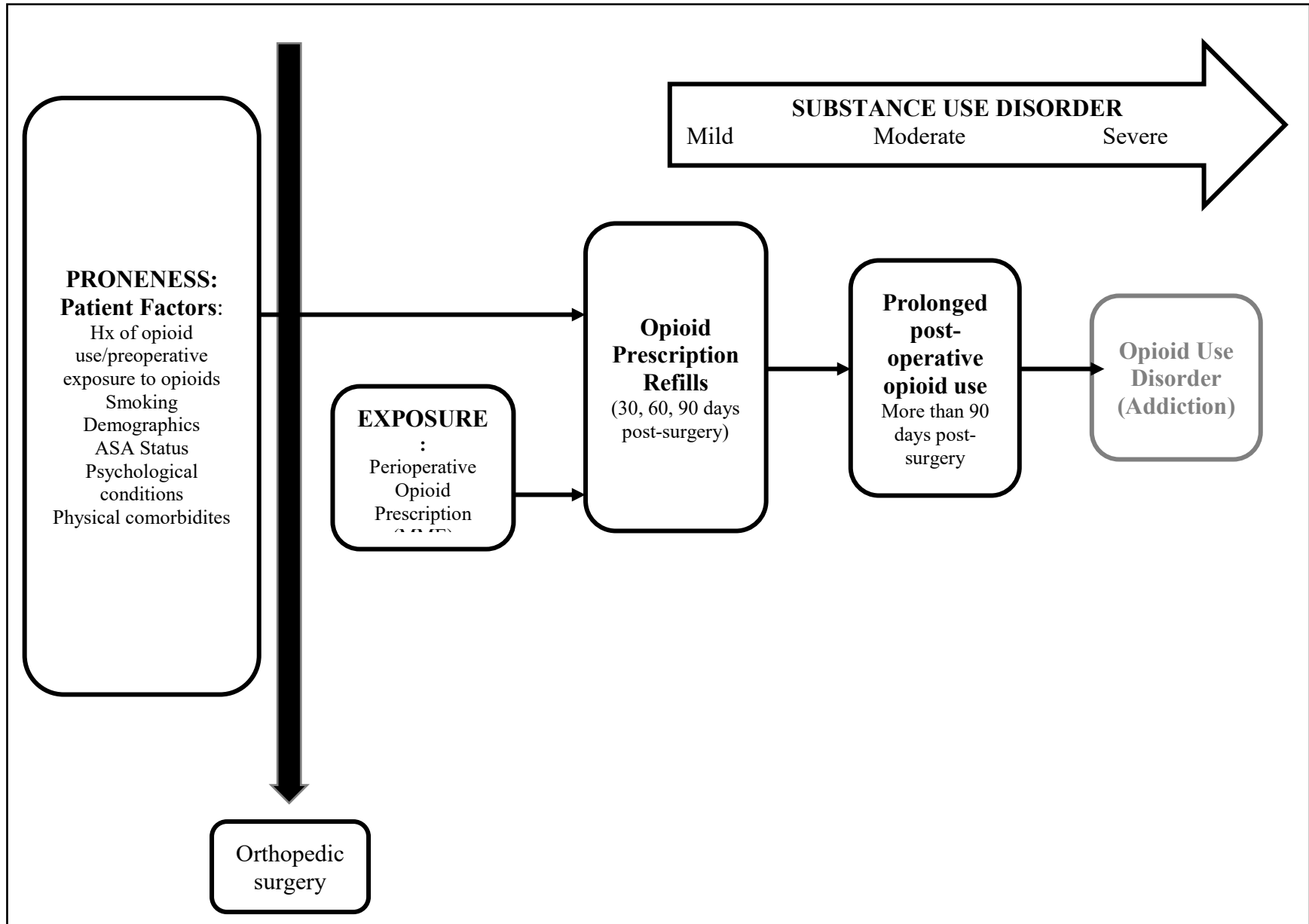
The design of this dissertation research is based on *The Availability-Proneness Theory of Illicit Drug Abuse* (Smart, 1980). This theory can be tested empirically; support for this theory can be found in recent literature examining factors contributing to drug abuse (Ayllón & Ferreira-Batista, 2017; Barrett, Joe, & Simpson, 1990; Rigg & DeCamp, 2014; Rigg & Murphy, 2013; Zeinali & Vahdat, 2011). This theory remains timely: it is currently utilized to explain opioid dependence following exposure via prescriptions and was used to develop the Addiction Susceptibility Questionnaire to measure a person's likely predilection to drug abuse (Rigg & DeCamp, 2014; Rigg & Murphy, 2013; Zeinali & Vahdat, 2011).

Basic tenets of this theoretical framework include that drug abuse occurs when two factors are met: (1) the ease of access to drugs for an individual (exposure) and (2) the individual patient factors contributing to the likelihood of abuse (proneness) (Smart, 1980). Thus, the theory can be used to explain OUD in different populations, whether inner city, medical professionals with high access to opioids, or post-surgical patient populations. Proneness to drug abuse is a psychological construct. It describes a person's innate tendency to seek out and use drugs. Those

with low proneness will not seek out drugs, but may become dependent if there is a high availability, such as a postoperative prescription or if they live in an environment where illicit drugs are commonly available. Persons with certain predictive characteristics--proneness--will seek drugs out, even when availability is low.

Persons who otherwise would not experience opioid exposure do so postoperatively. Thus, this theory can be used to explain why some studies indicate a greater proportion of our opioid-naïve patients who convert to opioid misuse after surgery (exposure) do not fit our paradigm of drug abusers: they are young, female, and covered by private insurance (Johnson et al., 2016). It also may explain why the gap between males and females is closing, and why females of child-bearing age are greatly affected (*Addressing Prescription Drug Abuse in the United States*, 2013). The second prong of this theory associates individual patient factors with risk of SUD. If we identify predictors of abuse, we can identify high risk patients and intervene more readily to prevent subsequent SUD.

This dissertation research seeks to identify potential predictive factors of postoperative opioid use in these two domains through a retrospective EMR chart review. The theoretical framework as it applies to this research proposal is shown in Figure 1. Proneness is represented by patient factors (Table 1). We will examine patients undergoing orthopedic surgery and their subsequent initial exposure to opioids. According to our hypotheses, patient factors and initial exposure will be associated with subsequent prescription refills. We will measure prescription refills at 30, 60, and 90 days as described to determine prolonged use, which could lead to OUD.



Theoretical Framework (Adapted from The Availability Proneness Theory of Illicit Drug Abuse Model by Smart, 1980.)

Pathophysiology of Drug Abuse

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) describes SUD with four major categories: impaired control, social impairment, risky use, and pharmacological criteria such as tolerance and withdrawal. It can be classified as mild, moderate, or severe. Not all persons exposed to opioids will progress down the SUD continuum. The most severe form of SUD is estimated to affect 10% of the population (Volkow, Koob, & McLellan, 2016). Although addiction is not defined by the American Psychiatric Association, the term is still commonly used and represents the end of the SUD continuum; addiction can be considered the severe form of SUD (Volkow et al., 2016).

The disease model of addiction describes OUD similarly to other chronic health conditions such as diabetes and heart disease: it the result of a combination of genetic, behavioral, environmental, and biological factors. Changes in brain neurobiology in response to drug use include up and down regulation of neuronal receptors and neurotransmitter changes. This results in impaired dopamine release, conditioned responses, and re-setting of the brain-reward system, thus altering motivation and behavior (Volkow et al., 2016). Once the person has progressed to severe SUD, craving overrides behavioral control despite negative consequences. The disease is characterized by relapse and can be progressive, leading to disability and premature death. This definition is accepted by the American Medical Association and the American Society of Addiction Medicine (ASAM) ("Definition of Addiction," 2017).

Fit with National Priorities

The National Institute on Drug Abuse (NIDA), in response to this epidemic, released its strategic plan for 2016-2020 with goals and objectives to stem the tide. Goal #2 is to “*Develop new and improved strategies to prevent drug abuse and its consequences.*” One objective of the

goal is to determine the mechanisms that underlie individual risk and resilience for addiction and common comorbidities, which is a fit with the proposed retrospective EMR chart review dissertation study by a nurse scientist (*2016 National Drug Threat Assessment Summary*, 2016).

Innovation

This innovative dissertation research will provide new insight into developing strategies to combat the national opioid epidemic by using a theoretically grounded approach to studying the effect of prescribing practice (exposure) and the predictors of SUD (proneness) together. The innovation of this research lies in the ability to examine both prescribing practices and patient characteristics for comparison and analysis of their relative contributions to prolonged opioid use.

As mentioned earlier, previous studies have not examined the impact of prescribing practices in conjunction with predictors of prolonged postoperative opioid use (Clarke et al., 2014). For example, Johnson et al. (2016) examined the predictors of prolonged opioid use in opioid naïve patients after common hand surgeries, but did not examine the medications prescribed, medication dosages, or number of pills dispensed. Sun et al. (2016) concluded that opioid naïve patients are put at risk for long-term opioid use after surgery, but the research did not examine the provider prescribing practices that may have influenced the outcomes. In a review by Manchikanti and colleagues (2012), the authors conclude that the greatest contributors to the current opioid epidemic are prescribing patterns based on misinformation, lack of education, the perceived safety of opioids, lack of willingness of patients to use other pain control modalities, and health system barriers. Thus, research to date has tended to focus on either prescribing or exposure, but has not considered both together.

In short, this project will move science forward by examining the post-surgical provider prescribing practices (exposure) and the predictors of prolonged use (proneness) in tandem. This will, in turn, lead to identification of patients at high risk for postoperative opioid misuse, development of pain management protocols and prescribing guidelines, increase in the use of multi-modal anesthetics targeting different pain pathways, and the development of educational strategies for patients, clinicians, and stakeholders, ultimately decreasing postoperative opioid misuse, a national crisis.

Research Design and Methods

Overview and Research Design

We propose a retrospective EMR chart review to (1) examine the temporal association of postoperative opioid exposure (measured in MME per kilogram of body weight and length of prescription in days) to prolonged opioid use at 30, 60, and 90 days post-surgery and (2) determine individual patient factors related to prolonged opioid use, including history of opioid use, demographics, smoking status, and certain physical and psychological conditions.

Setting

The EMR chart review will be conducted at University of Cincinnati Medical Center (UCMC), a large, urban teaching hospital that is part of an academic medical center. This site treats Medicare, Medicaid, private insurance, self-pay, and the uninsured. The data will be extracted by Biomedical Informatics, the institutional Honest Broker for UC Health. The data will be provided in a secure, HIPPA-compliant format ensuring patient confidentiality and protection will be maintained. There are five Epic-trained database analysts on the team and supporting faculty with broad informatics experience that will lend their expertise during this retrospective EMR chart review. Biomedical Informatics has provided a letter of support

confirming that they will provide the required data in a compliant and secure format along with supporting personnel. The UCMC Chief Nursing Officer and Vice President of Patient Care Services has also provided a letter of support confirming access to the Epic EMR for this research study.

Sample

The sample for this research will consist of orthopedic surgery patients who underwent surgery at UCMC. This class of surgery was selected because research of privately insured, 18 to 64-year-old patients, showed orthopedic surgeries to be the highest risk for prolonged postoperative opioid use and that preoperative opioid use is highest in orthopedic patients (Sun et al., 2016; Wilson et al., 2015). Inclusion criteria are (1) over age 18, (2) having had orthopedic surgery, and (3) received a perioperative opioid prescription in the time frame of 30 days prior to surgery through postoperative discharge. The exclusion criterion is patients without a current or previous diagnosis of cancer according to the ICD medical codes because cancer pain treatment is vastly different from acute pain treatment. Both opioid naïve patients and patients using opioids preoperatively will be included. For this research, opioid naïve is defined as patients who have not filled an opioid prescription in the past twelve months or who only filled a perioperative prescription; perioperative prescriptions are defined as thirty days or less prior to surgery so that patients have their pain medication available at home immediately following discharge.

Data Collection

Data will be extracted from the Epic EMR by an honest broker. Prescriptions for opioids will be extracted from the EMR. Data collected will include the medication prescribed; the number of pills and days prescribed; and the milligrams per pill. MME dosages will be calculated for comparison among different opioids. This method is often used in the literature for

comparison among opioids and is also used by clinicians. The patient’s body mass index (BMI) (kg/m²) will be calculated based on height and weight as documented in the medical record.

Table 1 summarizes the data to be extracted from the EMR.

Table 1
Data to be Collected and Coded from the Electronic Medical Record

	Variable	Data to be extracted	Coding
Patient Factors	Demographics	Age	Months, years
		Gender	Male (yes/no)
	Race	White or Caucasian	White or Caucasian
		Black or African American	Black or African American
		Asian	Asian
	Ethnicity	American Indian and Alaskan Native	American Indian and Alaskan Native
		Hispanic (yes/no)	Hispanic (yes/no)
Weight status	Height and Weight	BMI (Kg/m ²)	
Smoking status	Smoker	Yes/no	
Physical status	ASA Category	Status (I, II, III, IV, E)	
Type of insurance	Insurance at time of surgery	Private Insurance Medicaid Medicare No insurance or self-pay	
Medical Conditions	ICD Codes	Diabetes Chronic obstructive pulmonary disease Emphysema Coronary artery disease Hypertension Obesity Mood disorders Chronic pain Cerebrovascular disease Chronic Kidney disease Liver disease Alcoholism Drug abuse	
Preoperative Prescriptions	Type of medication	Antidepressants Antipsychotics Antianxiety Opioid * Non-opioid pain medication Other	
Person undergoes surgery	Type of Surgery	Specific orthopedic procedure	Total knee arthroplasty Total hip arthroplasty Spine surgery

			Shoulder surgery Upper extremity surgery (non-joint replacement) Lower extremity surgery (non-joint replacement) Other
		Trauma	Yes/No
Exposure	Perioperative & Postoperative Opioid Prescriptions	Number of pills, number of days, mg per pill Date of prescription	Morphine milligram equivalents (if applicable) > 30 days pre-surgery < 30 days pre-surgery At time of surgery * 30-59 days post-surgery 60-89 days post-surgery 90-180 days post-surgery *
		Refill	Yes/no *

* Primary outcome = Prolonged opioid use defined as opioid prescription refills 90-180 days post-surgery (categorical)

Power and Sample Size

Based on power of .80, .05 for alpha, an odds ratio of 1.5, with the proportion of people at 13% ($\Pr(Y=1|X=1)$) and a two-tailed test, a sample size of 422 is needed (Faul, Erdfelder, Buchner, & Lang, 2009; Johnson et al., 2016). Due to the change in opioid prescribing practices over time, orthopedic surgery patients from 2012 forward will be considered (Wunsch, Wijeyesundera, Passarella, & Neuman, 2016). As the cost of analyzing more EMRs does not increase with a greater sample size, we will collect data on the maximal number of patients available in the specified time period.

Data Analysis

Data analysis will be completed by the PhD student PI working with a data analyst under the supervision of a statistician. Following data extraction by an honest broker from the EMR, a research assistant will help with data cleaning and creation of a data dictionary. Completeness of records will not be known until data pulled and will be addressed with statistician. We will begin

by examining the primary outcome variable to see how many patients have refilled a prescription at 90 days (primary outcome; binary). We will also calculate variables such as MME.

Descriptive analyses will be run for means and standard deviations for continuous predictor variables, and frequency and ranges of scores will be examined for categorical variables, to identify any outliers. For continuous variables that are non-normally distributed (e.g. number of days from the initial opioid prescription), we will examine the distribution to create categories (e.g. more or less than one week). Any three-category variables will be dummy coded in preparation for modelling. Reference groups will be labelled as zero.

Following the descriptive analysis and recoding, Chi-squared analysis will be run based on use at 90-days post-surgery and each categorical variable individually. We will run cross-tabs to make sure we have sufficient number of observations at each crosstab (5 or more in each cell). All variables that are statistically significantly related to the 90-day outcome will be considered for the modelling. Before beginning the modeling, tests for multicollinearity, influential cases, and linearity of logit will be conducted to verify that all assumptions of the logistical regression model are met.

A logistic regression model will be used to evaluate study hypotheses and identify factors that predict prolonged opioid use. The categorical variable of refill at 90 days will be entered as the dependent outcome variable, and the variables that were identified from the individual Chi square analyses as the independent predictor variables. The Wald statistic will be used to determine the contribution of each predictor to the model. The beta weight will be used to evaluate the strength and direction of the association. Cox and Snell pseudo R squared will be used to determine the explanatory power of the model in relation to the variance in the dependent variable that is due to the independent variable. The odds ratio for each of the predictors will

allow us to determine how many times that predictor increases the odds of refilling a prescription at 90 days. A p-value $< .05$ will be used as the criterion for determining significance.

Study Hypotheses will be Evaluated as Follows

Hypothesis 1. Exposure (converted to morphine milligram equivalents [MME] per kilogram of body weight and length of prescription in days) will be significantly associated with continued use (prescriptions refills at 30-, 60-, and 90-days post-surgery). The predictor variable will be MME and the outcome variable will be refills at 90 days.

Hypothesis 2. Patient factors (e.g., history of opioid use, smoking status, psychological conditions, and increased number of comorbid conditions) will be significantly associated with continued use (prescription refills at 30-, 60-, and 90-days). A hierarchical variable model where the variables observed to be related to the outcome will be entered based on their theoretical importance (forward entry). In addition, Chi-square change in fit of each successive model will be examined to determine significance of the added predictor variable.

Exploratory aim. We will evaluate the relative contributions of exposure and patient factors in a multiple logistic regression model predicting opioid use at 90-days. A logistic regression analysis will be run with prolonged opioid use as the dependent variable and the variables that were retained in the evaluation of hypotheses 1 and 2 as the independent variables, using an approach similar to that outlined above to explore the relative contributions of exposure and patient characteristics.

Limitations

This dissertation study has several limitations: (1) this research will examine orthopedic patients so the results may not be generalizable to all surgery patients, (2) this study may not reflect the population of the nation as a whole, and (3) patients may seek opioids from outside

sources that will not be captured in the EMR. It is also possible that there will not be sufficient variability in prescribing practices or the outcome variable to conduct the modeling and detect the anticipated effects, and if we encounter this pitfall, the descriptive findings will inform and guide future work.

Future Directions

The proposed study is the first step in a research career in a high priority area. Results will be published in peer-reviewed journals, presented at interprofessional conferences, and used to support future grant applications. Ultimately, this body of research will lead to the development of pain management protocols and postoperative prescribing guidelines, increased use of multi-modal anesthetics targeting different pain pathways, increased regional anesthetic techniques, and the development educational strategies for patients, clinicians, and stakeholders.

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Appendix A
American Society of Anesthesiologist Physical Status Classification

Status	Definition	Examples (not an exhaustive list)
ASA I	Normal, healthy patient	
ASA II	A patient with mild systemic disease	Smoker, mild alcohol use, pregnancy, 30< BMI<40, well controlled diabetes and high blood pressure, mild lung disease
ASA III	A patient with severe systemic disease	Poorly controlled diabetes or high blood pressure, morbid obesity (BMI >40), alcohol dependence, history of stroke, myocardial infarction, coronary artery disease, pacemaker, dialysis
ASA IV	A patient with severe systemic disease that is a constant threat to life	Symptomatic lung disease, symptomatic heart disease, hepatorenal failure. Has at least one disease that is poorly controlled (hypertension, diabetes)
ASA V	Patients not expected to survive more than 24 hours without surgery	Multi-organ system failure
ASA VI	A declared brain-dead patient	Organ procurement

From American Society of Anesthesiologists <https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system>. Retrieved May 2017.

Appendix B
Morphine Milligram Equivalent Conversion Table

Opioid (doses in mg/day except where noted)	Conversion Factor
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Methadone	4
1-20 mg/day	4
21-40 mg/day	8
41-60 mg/day	10
≥ 61-80 mg/day	12
Oxycodone	1.5
Oxymorphone	3

Appendix C

Protection of Human Subjects

The proposed dissertation study involves a retrospective chart review utilizing data from the electronic medical record (EMR) at the University of Cincinnati Medical Center. Because the data to be extracted from the EMR were not collected specifically for the proposed dissertation study, and no one on the study team will have access to patients' identifying information, the study is not considered human subjects research. Expedited Internal Review Board (IRB) approval will be obtained. Because this dissertation research involves both the University of Cincinnati and Duquesne University, IRB will be obtained from both institutions. Initial approval will be sought from Duquesne. Once approved, an IRB/Independent Ethics Committee Authorization Agreement form will be submitted to the University of Cincinnati IRB for approval along with any other required documentation.

Following approval by the IRBs at Duquesne University, where the PI is a doctoral student, as well as the University of Cincinnati, an honest broker from Biomedical Informatics will extract and provide the data in a de-identified, HIPAA compliant, and secure format that will not allow linkage to the patient. There are five Epic data based trained analysts on the team along with supporting faculty with broad informatics experience to assist in procuring and providing the data to the research team in this secure format. The de-identified dataset will be stored on a password protected computer, and will only be accessible to members of the research team.

2.0 INTEGRATIVE REVIEW OF THE LITERATURE

Manuscript #1

THE IMPACT OF PATIENT CHARACTERISTICS AND POSTOPERATIVE OPIOID EXPOSURE ON PROLONGED POSTOPERATIVE OPIOID USE— AN INTEGRATIVE REVIEW

This chapter is a pre-print version of the article accepted for publication by *Pain Management Nursing*.

2.1 Abstract

The United States is experiencing an opioid overdose crisis. Research suggests prolonged postoperative opioid use, a common complication following surgery, is associated with opioid misuse, which, in turn, is the greatest risk factor of heroin misuse.

Objectives: To evaluate how postoperative opioid exposure relates to prolonged use and to identify factors that predict prolonged postoperative opioid use.

Design: An integrative review of the literature

Data Sources: Electronic and hand searching methods were used in PubMed, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CINAHL, and SCOPUS. Search terms included opioid, opiate, postoperative pain, drug administration, prescribing pattern, prescription, inappropriate prescribing, self-medication, patient-controlled analgesia, opioid-naïve patients, and prolonged opioid use.

Review/Analysis Methods: Data was synthesized by identifying themes reflecting the results of the review. A quality assessment of the articles was also conducted.

Results: Fourteen articles were included and two main themes emerged: (1) Surgery places opioid naïve patients at risk for prolonged opioid use and (2) Certain patient characteristics may be predictive of prolonged postoperative opioid use.

Conclusions: Prolonged postoperative opioid use is related to factors in addition to prescribing practices. Researchers consistently found that patients who are already on opioids, benzodiazepines, or addicted to alcohol; who have mental health disorders, depressive symptoms, or a self-perceived risk of addiction; and patients with multiple co-morbidities are at greater risk of prolonged use; demographics were inconsistent.

Nursing Implications: Studies are needed to determine the predicting characteristics of prolonged postoperative opioid use, the type of surgeries that place patients at most risk, and the effect postoperative exposure to opioids has on prolonged use. This information can be used to develop and implement protocols to prevent misuse among high-risk patients.

2.2 Background

The opioid crisis in the United States (U.S) has reached epidemic proportions (*Understanding the Epidemic*, 2017). Opioid overdose deaths nearly tripled in the fifteen years between 1999 and 2014 (Rudd, Seth, David, & Scholl, 2016). There were 52,404 drug overdose deaths in 2015, up from 47,055 in 2014 (Rudd et al., 2016). Of these deaths, 63% (33,091) were attributed to opioids, the highest rate ever recorded in a single year (Rudd et al., 2016). Provisional data for 2017 indicates 64,070 people will die from unintentional drug overdoses, a 20% increase from the previous year (*Provisional Counts of Drug Overdose Deaths, as of 8/6/2017*, 2017).

The rate of drug overdose deaths is increasing significantly in both males and females and among all adult age groups (Rudd, Akeshire, Zibbell, & Gladden, 2017). Although men

continue to misuse opioids more than women, the gap is narrowing ("Prescription Painkiller Overdoses," 2013). The Centers for Disease Control and Prevention (CDC) reported a 265% increase among men compared to a 400% increase in use among women since 1999; the female age groups most affected are women of childbearing age ("Prescription Painkiller Overdoses," 2013). In addition to the human toll, the economic burden of the opioid epidemic is staggering. The CDC's estimated direct costs to insurers in 2011 for nonmedical use of prescription drugs was over \$72 billion per year ("Prescription Painkiller Overdoses in the U.S.," 2011).

In response to this epidemic, there has been an urgent call to action at the national level by the U.S. Congress, the CDC, the Department of Health and Human Services (*Addressing Prescription Drug Abuse in the United States*, 2013), the U.S. Department of Justice Drug Enforcement Administration (DEA) (*2016 National Drug Threat Assessment Summary*, 2016), and the National Institutes of Health (*National Institute on Drug Abuse 2016-2020 Strategic Plan*, 2016). In fact, the DEA reports that opioids--such as prescription drugs, fentanyl, and heroin--are the most significant drug threats facing our country (*2016 National Drug Threat Assessment Summary*, 2016). The strongest predictor of heroin abuse is previous prescription opioid misuse, and those who misuse opioids are forty times more likely to become dependent on heroin; people often turn to heroin when they are unable to obtain opioid analgesics (Compton, Jones, & Baldwin, 2016; Rudd et al., 2016).

Research suggests that prolonged postoperative opioid use is a common complication of elective surgery (Brummett et al., 2017). Opioids are often overprescribed postoperatively for post-surgical pain management, and research indicates that only 28% to 58% of the prescribed pills are used by patients after elective procedures (Bates, Laciak, Southwick, & Bishoff, 2011; Harris et al., 2014; Harris et al., 2013; Hill, McMahon, Stucke, & Barth, 2017; Kim et al., 2016;

Rodgers, Cunningham, Fitzgerald, & Finnerty, 2012). Additionally, wide variation in prescriber practices are found not only nationally, but also among surgeons practicing at the same facilities (Harris et al., 2014; Hill et al., 2017). The average duration of opioid prescriptions has not increased over time; however, the mean morphine equivalents prescribed to opioid naïve patients, defined as no opioid prescription in the six months preceding surgery, showed increases from 2004 to 2008 and again from 2008 to 2012 in a study examining four common surgical procedures: carpal tunnel release, laparoscopic cholecystectomy, inguinal hernia repair, and knee arthroscopy (Wunsch, Wijeyesundera, Passarella, & Neuman, 2016).

A review article examining postoperative discharge opioid prescribing reported on three studies and concluded that there is evidence of unintended prolonged postoperative opioid use (Macintyre, Huxtable, Flint, & Dobbin, 2014). Prescribing practices and predictive patient characteristics were not examined in this review. Current research includes findings regarding prolonged postoperative opioid use, characteristics that may contribute to prolonged use, and prescribing practices. However, no previous literature reviews were discovered evaluating postoperative opioid exposure and the predictive patient characteristics of prolonged opioid use after surgery.

Prescription opioid misuse is a complex and multifaceted problem. Contributors are biological, psychological, social, and institutional (*Addressing Prescription Drug Abuse in the United States*, 2013; "Definition of Addiction," 2018). Prolonged opioid use has been described as continued use beyond the normal and expected time for healing, with 90 days being the cutoff based on multiple definitions and regulations according to the American Society of Interventional Pain Physicians Guidelines (Manchikanti et al., 2012). A better understanding of patient factors and prescribing practices on prolonged postoperative opioid use may facilitate

development of patient focused interventions including screening tools to identify high risk patients, pain management protocols and prescribing guidelines, and educational strategies for patients, clinicians, and stakeholders. Ultimately, this information may lead to implementation of best practice guidelines for acute postoperative pain management.

2.2.1 Objectives

The purpose of this integrative review is to evaluate and synthesize current scientific literature and evidence on how postoperative opioid exposure is related to prolonged use and to identify potential predictive patient characteristics of prolonged postoperative opioid use in the U.S. The following questions guided this review:

- (1) Is postoperative exposure to opioids associated with prolonged use?
- (2) Are there specific patient characteristics associated with prolonged postoperative opioid use?

2.3 Methods

2.3.1 Design

An integrative review was conducted according to the methodology of Whitemore and Knafl (2005). This type of review includes various types of evidence, both empirical and theoretical, and may include randomized controlled trials, qualitative studies, observational studies, clinical experts, and gray literature (Whitemore & Knafl, 2005). The components of this method are problem identification, literature search, data evaluation, data analysis, and presentation (Whitemore & Knafl, 2005, p. 549). The literature search was conducted with the aid of health sciences librarians to ensure a thorough and complete search. This review was also conducted in accordance with the latest Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & PrismaGroup, 2009).

2.3.2 Data Sources

The clinical databases included in the search process were PubMed, Embase, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and CINAHL. In addition, ClinicalTrials.gov and abstracts from the Annual Meeting of the American Pain Society were searched by title for relevancy of unpublished documents for this review; no articles were added from either of these two sources. Scopus was also used to check relevant article reference lists and citing articles. An ancestry search of the reference section of included articles was conducted for completeness. Search strategies were developed by a team of researchers based on the clinical question and key terms.

Two librarians added additional terms and appropriate subject headings depending on the particular database searched (i.e. Medical Subject Headings (MeSH), the National Library of Medicine controlled vocabulary; Emtree, the Embase database controlled vocabulary; and CINAHL subject headings). The following key search terms were used in strategies specific to each database and organization: opioid; opiate; postoperative pain; drug administration; prescribing pattern; prescription; inappropriate prescribing; self-medication; patient-controlled analgesia; opioid-naïve patients; and prolonged opioid use. See the specific search strategies in Table 1.

Titles and abstracts were screened by the first and second authors to determine if the articles met the subject of interest and the inclusion criteria. Articles were included if they were published in original, peer-reviewed journals, written in English, from the U.S., and studies of adult patients. No date restriction was imposed in any database except CINAHL (January 1, 2011). Notably, the review by Macintyre (2014) found no articles predating 2012 in their search. Articles outside the U.S. were excluded due to different drug formularies and different laws

regarding prescribing practices in other countries. Searches in all resources were done through June 21, 2017 (See PRISMA Diagram Figure 1).

After applying the inclusion and exclusion criteria and removing duplicates, 683 titles and abstracts were screened. Nineteen articles were initially selected for full text review. Seven articles were excluded after the full text review: a study on guideline implementation at a single center, a pilot study for an included study, an intervention for preoperative counseling, and four that did not meet the inclusion criteria. The ancestry search of the twelve included articles produced two more articles, and in total fourteen articles were included in this review. A summary of the articles is presented in Table 2.

2.3.3 Review Methods

Data were synthesized by categorizing, summarizing, comparing, and interpreting findings across all fourteen articles to identify themes that reflect the focus of the integrative review. Key components included: author and publication year, purpose, design, sample/setting, statistical analysis, findings, limitations, and recommendations for future research. A matrix of studies reviewed is displayed in Table 2. A quality assessment was conducted on articles included in the review using a scale adapted from other integrative reviews (Clark, Wilder, & Winstanley, 2014; Jinks, Cotton, & Rylance, 2011). The results of the quality assessment are listed in Table 3. Six articles did not describe attrition or the process for handling missing data. Three articles did not adequately address ethical considerations, specifically whether Institutional Review Board approval or consent was obtained.

2.4 Results

2.4.1 Description of Studies

A total of fourteen articles were included in the final analysis. Five retrospective database analyses were included (Brummett et al., 2017; Johnson et al., 2016; Sun, Darnall, Baker, & Mackey, 2016; Waljee et al., 2016; Wunsch et al., 2016). The database analyses all consisted of commercial insurance claims to examine factors of prolonged opioid use after certain surgeries. These studies were limited to patients 18 to 64 years of age with private insurance; Medicare, Medicaid, and patients without insurance were not examined. There were three prospective observational studies, one of which was a pilot study (Carroll et al., 2012; Harris et al., 2013; Kim et al., 2016). One single site study included both a retrospective chart review and a patient survey (Hill et al., 2017). There were two single site retrospective chart reviews (Harris et al., 2014; Rozet et al., 2014) and two studies based on patient surveys (Bates et al., 2011; Rodgers et al., 2012). Lastly, there was one secondary analysis of data (Goesling et al., 2016). The matrix of studies is displayed in Table 2.

Three of the five database analyses used the Truven Health MarketScan Commercial Claims and Encounters data set. This is comprised of 100 U.S. health plans (Johnson et al., 2016; Sun et al., 2016; Waljee et al., 2016). In one study, the records of 77,573 opioid naïve patients (defined as no opioid prescription filled in the eleven months prior to surgery) who underwent common elective hand surgeries (carpal tunnel release, carpometacarpal arthroplasty/arthrodesis, cubital tunnel release, trigger finger release) and common hand surgeries for trauma (closed distal radius fracture fixation, flexor tendon repair, metacarpal fracture fixation or phalangeal fracture fixation) were examined to determine the risk of prolonged (greater than 90 days) postoperative opioid use (Johnson et al., 2016). Another analysis examined the records of

296,452 patients who underwent the following common hand surgeries to evaluate opioid use due to procedure type and patient factors including preoperative opioid use: carpal tunnel release, trigger finger release, cubital tunnel release or thumb carpometacarpal arthroplasty (Waljee et al., 2016). A third analysis examined 641,941 opioid naïve surgical patients (defined as no opioid prescription filled in the twelve months prior to surgery) undergoing eleven common surgeries and 18,011,137 opioid naïve non-surgical patients for comparison to see which patients were at highest risk for continued opioid use at one year (Sun et al., 2016).

The data for two of five database analyses were obtained from a managed care company affiliated with OptumInsight© through the Clinformatics Data Mart© Database. One examined 155,297 opioid naïve patients (defined as no opioid prescription filled in the six months prior to surgery) undergoing carpal tunnel release, laparoscopic cholecystectomy, inguinal hernia repair, and knee arthroscopy in 2004, 2008, and 2012 to analyze the change in prescribing patterns over time (Wunsch et al., 2016). The other examined 36,177 patients with private insurance undergoing major and minor surgical procedures for comparison (Brummett et al., 2017).

There were three prospective observational studies included (Carroll et al., 2012; Harris et al., 2014; Harris et al., 2013; Kim et al., 2016). One study enrolled 109 patients having total hip replacement, total knee replacement, thoracotomy, mastectomy, or lumpectomy procedures in a pilot study (Carroll et al., 2012). Preoperatively, psychological tests were administered and a history of substance abuse performed to measure these determinants on prolonged postoperative opioid use. Another study examined 212 adults undergoing dermatological surgery to determine characteristics associated with opioid prescribing practices and postoperative opioid consumption in this surgical population (Harris et al., 2013). The researchers then conducted a retrospective chart review of 233 dermatological surgical patients along with a survey emailed to

members of the American Society for Dermatological Surgery to increase understanding of prescribing practices in this population (Harris et al., 2014). The third prospective study examined 1,419 patients age 18 to 93 after outpatient procedures involving the hand, wrist, forearm, or shoulder (Kim et al., 2016). Data was collected prospectively and a telephone interview determined the number of opioid pills used after surgery.

Three studies used patient surveys to obtain data (Bates et al., 2011; Hill et al., 2017; Rodgers et al., 2012). In one study, a sample of urology surgery patients was used to examine prescribing practices, opioid consumption, and disposal of surplus medication (Bates et al., 2011). Another examined 250 patients undergoing elective outpatient upper extremity surgeries using a post-surgical phone interview to assess pain control and consumption of opioids postoperatively (Rodgers et al., 2012). In the third study, researchers contacted opioid naïve patients (defined by the researchers as no opioid use 30 days prior to surgery) undergoing five common general surgery procedures (partial mastectomy, partial mastectomy with sentinel lymph node biopsy, laparoscopic cholecystectomy, laparoscopic inguinal hernia repair, and open inguinal hernia repair) to determine how many opioid pills were taken postoperatively (Hill et al., 2017). Lastly, a retrospective chart review of 145 veterans undergoing knee arthroscopies to identify risk factors for chronic postoperative pain, especially post-traumatic stress disorder (PTSD) was completed (Rozet et al., 2014). This study reviewed medical and pharmacy records of 18 to 50-year-old patients at a single site.

2.4.2 Synthesis of Studies

The purpose of this review was to synthesize current scientific literature and evidence on how postoperative opioid exposure is related to prolonged use and to identify potential predictive

characteristics of prolonged postoperative opioid use. Careful analysis and synthesis of these articles resulted in the emergence of two major themes.

2.4.2.a. Surgery places patients at risk for prolonged opioid use.

Five studies suggest that surgery places opioid naïve patients at risk for prolonged postoperative opioid use (Brummett et al., 2017; Carroll et al., 2012; Goesling et al., 2016; Johnson et al., 2016; Sun et al., 2016). Prolonged use was defined as (1) filling an opioid prescription 90 to 180 days after surgery (Brummett et al., 2017; Johnson et al., 2016), (2) filling either more than 120 days' supply of opioids or 10 or more refills 90 to 365 days after surgery (Sun et al., 2016), or (3) filling a prescription more than 180 days after surgery (Goesling et al., 2016). In a study of patients undergoing major surgeries such as mastectomies, thoracotomies, and total joint replacements, median time to opioid cessation post-surgery was calculated: 6% of opioid naïve patients continued to use opioids more than 150 days after these procedures (Carroll et al., 2012). Compared with the 0.136% baseline rate of opioid use measured in nonsurgical reference groups, rates of opioid use more than 90 days after surgery were significantly greater for all surgical procedures other than cesarean sections (Sun et al., 2016). In this study, patients undergoing total knee replacements (TKA) had the highest rates of chronic opioid use (1.41%) followed by two common surgeries: simple mastectomies and total hip replacements (THA) (0.6%). Similarly, 6.5% of patients undergoing major surgeries such as colectomies, bariatric surgeries, and hysterectomies and 5.9% of patients undergoing minor surgical procedures such as thyroidectomies, parathyroidectomies, and laparoscopic cholecystectomies were still taking opioids more than 90 days after their surgery (Brummett et al., 2017). There was no significant difference between the two surgical groups in regard to prolonged postoperative opioid use. There was a significant difference, however, when compared to the 0.4% rate of new persistent

opioid use in the nonsurgical control group (Brummett et al., 2017). Patients undergoing TKA and THA were surveyed at one, three, and six months post-surgery. At six months, 8.2% of TKA and 4.3% of THA patients were still using opioids (Goesling et al., 2016). Lastly, in patients undergoing common elective hand surgeries, 13% of opioid naïve patients continue to fill prescriptions 90 days after their surgical procedure (Johnson et al., 2016).

Among these studies, evidence varies on how the type of surgery influences prolonged postoperative opioid use. In a study of 11 procedures, research suggests total joint replacements, mastectomies, and open and laparoscopic cholecystectomies and hernia repairs are more likely to lead to prolonged postoperative opioid use than open and laparoscopic appendectomies, functional endoscopic sinus surgeries, cataract surgeries, transurethral prostate resections, and simple mastectomies (Sun et al., 2016). However, other findings suggest no significant difference in prolonged opioid use between patients undergoing major and minor surgeries (Brummett et al., 2017). In addition, no association was found between change in joint pain over time and prolonged opioid use in patients undergoing joint replacement surgeries (Goesling et al., 2016). The percentage of opioid naïve patients continuing to use opioids more than 90 days across diverse procedures after their procedure indicates that this prolonged use should be viewed as a surgical complication (Brummett et al., 2017).

Lastly, many studies suggest that postoperative opioid prescribing practices may contribute to prolonged use. Multiple studies indicate that opioids are overprescribed after surgery, leading researchers to conclude that this could potentially contribute to misuse and diversion (Bates et al., 2011; Harris et al., 2014; Harris et al., 2013; Rodgers et al., 2012). Two studies show wide variation in prescribing practices, even for the same surgery; whether this is

due to varying patient needs or other provider factors is not clear (Harris et al., 2013; Hill et al., 2017).

2.4.2.b Certain patient characteristics may be predictive of prolonged postoperative opioid use.

Patient characteristics may be predictive of prolonged postoperative opioid use, but these are inconsistently reported across studies. Demographics such as gender, age, race, ethnicity, and socioeconomic status were particularly inconsistent as predictors. For instance, in one analysis, patient demographics predicting prolonged postoperative opioid use were significant for those less than 65 years of age, female gender, household income under \$60,000 per year, and private insurance (Johnson et al., 2016). Conversely, in another database analysis, men and those over 50 years of age had higher rates of prolonged use (Sun et al., 2016). Yet another study found no difference in opioid use six months after surgery by age, gender, ethnicity, or type of surgery (Goesling et al., 2016). Rates also varied by geographic location. Statistically significant higher rates of prolonged postoperative opioid use were found in the U.S. Census Bureau West South Central (7.02%) and East South Central (7.85%) regions compared to the Middle Atlantic Region (3.78%) (Brummett et al., 2017).

Researchers consistently found that patients who are currently using opioids, benzodiazepines, or addicted to alcohol were at increased risk of prolonged postoperative use (Brummett et al., 2017; Goesling et al., 2016; Johnson et al., 2016; Rozet et al., 2014; Sun et al., 2016; Waljee et al., 2016). In fact, mental health disorders such as anxiety and depression, tobacco and alcohol abuse, multiple co-morbidities, and pre-existing pain conditions were independent predictors of prolonged postoperative opioid use across all surgical procedures (Brummett et al., 2017; Johnson et al., 2016). Preoperative opioid prescriptions, depressive

symptoms, and self-perceived risk of addiction were better predictors of prolonged use than the reported postoperative intensity and duration of pain (Carroll et al., 2012). One study found that a preoperative opioid prescription greater than 60 morphine milligram equivalents per day was associated with prolonged use after surgery (Goesling et al., 2016). Additionally, patients already on opioids preoperatively were often overprescribed opioids postoperatively (Waljee et al., 2016). Lastly, PTSD and preoperative opioid use were factors leading to chronic postoperative opioid use in young veterans having minor elective surgeries (Rozet et al., 2014).

2.5 Discussion

Studies included in this integrative review indicate that 4% to 13% of opioid naïve patients are taking opioid pain relievers three months or more after their procedure, suggesting that prolonged postoperative opioid use occurs frequently after elective surgery in this population (Brummett et al., 2017; Carroll et al., 2012; Goesling et al., 2016; Johnson et al., 2016; Sun et al., 2016). It is unclear which surgeries, if any, carry the highest risks for patients. Moreover, research findings suggest that prolonged opioid use after surgery is related to factors other than the type and duration of surgical pain (Carroll et al. 2012).

Current evidence suggests that prolonged postoperative opioid use is related to exposure through prescriptions and to patient characteristics. Across multiple studies, patients who were already using opioids, benzodiazepines, antidepressants, anxiolytics, tobacco, or abusing alcohol were at higher risk for prolonged postoperative opioid use (Brummett et al., 2017; Goesling et al., 2016; Johnson et al., 2016; Rozet et al., 2014; Sun et al., 2016; Waljee et al., 2016). Mental health disorders, depressive symptoms, a self-perceived risk of addiction, and multiple co-morbidities also independently predicted prolonged use (Brummett et al., 2017; Carroll et al., 2012; Johnson et al., 2016). The contribution of patient demographics is unclear. Further

evidence is needed to ascertain the contribution of patient characteristics to prolonged postoperative opioid use.

Large prospective studies are needed to determine which surgeries place patients at an increased risk for prolonged opioid use, how prescribing practices affect prolonged use, and which patient factors contribute to prolonged use. Notably, there are inconsistencies among researchers as to the definitions of “prolonged opioid use” and “opioid naïve.” Standard definitions would provide consistency and allow comparison of results across studies. Ultimately these studies will lead to evidenced based prescribing practice guidelines and improved perioperative pain management.

2.6 Implications for Nursing

Based on current evidence, two million patients undergoing elective surgeries each year will use opioid analgesics more than 90 days after their procedure (Brummett et al., 2017). It is imperative that nurses and other clinicians appropriately manage surgical patients preoperatively, intraoperatively, at discharge, and throughout the recovery period in order to prevent prolonged use of these medications. Nurses need to screen opioid naïve patients preoperatively using the factors we have uncovered placing them at higher risk for prolonged postoperative opioids use: patients currently taking, benzodiazepines, antidepressants, anxiolytics, tobacco, or abusing alcohol, as well as those patients with mental health disorders, depressive symptoms, a self-perceived risk of addiction, and multiple co-morbidities. Nurses also need to educate patients on postoperative pain control expectations, expected time to recovery, and follow the patients closely after discharge. The wide variations in prescriber practices, the large percentage of unused opioids, and the increase in potency of opioids prescribed highlights the need for postoperative prescribing guidelines (Bates et al., 2011; Harris et al., 2014; Hill et al., 2017; Kim

et al., 2016; Rodgers et al., 2012; Wunsch et al., 2016). Nurses can counsel patients on appropriate use and disposal of opioids, non-narcotic pain relievers, and non-traditional pain control techniques. Additionally, acute pain should be managed through multi-modal pain relief techniques including perioperative anesthetics that are opioid sparing.

Both qualitative and quantitative studies are needed for a better understanding of factors related to prolonged postoperative opioid use, the type of surgeries that place patients at most risk, and the effect postoperative exposure to opioids has on prolonged use. This will facilitate development of patient focused interventions including screening tools to identify high risk patients, pain management protocols and prescribing guidelines, and educational strategies for patients, clinicians, and stakeholders. Nurses are poised to develop and refine evidenced based tools that will inform best practices for acute postoperative pain management.

2.7 Limitations

There are several limitations to this integrative review. First, there is a relatively small body of research related to this topic and some of the studies were by the same author group, indicating a need to replicate the research in other samples. There are also a variety of methodological limitations to the studies analyzed. There are no randomized controlled trials and there were no qualitative analyses. Some studies relied on self-reports from patients and may therefore be biased by inaccurate recall or an unwillingness to be forthcoming about the medications used, especially if they are supplementing with illicit drugs. Several studies relied on insurance database information that may be incomplete or inaccurate. Additionally, the database reviews may not be reflective of the general population as those with Medicare and Medicaid, and the uninsured were not represented. Some of the databases were geographically limited.

In addition to methodological limitations, opioid naïve was defined differently by different authors. Furthermore, alternative methods for pain control, such as multi-modal analgesia techniques that augment the efficaciousness of opioids, were not discussed. The possibility of illicit drug use in patients was not investigated in these studies and should be included if possible in future research.

2.8 Conclusions

This integrative review includes a synthesis of the association between postoperative exposure to opioids and specific patient characteristics associated with prolonged postoperative opioid use. Findings from this review identify gaps in our current knowledge and support the need for future research. This review indicates that prolonged postoperative opioid use is common after surgical procedures and is related to postoperative opioid exposure and patient factors rather than the duration and intensity of post-surgical pain. Characteristics putting patients at higher risk were mental health disorders, multiple co-morbid conditions, and the preoperative use of opioids, benzodiazepines, antidepressants, anxiolytics, as well as tobacco or alcohol abuse. The contribution of patient demographics is unclear as is the type of surgery, whether major or minor. Further research describing the effects of postoperative opioid exposure on prolonged opioid use, postoperative opioid prescribing practices, and the identification of potential predictive characteristics of prolonged postoperative opioid use. It is crucial for advanced practice clinicians, surgeons, nurses, and other healthcare professionals to better understand which patient populations are at an increased risk and preemptively prevent misuse from occurring.

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PRISMA Flow Diagram for the Article Selection Process

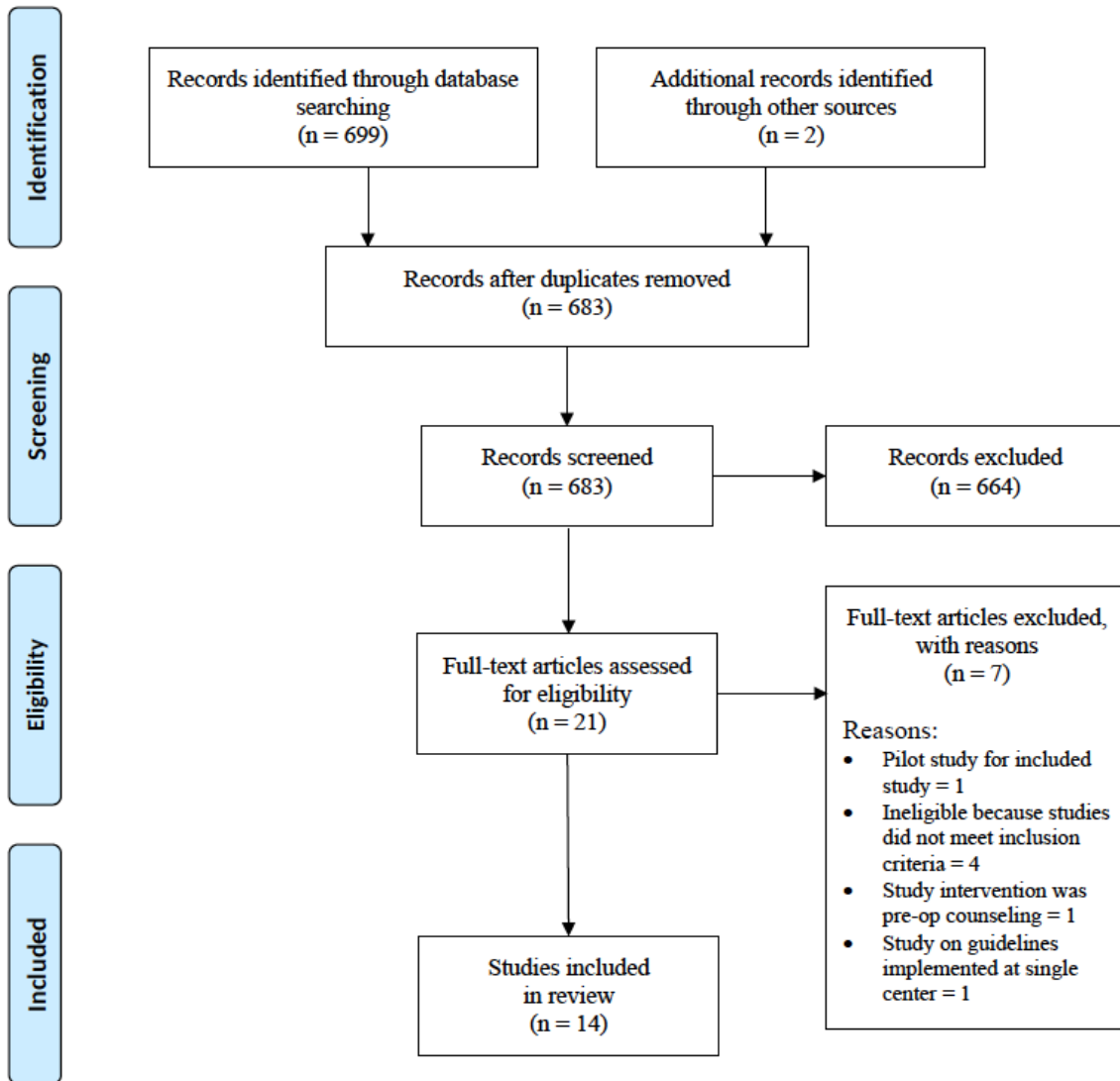


Table 1
Electronic Database Search Strategies

Electronic Database	Search Strategy
CINAHL	(MH "Postoperative Pain" OR MH "Patient-Controlled Analgesia" OR TI post* N4 pain* OR AB post* N4 pain* OR TI patient-controlled N4 analgesi* OR AB patient-controlled N4 analgesi*) AND (MH "Prescribing Patterns" OR MH "Inappropriate Prescribing" OR MH "Prescriptions, Drug" OR MH "Self Administration+" OR MH "Self Medication" OR TI prescrib* N4 practice OR AB prescrib* N4 practice) Limits: 2011/01/01 to 2017/06/21; United States
Cochrane Database of Systematic Reviews	((opioid or opiate or opioid-naive) OR ("substance use disorder" or "drug abuse")) AND (postsurgical or postoperative) AND ("prescribing practice" or prescribe or prescription)
Cochrane Central Register of Controlled Trials	((opioid or opiate or opioid-naive) OR ("substance use disorder" or "drug abuse")) AND (postsurgical or postoperative) AND ("prescribing practice" or prescribe or prescription)
EMBASE	('Opiate'/mj OR 'prescription'/mj OR 'prescription opioids':ab,ti OR 'inappropriate prescribing'/mj OR 'potentially inappropriate medication'/mj OR 'drug abuse'/mj OR 'opioid-naïve patients':ab,ti) AND ('surgical patient'/mj OR 'postoperative pain'/mj OR 'postoperative complication'/mj OR 'postoperative care'/mj OR 'prolonged opioid use':ab,ti) AND ([young adult]/lim OR [adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim) AND [english]/lim
PubMed	(("Practice Patterns, Physicians"[Mesh] OR prescribing pattern*[tiab] OR "Drug Administration Schedule"[Mesh] OR "Analgesics, Opioid"[Mesh] OR "opioid use"[tiab] OR "opioid-naive patients"[tiab]) AND ("surgery procedures"[tiab] OR surgery[tiab]) AND ("Pain, Postoperative"[Mesh] OR "postoperative period"[tiab] OR "postoperative pain"[tiab])) AND "united states"
ClinicalTrials.gov	postoperative opioid prescription Limits: Adults; United States
Annual Meeting of the American Pain Society	postoperative opioid

Table 2
Summary of Included Articles

Authors (year)	Objective	Method	Sample	Results
Bates et al. (2011)	To determine if urologists are overprescribing opioids after surgery	Patient surveys	275 patients undergoing urology surgery	Over 40% of prescribed opioids were not used and 67% of patients had leftover pain medication. Opioids are overprescribed after surgery.
Brummet et al. (2017)	To determine incidence of prolonged postoperative opioid use in opioid naïve patients after major and minor surgeries	Retrospective database analysis	36,177 patients from a managed care insurance affiliated with OptumInsight from Clinformatics Data Mart who underwent 13 common surgical procedures	5.9% to 6.5% of opioid naïve patients continued to use opioids > 90 days post-surgery whether the procedure was major or minor, suggesting factors other than pain contribute to long term use.
Carroll et al. (2012)	To determine if psychological distress and substance abuse are predictors of prolonged postoperative opioid use (pilot study)	Prospective, longitudinal observational study	109 patients undergoing mastectomy, lumpectomy, thoracotomy, total knee replacement, or total hip replacement	6% of patients continued on opioids > 150 days post-surgery. Predictors were preoperative opioid use, depression, and self-reported perceived risk of addiction.
Goesling et al. (2016)	To determine patient risk factors for chronic post-op opioid use, the effect of pain scores preoperatively and at 6 months after TKA and THA on opioid use, and to explore the natural course of opioid use in these surgical patients	Secondary analysis of data from a prospective outcome study that used telephone and mail surveys	574 patients who had TKA or THA	8.2 % of opioid naïve TKA and 4.3% of opioid naïve THA patients continued on opioids 180 days-post-surgery. Pre-op opioid dose > 60MME was independently associated with chronic opioid use, and there was no association found between change in joint pain over time and chronic opioid use.
Harris et al. (2013)	To understand (1) postoperative opioid prescribing by dermatologists, (2) the amount of postoperative pain	Prospective observational study utilizing telephone follow up	212 patients undergoing single skin excision surgical procedures	34% of patients received a postoperative opioid prescription. 86% of patients who filled a prescription had leftover pills and

medications actually used, and
(3) patient and surgical factors
associated with amount used

53% planned to store them for
future use. Female, younger age,
and surgery type were predictors of
increased opioid use
postoperatively, but the overall fit of
the model was limited. Surgery with
graft closures was the only surgical
characteristic indicative of increased
pain. Opioids are overprescribed
after surgery.

Harris et al.
(2014)

To understand postoperative
opioid prescribing practices

Retrospective chart
review and email
survey to
dermatologists

233 patients who had
undergone single skin
excision surgical
procedures and an email
survey of 556 members
of the American Society
for Dermatological
Surgery

There is wide variation in
prescribing practices among
dermatologists nationally and within
the same institution. Opioids are
overprescribed after surgery.

Hill et al. (2017)

To (1) examine opioid
prescribing practices after
general surgery and (2)
determine the number of pills
that should be prescribed

EMR chart review
& patient survey

642 patients undergoing
partial mastectomy,
partial mastectomy with
sentinel lymph node
biopsy, laparoscopic
cholecystectomy,
laparoscopic inguinal
hernia repair, and open
inguinal hernia repair

72% of prescribed opioids were not
used and there was a wide variety of
prescribing practices among
prescribers at same facility. Opioids
are overprescribed after surgery.

Johnson et al. (2016)

To evaluate opioid use in
opioid naïve patients after
common hand surgeries

Retrospective
insurance database
analysis

59,735 patients from the
Thomson Reuters
Truven MarketScan
Commercial Claims
Database

13% of opioid naïve patients
continued to fill opioid prescriptions
greater than 90 days post-surgery.

Kim et al. (2016)

To evaluate opioid usage after
outpatient upper extremity
surgery

Prospective
observational study

1,416 patients who had
outpatient upper
extremity surgery

66% of prescribed opioids were not
used; opioids are overprescribed
after surgery which could lead to
misuse and diversion. Procedure

				type and location, patient age, and type of insurance determined increased postoperative opioid consumption.
Rodgers et al. (2012)	To determine the amount of unused opioids after outpatient upper extremity surgery	Patient survey	250 outpatients who had upper extremity surgery	77% of patients took less than half of their prescribed opioids. The number of opioids used differed by insurance type.
Rozet et al. (2014)	To determine patient risk factors for chronic postoperative pain	Single center retrospective study	145 young veterans (age 18-50) having minor elective surgeries	Patients with PTSD are at higher risk for prolonged post-op opioid use. Preoperative opioid use is the primary risk factor for chronic pain post-surgery.
Sun et al. (2016)	To compare opioid naïve patients undergoing eleven types of surgery with nonsurgical patients to examine the relative risk of prolonged opioid use	Retrospective insurance database analysis	641,941 opioid naïve surgical patients and 18,011,137 opioid naïve non-surgical patients from the Thomson Reuters Truven MarketScan Commercial Claims Database	Increased rate of chronic opioid use in patients undergoing TKA, THA, open and laparoscopic cholecystectomy, open and laparoscopic appendectomy, simple mastectomy, FESS, and cesarean delivery. Patient factors contributing to prolonged opioid use were preoperative use of benzodiazepines, antidepressants, and history of drug abuse.
Waljee et al. (2016)	To evaluate opioid use after four common hand surgery procedures	Retrospective insurance database analysis	296,452 patients from the Thomson Reuters Truven MarketScan Commercial Claims Database	4.5% of patients received an opioid refill after minor hand surgery. Factors associated with refills were age, type of insurance, type of surgery, and preoperative opioid use.
Wunsch et al. (2016)	To examine trends in prescribing practices over time for opioid naïve patients undergoing four low risk surgeries. Time points	Retrospective insurance database analysis	155,297 opioid naïve patients from the Clinformatics Data Mart Database undergoing	The proportions of patients filling prescriptions for any opioid increased over time and the mean morphine equivalents prescribed increased over time.

examined were 2004, 2008,
2012

low risk surgical
procedures

Note: TKA = total knee arthroplasty; THA = total hip arthroplasty; MME = morphine milligram equivalent dose; EMR = electronic medical record; PTSD = post-traumatic stress disorder; FESS = functional endoscopic sinus surgery

Table 3
Quality Assessment of Included Articles

	Research questions/objectives/hypotheses clear and appropriate	Clear overview of intervention with use of appropriate outcome measures	Sample size given	Attrition rate/missing data discussed	Data analysis adequately described and rigorous	Outcomes clearly described	Ethical issues are suitably addressed	Total Score
Bates et al. (2011)	1	1	1	1	1	1	1	7
Brummet et al. (2017)	1	1	1	1	1	1	1	7
Carroll et al. (2012)	1	1	1	0	1	1	0	5
Goesling et al. (2016)	1	1	1	1	1	1	1	7
Harris et al. (2013)	1	1	1	0	1	1	1	6
Harris et al. (2014)	1	1	1	1	1	1	1	7
Hill et al. (2017)	1	1	1	1	1	1	1	7
Johnson et al. (2016)	1	1	1	1	1	1	1	7
Kim et al. (2016)	1	1	1	0	1	1	1	6
Rodgers et al. (2012)	1	1	1	1	1	1	0	6
Rozet et al. (2014)	1	1	1	0	1	1	1	6
Sun et al. (2016)	1	1	1	0	1	1	N/A	5
Waljee et al. (2015)	1	1	1	1	1	1	0	6
Wunsch et al. (2016)	1	1	1	0	1	1	1	6

Note. N/A, not applicable. Criteria adapted from Clark, A. K., Wilder, C. M., & Winstanley, E. L. (2014). A systematic review of community opioid overdose prevention and naloxone distribution programs. *J Addict Med*, 8(3), 153-163 and Jinks, A., Cotton, A., & Rylance, R. (2011). Obesity interventions for people with a learning disability: an integrative literature review. *J Adv Nurs*, 67(3), 460-471.

3.0 RESEARCH METHODOLOGY AND FINDINGS

Manuscript #2

THE ASSOCIATION OF PRESCRIPTION OPIOID EXPOSURE AND PATIENT FACTORS WITH PROLONGED POSTOPERATIVE OPIOID USE IN OPIOID NAÏVE PATIENTS

This chapter has been removed as the article is under submission with a publisher which does not allow pre-print versions to be posted.