PREVALENCE, PATTERNS, AND OUTCOMES OF OPIOID USE BY INJURED WORKERS IN TENNESSEE

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE UNIVERSITY OF HAWAIʻI AT MĀNOA IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

EPIDEMIOLOGY

May 2018

by

Zoë Durand

Dissertation Committee:

Eric Hurwitz, Chairperson
Alan Katz
Claudio Nigg
Yan Yan Wu
Kristine Qureshi

Keywords: injured worker, opioid, benzodiazepine, long-term use, overdose

Abstract

In this dissertation, three separate but related studies describe opioid use by injured workers in TN, identify patterns of opioid use by injured workers that are associated with nonfatal overdose, and develop a predictive model for the development of long-term opioid use in injured workers who were opioid-free at the time of injury. These studies link statewide databases to connect Workers' Compensation records of injured workers to their prescription history in TN's prescription drug monitoring program, hospital and emergency room records in TN's Hospital Discharge Data System, and death certificates in TN's Vital Statistics death certificates dataset. In a cross-sectional study, the prevalence of opioid use in injured workers is calculated and Poisson regression is used to assess prevalence ratios of the association between demographic and injury variables with opioid use. In a case-control study, the incidence of nonfatal overdose is calculated and conditional logistic regression is used to examine demographic, injury, and opioid use patterns that are associated with overdose. In a cohort study, unconditional logistic regression is used to build a predictive model of demographic, injury, and opioid use patterns that are associated with the development of long-term opioid use in previously opioid-free injured workers. These studies found that opioid use is widespread in injured workers after injury, but occurs largely within limits set by prescribing guidelines and tends to be discontinued within a month or two. Overdose and the development of long-term opioid use are rare, but affect vulnerable subsets of the population which may benefit from a different prevention and treatment approach than the overall population.

These studies were supported by funding from the Centers for Disease Control and Prevention's Prescription Drug Overdose: Prevention for States program, grant number 5 NU17CE002731-02-00

Acknowledgements

Over the past five years, a great number of people have enriched my education experience. Eric Hurwitz in particular has contributed a great deal as my committee chair. His guidance has made this a thoughtful and rewarding journey.

I would like to thank my dissertation committee of Kristine Qureshi, Alan Katz, Claudio Nigg, and Yan Yan Wu for their support over the past few years as I moved from an idea to a completed series of studies.

During planning and writing, Sarah Nechuta and Melissa McPheeters advised on epidemiologic methods. During analysis, Shanthi Krishnaswami provided help in checking results, Molly Golladay advised on data cleaning and linkage, and Sutapa Mukhopadhyay geocoded addresses.

My spouse, Ryan Brod, supported me through graduate school and has been a steadfast partner throughout.

My parents, Mark Durand and Beverly Green, have been my unwavering supporters and advocates from the very beginning.

My sister, Alex, has given me years of fortifying encouragement, from offering to proofread my papers late at night when she had homework of her own to do to helping me find the job that this dissertation grew out of.

Table of Contents

List of Tables

List of Figures

Abbreviations

Centers for Disease Control and Prevention (CDC)

Confidence interval (CI)

Controlled Substances Monitoring Database (CSMD)

Morphine milligram equivalents (MMEs)

Medication-assisted treatment (MAT)

Prevalence ratio (PR)

Odds ratio (OR)

Standard deviation (SD)

Tennessee (TN)

Workers' Compensation (WC)

Polydamna's gift

"Presently she cast a drug into the wine whereof they drank, a drug to lull all pain and anger, and bring forgetfulness of every sorrow. Whoso should drink a draught thereof, when it is mingled in the bowl, on that day he would let no tear fall down his cheeks, not though his mother and his father died, not though men slew his brother or dear son with the sword before his face, and his own eyes beheld it."

- Homer. *The Odyssey, Book IV*.

"Seductive and dangerous, full of promise and destruction, opioids are both revered and feared by Western culture."

- Mehendale, A. W., Goldman, M. P., & Mehendale, R. P. (2013). Opioid overuse pain syndrome (OOPS): the story of opioids, prometheus unbound. *J Opioid Manag, 9*(6), 421-438. doi:10.5055/jom.2013.0185


Papaver
Somniferum
ZD

Chapter 1 Introduction

Background

When scored with a razor, the unripe seed pods of the poppy *Papaver Somniferum*, which the Sumerians called Hul Gil or "flower of joy" seep a milky latex sap that turns fragrant and tarry when dried (Public Broadcasting Service, 1998). This is opium, which exerts such a powerful control over those who taste it that it has been cultivated for over 4000 years, associated with gods in the ancient world, and caused wars between modern civilizations (Katz, 2007; Pletcher, 2015). Today, drugs derived from or based on opium are at the center of the worst iatrogenic problem of our time: the opioid epidemic.

Context of the opioid epidemic.

Opioids were the leading cause of injury in the United States (U.S.) at the time this dissertation was written (U.S. Department of Health and Human Services, 2017), but the roots of the epidemic lie several decades earlier. In the 1980s, a campaign led by the American Society of Anesthesiologists touting the alleged undertreatment of pain began a national discourse on the right to pain relief. Where opioids had previously been reserved for end-of-life care, extreme trauma, and surgery, this campaign advocated for pain assessment at every patient visit and designated pain as the "fifth vital sign" (Morone & Weiner, 2013). Pain treatment as a normal part of patient-provider interactions became ratified in guidelines by the American Pain Society in 1995 and the Joint Commission on Accreditation of Health Care in 2000, and patient self-reported pain was incorporated into hospital quality control measures (Morone & Weiner, 2013; National Pharmaceutical Council). This lobbying by professional organizations was accompanied by a massive and misleading marketing campaign by pharmaceutical companies, led by Purdue Pharma as the owner of Oxycontin, with the result that opioid prescribing, and use, became normalized for many diverse types of pain (Alam & Juurlink, 2016). The abrupt flourishing of opioids occurred despite a lack of robust evidence signifying their safety, and subsequent research quantifying their harms failed to prevent the epidemic.

National trends.

Trends in the opioid epidemic are tracked with two main measures: opioid prescribing rates and opioid overdose rates. Nationally, opioid prescribing peaked in 2012 at 81.3

prescriptions per 100 persons and declined to a 10-year low in 2016 at 66.5 prescriptions per 100 persons (Prevention). In 2016, the average daily dose per opioid prescription was 47.1 morphine milligram equivalents (MMEs) and the prescribing rate of high dosage opioids (≥90 daily MMEs) was 6.1 per 100 persons (Centers for Disease Control and Prevention, 2017). While prescribing rates are decreasing, however, rates of overdose continue to increase exponentially (Centers for Disease Control and Prevention, Opioid Data Analysis). In 2015, the age-adjusted opioid-involved mortality rate was 10.4 deaths per 100,000 persons, a 15.6% increase from the rate in 2014 of 9.0 deaths per 100,000 persons (Rudd, Seth, David, & Scholl, 2016). This acceleration appears to be driven by increases in overdoses on heroin and synthetic opioids like fentanyl that have been linked to illicit markets (National Institute on Drug Abuse, 2017). These measures do not fully capture the scale of the epidemic, and survey data indicates that tens of millions of people use illicit drugs or misuse prescription drugs every year in the U.S.. In 2015, an estimated 4.7% of adults over the age of 12 reported having used prescription pain relievers nonmedically in the past year (Substance Abuse and Mental Health Services Administration, 2016).

Figure 1.1: Overdose deaths involving opioids by type of opioid, United States 2000-2016

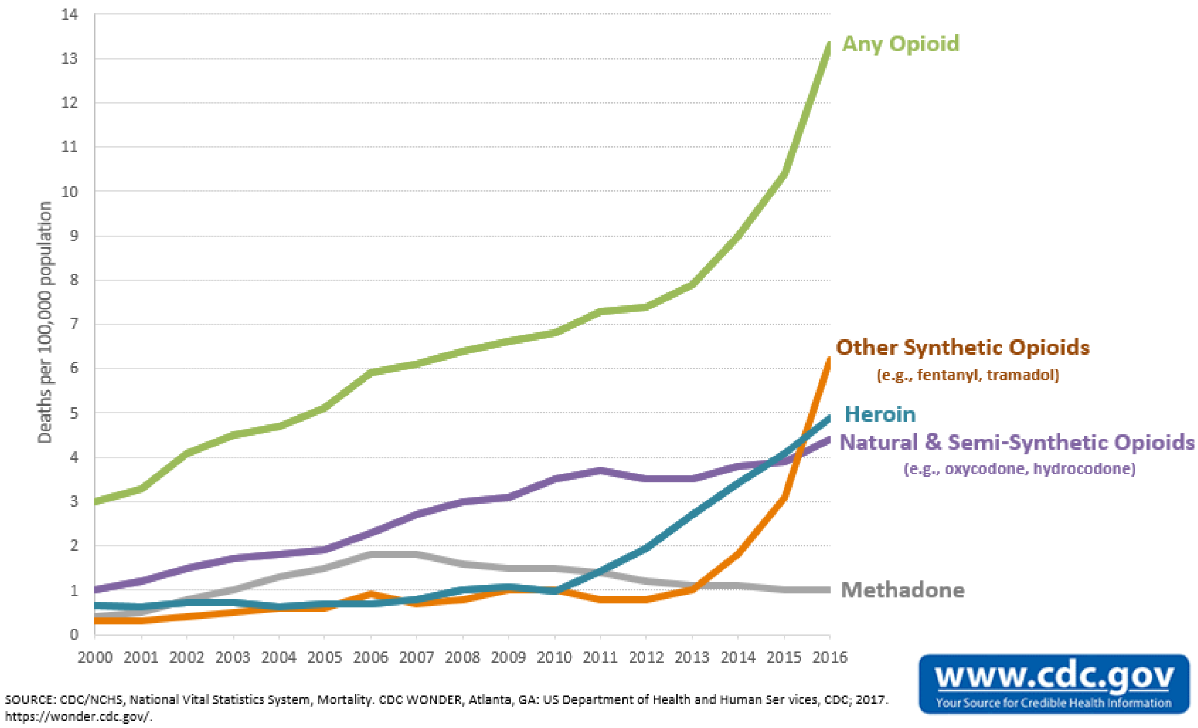


Figure source: Centers for Disease Control and Prevention, Prescription drug overdose: Understanding the epidemic: Data overview, 2017

Tennessee trends.

Tennessee (TN) is among the hardest-hit states in the U.S. by the epidemic, with the third-highest prescribing rate of opioids (107.5 opioid prescriptions per 100 persons in 2016). Compared to other U.S. states, TN has the second highest rate of prescribing long-acting opioids (11.0 prescriptions per 100 persons) and the fifth highest rate of prescribing high-dosage opioids (≥90 daily morphine milligram equivalents, rate=9.8 prescriptions per 100 persons). Like the overall U.S., TN's prescribing rate has decreased over the past few years, from 127.1 prescriptions per 100 persons in 2014 to 107.5 in 2016 (Centers for Disease Control and Prevention, U.S. State Prescribing Rates). TN's opioid overdose rate shows the same accelerating trend in overdoses as the overall U.S., and TN is one of twenty five states driving national increases. In TN, the opioid overdose age-adjusted mortality rate increased by 10.4% from 22.2 deaths per 100,000 persons in 2015 to 24.5 in 2016 (Centers for Disease Control and Prevention, 2017). 2016 was the worst year on record for opioid overdoses in TN, with 1,186 opioid overdose deaths, 13,034 overdose outpatient admissions (rate=197.5 per 100,000 persons), and 7,072 inpatient admissions (rate=107.4 per 100,000 persons) (Tennessee Department of Health, Data Dashboard). In 2012-2014, an estimated 4.18% of Tennessee adults over the age of 12 reported using prescription pain relievers nonmedically in the past year (Substance Abuse and Mental Health Services Administration, *State and substate estimates of nonmedical use of prescription pain relievers*, 2017).

Figure 1.2: All drug and opioid overdose deaths, Tennessee 2012-2016

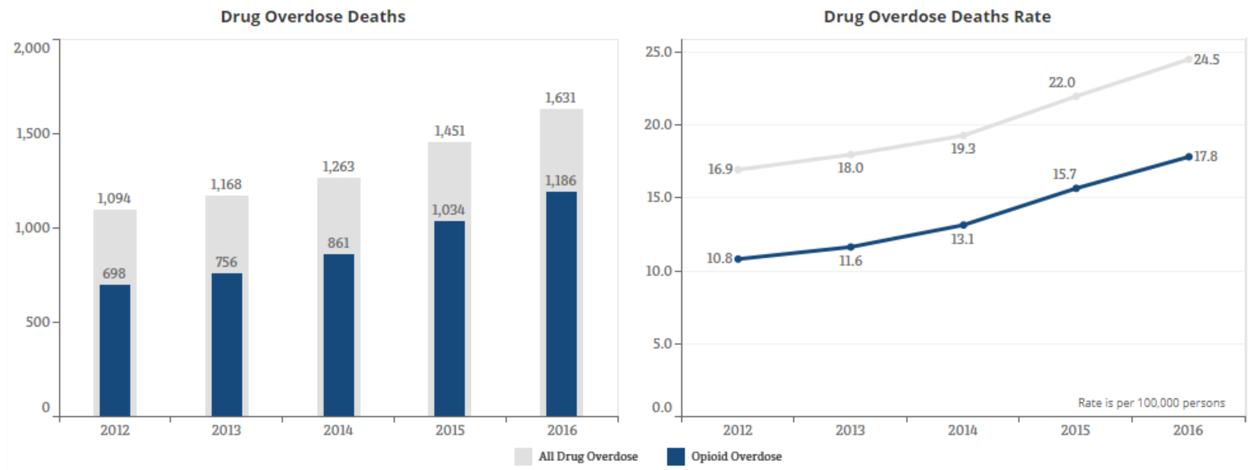


Figure source: Tennessee Department of Health, Data Dashboard

Opioids and injured workers.

What is known.

Injured workers are a population with special needs for the treatment of pain, where pain management and rehabilitation are sometimes competing aims (Lai, Szeto, & Chan, 2017). As Newton-John and McDonald describe, “The clinical management of chronic pain is a biopsychosocial challenge in itself; however, when the pain occurs in the context of workers compensation, there is even greater clinical complexity” (Newton-John & McDonald, 2012). The Workers’ Compensation (WC) and Social Security Disability systems add an additional layer of complexity by providing an incentive to emphasize pain and downplay improvement in some cases (Harris, Mulford, Solomon, van Gelder, & Young, 2005).

Research on opioid use by injured workers typically relies on WC records, which only measure opioids that are paid for by WC and dispensed to approved claimants. These data sources (every state has its own) show that opioid use is widespread in claimants. Prevalences of receiving an opioid vary across the nation, ranging from 19.2% of claimants receiving an opioid during the time that their claim was open in Ohio to 46.4% receiving an opioid within one year of injury in Louisiana (Dembe, Wickizer, Sieck, Partridge, & Balchick, 2012; Lavin, Tao, Yuspeh, & Bernacki, 2014). Opioids given to WC claimants tend to be prescribed early in therapy and in high doses (Bernacki, Yuspeh, Lavin, & Tao, 2012; Franklin, Stover, Turner, Fulton-Kehoe, & Wickizer, 2008). In Washington State in 2002-2003, 52% of claimants who received opioids got that opioid at their first medical visit (Stover, Turner, Franklin, Gluck, Fulton-Kehoe et al., 2006). In a large, combined sample of U.S. WC claimants with low back pain, the median time that opioids were initiated was eight days after the first medical visit, and 9.4% of claimants who received an opioid got a potent long-acting formula within two years of injury (Cifuentes, Webster, Genevay, & Pransky, 2010).

Among injured workers, recent research indicates that the receipt of an opioid for pain is not associated with improved outcome. On the contrary, there is a trend of earlier prescribing of opioids leading to longer disability and higher costs in WC claimants (Franklin et al., 2008; Gross, Stephens, Bhambhani, Haykowsky, Bostick et al., 2009; Volinn, Fargo, & Fine, 2009; Webster, Verma, & Gatchel, 2007) even when baseline disability, pain, duration of symptoms, coping style, and pain self-efficacy are controlled for (Ashworth, Green, Dunn, & Jordan, 2013).

Knowledge gaps.

As opioid use has changed in the overall population over the past five to ten years, there is a lack of recent estimates of opioid use by injured workers to keep the field current. Additionally, previous estimates made using WC records likely underestimate the true extent of opioid use by injured workers because the high variance in which claims are accepted by WC, the presence of multiple provider episodes (a patient visiting multiple prescribers in order to gain access to greater levels of controlled substances), and long periods between the date of injury and date of claim approval introduce opioids that are unaccounted for in WC records. These additional sources of opioids bias estimates of opioid use prevalence and associations that are made with WC records alone.

Tennessee-specific knowledge gaps.

Opioid use prevalence and mortality have been researched by the TN Department of Health for the overall population, but no one has examined opioids in injured workers in TN. This topic has only been researched in a few states in the U.S., and high inter-state variability in culture and opioid use trends (Webster, Cifuentes, Verma, & Pransky, 2009) limit the extent to which findings from other states can be generalized. TN is a forerunner in pioneering opioid analyses using a prescription drug monitoring program, but neither baseline rates nor associations and trends of opioid use by injured workers are known.

Innovation

The studies included in this dissertation are the first in TN to study opioid use by injured workers and among the first nationally to use a prescription drug monitoring program for this purpose. TN's prescription drug monitoring program includes a record of every prescription for opioids and other controlled substances that are dispensed legally in Tennessee, and provides an opportunity for a much more comprehensive picture of opioid use than WC records alone are capable of. Using a prescription drug monitoring program allows for higher accuracy of estimates, and richer detail in analyses of the correlates and outcomes of opioid use. This is important to study in TN because, although the rate of opioid use by injured workers is unknown, high opioid use and misuse by the overall population indicate that use and misuse may also be high for this group. A greater understanding of the landscape and context of opioid use by injured workers in Tennessee is needed in order to protect individual and community health and allocate state resources to the areas of greatest need. The studies in this dissertation provide a previously unavailable picture of the prevalence, patterns, and outcomes of the opioid epidemic in this population.

Purpose of this dissertation

This dissertation presents three separate but related studies to 1) describe opioid use by injured workers in TN, 2) identify patterns of opioid use by injured workers that are associated with nonfatal overdose, and 3) develop a predictive model for the development of long-term opioid use in injured workers who were opioid-free at the time of injury.

Research questions

Chapter 2 - Prescription opioid use by injured workers: A descriptive study using linked statewide databases in Tennessee.

Cross sectional study

Research questions (RQs):

RQ 2.1: What is the percentage of injured workers who receive opioids within one week, one month, and six months of injury from 2013 through 2015?

Hypothesis: Tennessee falls in the upper range of states for opioid use by injured workers with the percentage receiving an opioid use after injury of >20% within one week, >25% within one month, and >30% within six months.

RQ 2.2: Do injured workers who received opioids in the six months after injury differ by sex, age, residence area, or injury type compared to the injured workers who did not receive opioids?

Hypothesis: Men, people of middle age groups, people living in east Tennessee, and people with more traumatic injuries have higher prevalence of receiving opioids (PR>1). Sex and age interact so that middle aged women have greater prevalence ratio than other sex and age groups of receiving opioids (PR of the interaction >1), and age and injury type interact so that older people with more traumatic injuries have higher prevalence ratio of receiving opioids (PR of the interaction>1) than people with less traumatic injuries.

RQ 2.3: Among injured workers with one or more opioid prescriptions in the first six months after injury, what is the percentage who experienced any of five key high-risk patterns of opioid use compared to not experiencing that pattern: receiving greater than 80 mean daily morphine milligram equivalents (MMEs), receiving greater than 100 mean daily MMEs, combined opioid and benzodiazepine use, receiving a long-acting opioid, and having a multiple provider episode from 2013 through 2015?

Hypothesis: Among injured workers who received opioids, the percentage receiving greater than 80 mean daily MMEs, combined opioid and benzodiazepine use, and a long-acting opioid are high (30%) while the proportion receiving greater than 100 mean daily MMEs is lower but still high (20%) and the proportions with a multiple provider episode is low but still present (10%).

Chapter 3 - Patterns of prescription opioid use associated with nonfatal opioid overdose: A case-control study using linked statewide databases in Tennessee.

Nested case-control study

Research questions (RQs):

RQ 3.1: How do the incidence rates of nonfatal opioid-involved overdose amongst injured workers compare to the incidence rates in the general population of Tennessee?

Hypothesis: Opioid-involved overdoses are less common in injured workers than in the general population (incidence rate ratios <1).

RQ 3.2: What are the associations of type of injury, early initiation of opioid therapy, prior history of opioid use, long-acting opioids, cash payment, combined opioid and benzodiazepine use, and multiple provider episodes with the odds of nonfatal overdose amongst injured workers with one or more opioid prescriptions?

Hypothesis: More traumatic injuries, early initiation of opioid therapy, prior history of opioid use, long-acting opioids, cash payment, combined opioid and benzodiazepine use, and multiple provider episodes are associated with nonfatal overdose (OR>1).

RQ 3.3: Is mean daily morphine milligram equivalents (MME) a mediator in the associations between type of injury, early initiation of opioid therapy, prior history of opioid use, long-acting opioids, cash payment, combined opioid and benzodiazepine use, and multiple provider episodes and the odds of nonfatal overdose amongst injured workers with one or more opioid prescriptions?

Hypothesis: Mean daily MME partially mediates the associations between more traumatic injuries, early initiation of opioid therapy, prior history of opioid use, long-acting opioids, cash payment, combined opioid and benzodiazepine use, and multiple provider episodes and the odds of nonfatal overdose (MME is associated with overdose with OR>1 and ORs of other variables decrease but do not reach null after the inclusion of MME in the model).

Chapter 4 - A predictive model for injury as a gateway to long-term opioid use: A retrospective cohort study using linked statewide databases in Tennessee.
Cohort study

Research questions (RQs):

RQ 4.1: What percentage of injured workers are opioid-free at the time of their injury?

Hypothesis: More than half (>50%) of injured workers are opioid-free at the time of their injury.

RQ 4.2: Among injured workers who were opioid-free at the time of injury but who received an opioid in the month after injury, does a three or four month follow-up period capture more cases of long-term opioid use?

Hypothesis: Measuring opioid use as receiving an opioid on most days in a four month period captures more cases than measuring opioid use as receiving an opioid on most days in a three month period.

RQ 4.3: What demographic factors (sex, age, residence area, injury type, and part of body injured) and opioid use patterns (early initiation of opioid therapy, combined opioid and benzodiazepine use, long-acting opioids, higher mean daily MME, higher day's supply, multiple prescribers and pharmacies, cash payment) predict a previously opioid-free injured worker developing long-term opioid use after injury?

Hypothesis: Female sex, middle age group, residence in east TN, more traumatic injuries, early initiation of opioid therapy, long-acting opioids, higher mean daily MME, using multiple prescribers and pharmacies, and cash payment predict long-term opioid use (ORs>1). Part of body injured does not predict long-term opioid use (OR=1).

Main Data Sources

The following data sources will be used in the proposed set of three research studies. All data sources will be accessed through a Health Enterprise Warehouse maintained by the TN Department of Health.

Workers' Compensation (WC) Records.

WC is an employer-buy in insurance program that pays medical care costs and wage replacement for employees who are injured at work. In TN, WC is mandatory for all construction and coal-mining employers and for nongovernmental employers with greater than 5 employees. WC is optional for government agencies (state and local) and employers of farm laborers or domestic help. The percentage of businesses covered by WC in TN is unknown. WC records are kept in a database by the Bureau of Workers' Compensation in the Tennessee Department of Labor and Workforce Development. The records that form the database used by these studies are drawn from the "Employer's First Report of Work Injury or Illness" form, which employers are required to submit within 30 days for illnesses and injuries occurring in the workplace (Appendix 1). Submission of this form is mandatory even if the injured worker does not intend to seek care or compensation, but exempt if the illness or injury requires only first aid to treat. Underreporting of workplaces injuries is estimated to be as high as 66% (United States. Cong. House. Committee on Energy and Commerce Subcommittee on Oversight and Investigation, 2014). This estimate is likely inflated by the huge number of superficial and minor injuries (which would not require opioids for treatment), but employers may also be incentivized to underreport injuries in order to avoid paperwork and negative attention (Wuellner, Adams, & Bonauto, 2016). There has not been any research in TN on the extent of underreporting.

Electronic records of years 2013-2015 of the "Employer's First Report of Work Injury or Illness" form were shared by the TN Department of Labor for this research. In this form, workers are identified with social security number, name, and date of birth. The form includes mandatory and optional fields. In the electronic database that was used for research, mandatory fields had ≤0.02% missing data and optional fields had 16.7% - 100% missing data. To avoid reporting bias, these studies only analyzed mandatory reporting variables. Marital status, an optional variable, was occasionally included for descriptive purposes.

Controlled Substances Monitoring Database (CSMD).

The CSMD is a database that monitors every controlled substance that is legally dispensed in TN and is kept by the Controlled Substance Monitoring Database Program in the TN Department of Health. The CSMD contains drug, patient, prescriber, and dispenser information to capture detailed information on every controlled substance given to every patient. Prescription information that is collected includes the date the prescription was written, the date the prescription was filled, the name, type, and schedule of the drug, the dose and days' supply, the method of payment, the address and identifier of the prescriber, the address and identifier of the pharmacist, and the address and identifier of the patient. This detail of prescription information is a key strength of the studies outlined in this paper.

The CSMD was established in 2002 and data entry by dispensers was made mandatory in 2006 (TN Department of Health "Controlled substance"). However, due to slow uptake and lack of funding, data quality is poor prior to 2012. For years 2013 and later (after implementation of the Prescription Safety Act of 2012 which reaffirmed required use of the CSMD and funded maintenance for the database), the CSMD is considered to be a near-complete record of controlled substances dispensed in TN. There are several instances where a prescription would not be entered in the CSMD, including: 1) controlled substances dispensed by some licensed physician-dispensers through their office instead of through a pharmacy, 2) prescriptions that are written in TN but filled out-of-state, and 3) controlled substances dispensed through military sources or narcotic treatment programs. However, these instances are estimated to be less than 1% of the total number of prescriptions filled through pharmacies in the state.

Patients are identified in the CSMD with name and date of birth rather than with social security number or another unique identifier, leading to challenges in matching people to their prescriptions. For these studies, injured workers were linked to the CSMD on cleaned and standardized first name, last name, and date of birth.

Hospital Discharge Data System (HDDS).

HDDS is a billing log of inpatient and outpatient treatment provided to patients at all hospitals licensed by the TN Department of Health. HDDS includes data for patients seen in emergency rooms but does not include data for patients seen at private clinics located outside of hospitals. HDDS is used nationwide and TN records are held by the TN Department of Health. HDDS includes information on patient, injury or illness, and treatment. Diagnoses are recorded with ICD-9 codes prior to the third quarter of 2015, and ICD-10 codes after. HDDS is a complete or near-complete record of hospital visits due to legally required reporting and the use of mandatory fields, but has some error due to misdiagnoses, incorrect identification of procedure/patient/site, and data entry errors. Challenges using HDDS include underestimation of counts and rates due to people who did not seek care at a hospital and misestimates of counts and rates due to misdiagnoses. For example, someone who had cardiac arrest caused by a drug overdose may be coded only as "cardiac arrest." In HDDS, patients are identified with social security number.

Vital Statistics Death Certificates.

Vital Statistics death certificates is a database of death certificate records for every decedent who was a resident of TN or who died in TN. Death certificates have been recorded electronically in TN since at least 2002, but major changes to the format of variables occurred in 2012. This study will use data collected after 2012. Vital demographics (e.g. age, race/ethnicity, education, income, marital status), residence, location of death, and cause of death information is collected by medical examiners, coroners, and local health departments and reported using a standard form (Appendix 1). After initial receipt by the Department of Health, death certificate records are revised according to autopsy findings and hospital records if needed before being made available for research. Vital Statistics death data is kept by the Office of Policy, Planning, and Assessment in the TN Department of Health. Decedents are identified with social security number. Vital Statistics death certificates are considered to be the best currently available record of everyone who died in TN, although validation studies have shown that overdose deaths are often underestimated due to underreporting and not specifying a type of drug. Nationwide, approximately 25% of overdose deaths do not specify a drug on the death certificate (Slavova et. al., 2015).

Chapter 2

Prescription opioid use by injured workers: A descriptive study using linked statewide databases in Tennessee.

Abstract

Background Injured workers bear a high burden of opioid use in southern and central states of the U.S., putting them at risk for drug dependence, delayed recovery, and other opioid-associated adverse effects. Research from other states shows that opioid use after injury is high, but previous estimates conducted with Workers' Compensation (WC) records do not capture opioid use in injured workers who do not become claimants. A prescription drug monitoring program was used to measure opioid use in Tennessee (TN) injured workers who reported an injury to WC and describe trends in prescribing and the demographic and clinical characteristics of opioid users. This is the first study in TN to measure opioid use in injured workers and among the first nationally to use a prescription drug monitoring program to do so.

Objective A retrospective cohort study was conducted to evaluate the prevalence of filling an opioid prescription after injury and associated demographics and injury characteristics among workers who reported an injury to the TN Bureau of WC during 2013-2015.

Methods Injured workers identified in WC first report of injury forms 2013-2015 were linked to their prescription history in Tennessee's prescription drug monitoring database. Percentages of receiving an opioid within 1 week, 1 month, and 6 months, of injury were calculated by year. Associations between demographics and injury characteristics and receiving an opioid were assessed with Poisson regression. Among injured workers who received opioids within 6 months of injury the following patterns of opioid use were described: dose, days' supply, number of prescribers and dispensers visited, type of opioid, type of payment, receiving an opioid within 30 days of a benzodiazepine, receiving >100 mean daily morphine milligram equivalents, receiving a long-acting opioid, and having a multiple provider episode (≥3 prescribers and ≥3 dispensers in the 180 days after injury), and type of benzodiazepine.

Results This study included 172,256 injured workers who reported only one injury during 2013-2015. Injured workers were predominantly male (55.3%) and aged 35-54 years (43.5%). The prevalence of receiving an opioid after injury was 22.8% in 1 week, 29.7% in 1 month, and 33.3% in 6 months across all years. Receiving an opioid was associated with having a fracture (prevalence ratio [PR]=2.3, 95% confidence interval [CI] 2.22-2.36 vs. non-fracture, non-strain sprain or tear injuries) and having a record for opioid use prior to injury (PR=2.3, 95% CI 2.29-2.39 vs. no prior opioid use). Among people who received an opioid, the mean maximum dose received was 42.8 daily morphine milligram equivalents (standard deviation 39.26). Hydrocodone short-acting was the most commonly received opioid (69.5% of injured workers). Ten percent of injured workers who received opioids also received a benzodiazepine, and all received an opioid within 30 days of that benzodiazepine.

Conclusion Prescription opioid dispensing to injured workers in Tennessee is high with one in three workers receiving opioids within six months of injury, and is prevalent across demographic categories. Prescribers for this population appear to be following guidelines, at least in the first six months after injury, with mean and standard deviation dose and days' supply within recommended limits.

Background

Opioids are a powerful treatment for providing relief from acute pain but can cause serious health problems when taken non-medically, not as prescribed, chronically, at high doses, or in combination with other drugs or alcohol (Eriksen, Sjogren, Bruera, Ekholm, & Rasmussen, 2006). Improper prescription opioid use is associated with overdose, drug dependence, road traffic crashes, increased family stress, and heroin use (Kolar, Brown, Haertzen, & Michaelson, 1994; Orriols, Delorme, Gadegbeku, Tricotel, Contrand et al., 2010; Palamar, Shearston, Dawson, Mateu-Gelabert, & Ompad, 2016; Trang, Al-Hasani, Salvemini, Salter, Gutstein et al., 2015). Tennessee (TN) is among the hardest-hit states in the current prescription opioid epidemic and has the third highest prescribing rate (107.5 prescriptions per 100 persons in 2016) and the fifth highest prescribing rate of high dosage (≥90 daily MMEs) opioids (9.8 prescriptions per 100 persons in 2016) (Centers for Disease Control and Prevention, 2014, 2017). Injured workers are a special population with regard to opioid use because of the need to balance pain relief with rehabilitation (Harris et al., 2005; Newton-John & McDonald, 2012), but no studies have reported on opioid use by this population in TN.

One review of ten studies estimated that 31.8% of Workers' Compensation (WC) claimants worldwide receive an opioid prescription during their claim, but prevalence varied widely by country and by state in the U.S. (Dembe et al., 2012). Research on the prevalence of opioid use by claimants using WC records has yielded lowest estimates in Illinois (6.6% within

90 days of injury), intermediate levels in Ohio (19.2% within 2 years) and Michigan (27% during course of treatment), and highest in Washington State (42% within one year) and Louisiana (46.4% within one year) (Dembe et al., 2012; Franklin, Rahman, Turner, Daniell, & Fulton-Kehoe, 2009; Lavin et al., 2014; J. A. White, Tao, Artuso, Bilinski, Rademacher et al., 2014; J. A. White, Tao, Talreja, Tower, & Bernacki, 2012). Other studies have presented data from prescription drug monitoring programs and other government registries that are stratified by payment source, including WC, but to my knowledge, no study has used a prescription drug monitoring program to measure opioid use in injured workers accounting for all payment types (Kraut, Raymond, Ekuma, & Shafer, 2016). In prior studies, middle age, daily tobacco use, fractures and dislocation injuries, and back pain were associated with receiving an opioid, while associations with sex were mixed (Berecki-Gisolf, Collie, & McClure, 2014; Gross et al., 2009; Pensa, Galusha, & Cantley, 2017; Stover et al., 2006).

Observed prescribing patterns for injured workers may not follow prescribing guidelines, with opioids being prescribed for longer and at higher doses than is recommended (Cifuentes et al., 2010). In injured workers, opioid use is associated with increased medical and claim costs, delayed return to work, absenteeism, lost productivity, and progression to long-term disability (Kidner, Mayer, & Gatchel, 2009; Lavin et al., 2014; Rice, Kirson, Shei, Cummings, Bodnar et al., 2014). Adverse outcomes are more likely when opioids are received early after injury, in the presence of benzodiazepines, in long-acting formulas, and in high doses (Cifuentes et al., 2010; Franklin et al., 2009; Lavin et al., 2014). Visiting multiple prescribers and dispensers (doctor shopping) has also recently arisen as a key indicator for opioid misuse but few studies have evaluated doctor shopping as an adverse outcome in injured workers (Baumblatt, Wiedeman, Dunn, Schaffner, Paulozzi et al., 2014).

Many studies from other states underestimate opioid use by measuring it through claims records alone and missing prescriptions that are paid for with other insurance, cash, Medicare, or Medicaid, and differences in patterns of use by geographic region and population characteristics limits the extent to which other findings can be applied to TN. TN is notable in being both amongst the hardest-hit states in the opioid epidemic (Centers for Disease Control and Prevention, 2016) and, to my knowledge, the first to link WC records to a prescription drug monitoring program. A retrospective cohort study was conducted among workers with an injury reported to the TN Bureau of WC in 2013-2015 to evaluate 1) the prevalence of filling an opioid prescription after injury by year; 2) demographics and injury characteristics associated with opioid use in the first six months after injury; and 3) characteristics of opioid use after injury, including high-risk opioid prescribing patterns with the following research questions and hypotheses:

RQ 2.1: What is the percentage of injured workers who receive opioids within one week, one month, and six months of injury from 2013 through 2015?

> Hypothesis: Tennessee falls in the upper range of states for opioid use by injured workers with the percentage receiving an opioid use after injury of >20% within one week, >25% within one month, and >30% within six months.

RQ 2.2: Do injured workers who received opioids in the six months after injury differ by sex, age, residence area, or injury type compared to the injured workers who did not receive opioids?

> Hypothesis: Men, people of middle age groups, people living in east Tennessee, and people with more traumatic injuries have higher prevalence of receiving opioids (PR>1). Sex and age interact so that middle aged women have greater prevalence ratio than other sex and age groups of receiving opioids (PR of the interaction >1), and age and injury type interact so that older people with more traumatic injuries have higher prevalence ratio of receiving opioids (PR of the interaction>1) than people with less traumatic injuries.

RQ 2.3: Among injured workers with one or more opioid prescriptions in the first six months after injury, what is the percentage who experienced any of five key high-risk patterns of opioid use compared to not experiencing that pattern: receiving greater than 80 mean daily morphine milligram equivalents (MMEs), receiving greater than 100 mean daily MMEs, combined opioid and benzodiazepine use, receiving a long-acting opioid, and having a multiple provider episode from 2013 through 2015?

> Hypothesis: Among injured workers who received opioids, the percentage receiving greater than 80 mean daily MMEs, combined opioid and benzodiazepine use, and a long-acting opioid are high (30%) while the proportion receiving greater than 100 mean daily MMEs is lower but still high (20%) and the proportions with a multiple provider episode is low but still present (10%).

Methods

Data sources.

Data from 2013-2015 WC records and 2013-2016 Controlled Substances Monitoring Database (CSMD) was used in these studies. In TN, it is required by law for businesses with five or more employees and all construction and coal mining businesses to carry WC insurance (T.C.A. § 50-6-101 et seq., 2010). WC records were supplied by the Employer's First Report of Illness or Injury form, which is compliant with reporting requirements of the Occupational Safety and Health Administration and which WC requires employers to submit within 15 days for each illness or injury occurring at their workplace (Occupational Safety and Health Administration; Tennessee Bureau of Workers' Compensation). Years 2013-2015 of the data were provided to the TN Department of Health from the TN Department of Labor as part of an ongoing collaboration, and are representative of injured workers in Tennessee.

The CSMD includes data about every controlled substance that is legally dispensed in outpatient settings in TN. Data entry by dispensers is mandatory in most cases (excluding inpatient settings, drugs dispensed by veterinarians with ≤5 days' supply, drug samples and drugs given by a facility with ≤48 hours' supply, drug samples for schedule IV and V substances with ≤72 hours' supply, and narcotic treatment programs registered with and required to keep records by the Drug Enforcement Agency.) ("Prescription Safety Act of 2012," 2012), and the database has been funded since 2012 (T.C.A. § 53-10-3, 2012). This study uses data from the last quarter of 2012 through mid-2016, including prescriptions for each injured worker from two months before their date of injury through six months after injury.

Workers who reported an injury to the TN Bureau of WC from 2013 through 2015 were matched to their prescription history in the CSMD on name and date of birth. Names were cleaned to standardize formats, remove prefixes and suffixes, and separate multiple names into separate fields (maximum four). Dates were cleaned to remove improbable dates of birth and prescriptions where the date of birth fell on or after the date that the prescription was filled. Linkage between WC records and the CSMD was done deterministically, where two records were considered a match if they had a link between any of the four first name fields, a link between any of the four last name fields, and the same date of birth. This study was approved by the Institutional Review Boards at the Tennessee Department of Health and University of Hawaii.

Study population.

The main study population was Tennessee residents age 15-99 years old who reported only one injury to TN WC 2013-2015. Workers were excluded if they were missing date of birth or age <15 or ≥100 years at the time of injury, missing sex, had no physical injury, or resided out of state (Figure 1). Workers who were missing name or date of birth on their report of injury form were excluded to prevent error in matching to prescription records Workers with missing sex were excluded as sex was a key variable under study. Workers residing out of state were excluded to prevent underestimation of prescriptions received out of state. People whose nature of injury code indicated no physical injury were also excluded to limit opioids that were not prescribed for an injury. Workers who reported more than one injury were excluded from analyses to avoid confounding by previous injuries, but their demographics were presented for comparison to people who had only one injury.

Inclusion criteria for opioids were schedule II-IV drugs. Prescriptions from Veterans Affairs pharmacies (indicated by drug enforcement agency number for the pharmacy, n=548) were excluded to focus on a non-military population and prescriptions from veterinarians (indicated by prescriber’s educational degree, n=8) were excluded to remove opioids given to animals. Additionally, prescriptions for opioids indicated for medication assisted therapy (MAT, including all burprenorphine except butrans and belbuca, n=3746) were excluded to focus on opioids given for pain. Prescription exclusions only excluded prescriptions for eligible persons: no person was excluded from the study population based on these criteria.

Demographics and injury characteristics.

Age at the time of injury, sex, region of residence, marital status, type of injury, and part of body injured were collected from WC records and were selected based on availability, completeness of data, and previous literature identifying risk factors for opioid use including middle age, fractures and dislocation injuries, and back pain. Associations of opioid use with sex are mixed in previous literature on injured workers, with some studies showing more opioid use by females and some showing more by males (Berecki-Gisolf et al., 2014; Gross et al., 2009; Stover et al., 2006). The most frequently occurring types of injury were selected and remaining types of injury were grouped into an “other” category for analysis. When overlapping confidence intervals were observed among many injury groups in regression analyses, injury type was reclassified into strains, sprains, and tears, fractures, and other. Geographical region of residence was classified into east, middle, and west Tennessee based on geocoded zip code. East Tennessee covered Knoxville/Knox County, East Tennessee, Northeast Tennessee, Sullivan, Southeast, and Chattanooga-Hamilton regions. Middle Tennessee comprised South Central, Upper-Cumberland, Mid-Cumberland, and Nashville-Davidson regions. West Tennessee included Northwest, West Tennessee, Memphis/Shelby County, and Jackson/Madison County regions. Region of residence was also classified into urban and rural. The urban category included the counties with the 6 largest cities in Tennessee (urban region population density range 176.4 – 1,243.3 people per square mile) (Tennessee Department of Health, Local and regional health departments). To better describe the sample, the distribution of industry (from North American Industry Classification System codes) was also described.

Prescription outcome measures.

The primary outcome was filling a prescription for an opioid (hereafter referred to as receiving an opioid) within six months of injury. Secondary outcomes were receiving an opioid within one week and one month of injury, type of payment, and opioid prescribing patterns including dose in daily morphine milligram equivalents (MMEs), days' supply, type of opioid, and four high-risk opioid patterns: 1) receiving >100 daily MMEs, 2) receiving a long-acting opioid at any point within 6 months of injury, 3) receiving an opioid within 30 days of a benzodiazepine, and 4) having a multiple provider episode, defined here as visiting ≥3 prescribers and ≥3 dispensers in the 180 days after injury (Dowell, Haegerich, & Chou, 2016; Kowalski-McGraw, Green-McKenzie, Pandalai, & Schulte, 2017a).

Statistical analysis.

Frequencies, proportions, means, and standard deviations (SD) were used to describe the population. Means, standard deviations and proportions were used to describe the distribution of measures of opioid use in the six months after injury and other demographic and clinical characteristics within the study sample.

To identify associations between demographics and injury characteristics for our primary outcome of receiving an opioid within 6 months of injury, Poisson regression with a log link function was used to compute unadjusted and adjusted prevalence ratios (PRs) with 95% confidence intervals (CIs). Poisson regression was chosen because the model failed to converge when log-binomial regression was used. The covariates used for adjusted models were determined a priori and were age, sex, type of injury, part of body injured, region of residence, and opioid use before injury. Following reports that younger males and older females are groups of concern for opioid use in the overall U.S. population (Krueger, 2017; Substance Abuse and Mental Health Services Administration, *Opioid use in the older adult population*, 2017), two factor interactions were tested for between age and sex, age and prior opioid use, and sex and prior opioid use. Sensitivity analyses additionally adjusting for marital status and excluding workers with severe injury types were conducted. Respondents with missing or unknown values for the selected variables were excluded from the multivariable analysis.

Prescribing patterns were described with mean, standard deviation, and sample percentages. Trends by year in the percentage of injured workers receiving opioids and, among those receiving opioids, the percentage receiving a high risk pattern, were tested for with the Cochran-Armitage test. Although our analysis focuses on opioid analgesic use, the proportion of workers given opioids for MAT and benzodiazepines in the two months before and six months after injury, and the types of benzodiazepines that were prescribed were also reported. All statistical tests were two-sided with a statistical significance level of $p < 0.05$ and were conducted using SAS v 9.4 (SAS Institute, Cary, NC).

Results

Demographics and receipt of an opioid after injury.

Of 202,380 workers who reported injuries to TN WC 2013-2015, 188,608 reported only one injury (93.2%) and 172,256 (85.1%) were eligible for this study (Figure 2.1). The study population was predominantly middle aged (mean 42.1 years ± 13.39 years SD), male (55.3%), from rural areas of residence (61.6%), from middle TN (42.6%) and injured with strains, sprains, or tears (35.4%) (Table 2.1). In 2015, 21.7% of injured workers received an opioid within 1 week of injury, 28.4% received an opioid within 1 month of injury, and 31.8% received an opioid within 6 months of injury (Figure 2.2). Among workers who received opioids within 6 months of injury in 2015, 80% (n=14,544) were opioid-free at the time of injury (Appendix 2, Table S2.1).

Figure 2.1: Study population flowchart.

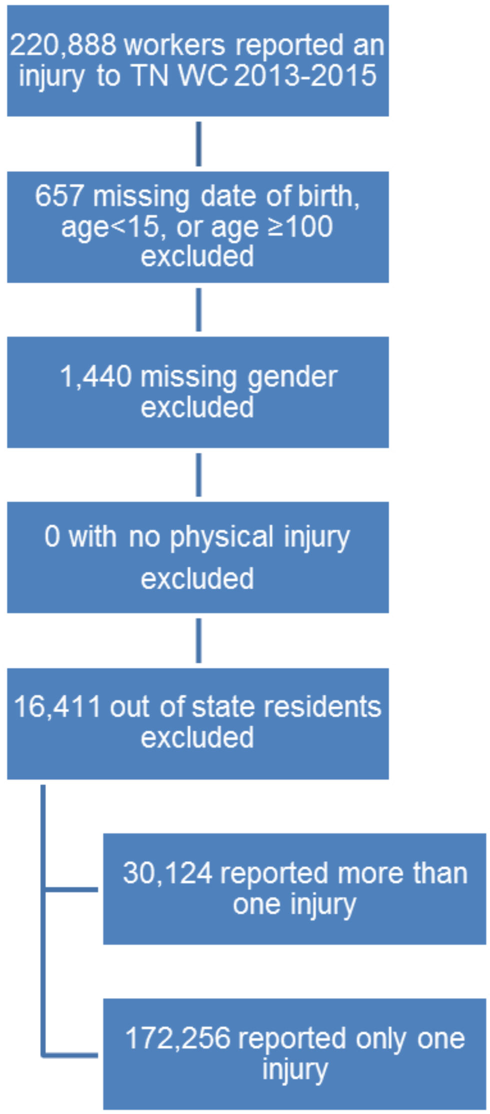


Table 2.1: Characteristics of injured workers who reported one injury compared to those who reported 2 or more injuries to TN Workers' Compensation 2013-2015 (N=202,380)				
Characteristic	Injured workers with one injury (N=172,256)		Injured workers with ≥ 2 injuries (N=30,124)	
Age in years, mean (SD)	40.3 (13.74)		40.7 (13.00)	
	n	**%**	**n**	**%**
Age, years				
15 - 34	66430	38.6	10857	36.0
35 - 54	74871	43.5	14160	47.0
55 - 99	30955	18.0	5107	17.0
Sex				
Female	76994	44.7	12716	42.2
Male	95262	55.3	17408	57.8
Marital Status				
Single	3719	2.2	599	2.0
Married	45424	26.4	8157	27.1
Widowed, separated, or divorced	42232	24.5	7318	24.3
Unknown or missing	80881	47.0	14050	46.6
Region of residence				
Rural	106185	61.6	18634	61.9
Urban	66071	38.4	11490	38.1
Geographical area				
East	61964	36.0	10098	33.5
Middle	73289	42.6	13812	45.9
West	37003	21.5	6214	20.6
Definitions: TN=Tennessee; SD=standard deviation				

Compared to injured workers who did not receive opioids within 6 months of injury, those who received opioids were older (mean 42.1 ± 13.39 SD vs mean 39.5 ± 13.84 SD) and more likely to be from a rural region (63.5% vs 60.7%). Women had slightly less opioid use than men (54.7% vs. 56.5%). Workers of middle age groups had overlapping prevalence ratio confidence intervals of receiving an opioid (data not shown), so age categories were collapsed into 15-34 years, 35-54 years, and 55-99 years and the association of age with opioid use was PR=1.3 (95% CI 1.28-1.33) for age 35-54 vs. 15-34 and PR=1.3 (95% CI 1.30-1.37) for age 55-99 vs 15-34 (Table 2.2). Industry had 56% missing values but, among those who had reported data, workers in wholesale and retail trades were more likely than those in other jobs to receive an opioid (Appendix 2, Table S2.2).

Table 2.2: Estimated associations (prevalence ratios [PRs] and 95% confidence intervals [CIs] of demographic characteristics and type of injury with receiving an opioid analgesic within 6 months of injury in workers who reported one injury to TN Workers' Compensation 2013-2015 (N=172,256): Results from Poisson regression analyses.

Characteristic	Opioid prescription filled within 6 months of injury		Unadjusted PR (95% CI)
	No (n=114,974)	Yes (n=57,282)	
Age, mean (SD)	39.5 (13.84)	42.1 (13.39)	
Age, years	n (%)	n (%)	
15 - 34	47892 (41.7)	18538 (32.4)	1.0 (ref)
35 - 54	47652 (41.4)	27219 (47.5)	1.3 (1.28-1.33)
55 - 99	19430 (16.9)	11525 (20.1)	1.3 (1.30-1.37)
Sex			
Female	52070 (45.3)	24924 (43.5)	1.0 (ref)
Male	62904 (54.7)	32358 (56.5)	1.05 (1.03-1.07)
Type of injury			
Other	73383 (63.8)	30109 (52.6)	1.0 (ref)
Strain, sprain, or tear	38996 (33.9)	21988 (38.4)	1.2 (1.22-1.26)
Fracture	2595 (2.3)	5185 (9.0)	2.3 (2.22-2.36)
Part of body			
Other	67374 (58.6)	32180 (56.2)	1.0 (ref)
Finger(s)	12773 (11.1)	5498 (9.6)	1.0 (0.97-1.03)
Lower back	10660 (9.3)	7005 (12.2)	1.2 (1.16-1.23)
Multiple body parts	7847 (6.8)	4680 (8.2)	1.2 (1.14-1.22)
Hand	8705 ((7.6)	3466 (6.0)	0.95 (0.92-0.99)
Knee	7615 (6.6)	4453 (7.8)	1.1 (1.10-1.18)
Region			
Rural	69827 (60.7)	36358 (63.5)	1.0 (ref)
Urban	45147 (39.3)	20924 (36.5)	0.9 (0.91-0.94)
Geographical area			
East	41538 (36.1)	20426 (35.7)	1.0 (ref)
Middle	49784 (43.3)	23505 (41.0)	0.97 (0.95-0.99)
West	23652 (20.6)	13351 (23.3)	1.1 (1.07-1.12)
Prior opioid use	5568 (4.8)	12052 (21.0)	2.3 (2.29-2.39)
Definitions: TN=Tennessee; PR=prevalence ratio; SD=standard deviation			

Having a fracture (PR=2.3, 95% CI 2.22-2.36 compared to having another injury) and having a record for opioid use prior to injury (PR=2.3, 95% CI 2.29-2.39) were most strongly associated with receiving an opioid in the 6 months after injury. Having a strain, sprain, or tear (PR=1.2, 95% CI 1.22-1.26) was also associated with receiving an opioid in the 6 months after injury, but associations differed by part of body with lower back strains, sprains, or tears being associated with more opioid use than strains, sprains, and tears in other parts of the body (Appendix 2, Table S2.3). Fractures were more likely to receive an opioid if they had a finger fracture and less likely if they had a wrist fracture.

Sensitivity analyses were conducted by adjusting for marital status (where data not missing) and excluding people with extreme injuries including crushing (n=1819), amputation (n=382), rupture (n=190), myocardial infarction (n=144), severance (n=109), AIDS (n=33), cancer (n=18), hepatitis C (n=12), and black lung (n=2). After adjustment, finger injuries and residence in Middle TN were no longer associated with opioid use but other associations were similar. No interactions were found between age and sex, age and prior opioid use, or sex and prior opioid use. There was a small but significant decrease in the percentage of injured workers receiving opioids by year (Appendix 2, Table S2.1), but controlling for year in the multivariable model did not alter associations between other variables and opioid use.

Patterns of opioid use.

Among workers who received opioids, the maximum doses (mean 42.8 ± 39.26 SD) and maximum days' supply (mean 9.4 ± 9.81 SD) were moderate. Only 5.0% (n=2866) received a prescription for >100 daily MMEs. The numbers of prescribers and dispensers visited were also low, with 80.2% of injured workers (n=38346) visiting only one prescriber and one dispenser. Two percent (n=1185) visited ≥3 prescribers and ≥3 dispensers and qualified as having a multiple provider episode. Only 39 injured workers who had one injury visited ≥5 prescribers and ≥5 dispensers for opioids in the six months after injury. Most workers received Hydrocodone short-acting (SA) (69.5%), Oxycodone SA (23.0%) and/or Tramadol SA (23.8%) (nonexclusive categories). The prevalence of receiving a long-acting opioid was 2.5% and receiving an opioid within 30 days of receiving a benzodiazepine was 9.5% (Table 2.3).

Table 2.3: Description of opioid analgesic use in the 6 months after injury by workers who reported one injury to TN Workers' Compensation 2013-2015 (n=57,282)^*		
	Mean (SD)	Median (IQR)
Maximum received daily MME	42.8 (39.26)	31.3 (21.43-50.00)
Maximum received days' supply	9.4 (9.81)	5.0 (3.00-10.00)
Number of prescribers visited	1.4 (0.76)	1 (1.00-2.00)
Number of dispensers visited	1.2 (0.52)	1 (1.00-1.00)
Most frequently received types of opioid*	n	%
Hydrocodone SA	39813	69.5
Oxycodone SA	13171	23.0
Tramadol SA	13647	23.8
Codeine	2084	3.6
Morphine LA	472	0.8
Type of payment*		
Commercial Insurance	37283	65.1
Workers' Compensation	11567	20.2
Cash	10599	18.5
Medicaid	3966	6.9
Medicare	1152	2.0
Military	10	0.02
Indian Nations	1	0.0
High-risk opioid prescribing pattern experienced		
Opioid received within 30 days of a benzodiazepine	5451	9.5
>100 mean daily MMEs	2866	5.0
Long-acting opioid	1437	2.5
Multiple provider episode**	1185	2.1
Received a benzodiazepine in the 6 months after injury	5785	10.1
Most frequently received types of benzodiazepine*		
Alprazolam	2683	4.7
Diazepam	1415	2.5
Clonazepam	1025	1.8
Lorazepam	652	1.1
Temazepam	221	0.4

Definitions: TN=Tennessee; SD=standard deviation; IQR=interquartile range; MME=morphine milligram equivalents; SA=short acting; LA=long acting
^ Table is limited to injured workers who received an opioid within 6 months of injury
* Categories are non-exclusive, injured workers may appear in more than one category
** Visiting ≥3 prescribers and ≥3 providers in the 6 months after injury

Prescription-level changes by year were assessed in the top ten prescribed opioids. There was no change by year in the top 7 prescribed opioids, but the 8th, 9th, and 10th most prescribed opioids in 2013 (Meperidine, Hydromorphone SA, and Methadone, all 0.4% prevalence) changed in 2015 (Hydromorphone SA 0.5%, Fentanyl LA 0.4%, and Meperidine 0.3% of prescriptions). Changes in high risk patterns by year were tested for and significant decreases were found for receiving >100 mean daily MME (5.6% in 2013 vs. 5.0% in 2015, $p<0.01$), receiving a long-acting opioid (2.8% in 2013 vs. 2.3% in 2015, $p<0.01$), and having a multiple provider episode (2.4% in 2013 vs. 1.9% in 2015, $p<0.01$). Receiving an opioid within 30 days of a benzodiazepine had no significant change.

Most workers used a private, commercial insurance to pay for opioids (65.1%) and one-fifth (n=11,567) used WC to pay for a prescription (Table 3). Five percent (n=3064) used both commercial insurance and WC, 1.9% (n=1106) used both cash and WC, and 0.5% (n=272) used both Medicaid and WC to pay for opioids. Very few prescriptions (n=867, 1.5%) had unspecified payment type.

Few (n=759) injured workers in this study population received buprenorphine for MAT (0.4% of the total 172,256). All had a record for receiving MAT prior to injury, with 198 (26.1%) also receiving an opioid analgesic after injury but no new courses of MAT were started within the six months after injury. Because of a short follow up time, later trends in MAT use could not be ascertained.

Benzodiazepine use was more widespread, with 5.6% (n=9,575) of the total sample and 10.1% (n=5,785) of workers who received opioids filling a prescription for this class of drug. All 5785 opioid users that received a benzodiazepine after injury also had a record for filling a benzodiazepine before injury, and all received an opioid within 30 days of a benzodiazepine. The most frequently used benzodiazepine was Alprazolam (n=2683 injured workers, 4.7%) (Table 2.3). Benzodiazepine use did not show a significant trend in changing over time. Type of benzodiazepine was not described by trends over time, dose, or days' supply due to small sample size.

Discussion

This population-based study of injured workers in Tennessee found widespread opioid use that generally fell within recommended guidelines. Almost one fifth of people who reported only one injury from 2013-2015 received an opioid within a week of injury, one fourth received an opioid within one month of injury, and one third received an opioid within six months of injury.

Among people who received opioids, mean dose and days' supply were within prescribing guidelines. The Tennessee Chronic Pain Guidelines set an upper threshold of 120 daily MME as the maximum dose that should be prescribed without referral to a pain specialist (Tennessee Department of Health, 2014), and 95% of injured workers in this study had their maximum dose fall below this threshold. Similarly, 85% of injured workers received no prescription over the maximum 30 days' supply allowed by Tennessee state law for schedule II and III controlled substances ("Prescription Requirements," 2013). The numbers of prescribers and dispensers visited were low (80.2% visited only one prescriber and only one dispenser), as was the prevalence of high-risk opioid use patterns such as receiving a long-acting opioid and having an opioid within 30 days of a benzodiazepine. A low proportion of the total sample received benzodiazepines. This proportion was doubled in people who received opioids, demonstrating a potential area for intervention.

The prevalence of opioid use observed in this study is consistent with a previous review of worldwide Workers' Compensation claimants from 2000-2010 that found an opioid use prevalence of 31.8% (Dembe et al., 2012). Compared to other states, the prevalence of opioid use after injury in Tennessee appears to be higher than Ohio (19.2% of Workers' Compensation claimants receive an opioid during their claim) and may be similar to the 42% prevalence observed in Washington or 46.4% prevalence observed in Louisiana if this study had the same 1-year follow up time like these studies (Dembe et al., 2012; Franklin et al., 2009; Lavin et al., 2014). However, these studies used WC records to measure opioid use and are likely underestimates due to their confinement to a single payer source. The estimates presented in this paper are expected to be more accurate due to measuring opioids received through all payer sources.

This study found similar associations between demographic and injury variables and opioid use as prior studies. Similar to the results in this study, a large study of U.S. WC claimants showed middle and older age groups were more likely than younger age groups to receive an opioid after injury (OR=2.6, 95% CI 1.81-3.87 for age >55 vs. <26) (Pensa et al., 2017). Another previous study in Alberta WC claimants found that fractures and dislocations had higher odds (OR=2.5, 95% CI 2.14-2.36) of receiving an opioid in a year after injury compared to back sprains (Gross et al., 2009).

The prevalence of high-risk opioid patterns observed in this study is consistent with previous literature. In Ohio 2008-2009, mean MME during a WC claim was 57.5 and 10% of injured workers received ≥120 daily MMEs. In this study, 75% of injured workers 2013-2015 received no more than 50 MMEs on all prescriptions, a decrease that may reflect a nationwide trend in decreasing MMEs over this time period (Dembe et al., 2012; Guy, Zhang, Bohm, Losby, Lewis et al., 2017). In Ottawa, WC claimants undergoing shoulder, knee, back, or carpal tunnel surgery received a comparatively lower mean dose of 11.25 daily MMEs (Kraut et al., 2016). In a nationwide study of WC claimants with low back pain, 9.4% received a long-acting opioid within 2 years of injury (Cifuentes et al., 2010). No research measuring multiple provider episodes in WC claimants or injured workers was found, and the results in this study indicate that it may not be a substantial problem. In the overall TN population in 2016, the rate of visiting ≥5 prescribers and ≥5 dispensers in six months was 49.96 per 100,000 persons (*Prescription Drug Overdose Program 2018 Report: Understanding and responding to the opioid epidemic inTN using Morbidity, Mortality, and Prescription Data*, January, 2018) Using the same metric in this population of workers who reported only one injury, the rate was 22.64 per 100,000 persons.

This study casts light on benzodiazepine use by injured workers. Of the 9,575 people who received a benzodiazepine in the two months before injury in the total sample, 60.4% (n=5,785) received an opioid after injury while continuing their benzodiazepine use and 39.6% did not receive an opioid. This is a higher proportion that than observed in a study of Workers' Compensation claims in Louisiana 1999-2002 (4.9%) and may reflect an increased use of benzodiazepines in recent years or in TN. In Louisiana, claimants with benzodiazepine use demonstrated benzodiazepine dose escalation over 3 years post injury, and claims with benzodiazepines and short-acting opioids cost triple those of short-acting opioids alone (Lavin et al., 2014).

Tennessee has implemented a number of legislative policies intended to combat the opioid epidemic. In 2012, Tennessee mandated participation in a prescription drug monitoring program (the CSMD, a key data source for this study) for prescribers and dispensers of controlled substances. This was followed by the release of updated Chronic Pain Guidelines in

2014, and a tightening of regulations on pain clinics and a repeal in 2015 of legislation known as "The Pain Patient's Bill of Rights" that virtually guaranteed access to opioids (Tennessee Department of Health, 2015). The decreases observed in the prevalence of opioid use in 2013-2015 may be early effects of these interventions and underscore the need for sustained attention toward controlling opioid prescribing. That observed prescribing patterns parallel recent prescribing guidelines underscores the success of involving clinicians and pharmacists as partners with regulators. The results of this study have high applicability to TN but may not be generalizable to other states.

Limitations.

This study controlled for type of injury reported to Workers' Compensation, but could not account for other, unreported injuries or comorbidities that may influence opioid use, including education, filling prescriptions out-of-state, concomitant medication, years on the job, socio-economic status, other alcohol, tobacco, and drug use, past drug-related hospitalizations, age at first opioid prescription, and criminal history. Particularly, this study could not control for mental health conditions that, especially depression and other drug use, are frequently associated with higher odds of both prescription opioid use and adverse effects from opioids (Hah, Sturgeon, Zocca, Sharifzadeh, & Mackey, 2017; Inacio, Hansen, Pratt, Graves, & Roughead, 2016; Kowalski-McGraw, Green-McKenzie, Pandalai, & Schulte, 2017b; Schoenfeld, Nwosu, Jiang, Yau, Chaudhary et al., 2017). Had these variables been available, they are expected to be key predictors of opioid use. However, the same factors that make people with mental health diagnoses more likely to use opioids after injury also influence their likeliness to use opioids prior to injury, thus prior opioid use is expected to be a confounder in the association between mental health diagnoses and opioid use after injury. Stratification would be a preferable strategy in this case to understand the effects of both mental health diagnoses and prior opioid use. Mental health diagnoses would also be expected to decrease the association between sex and opioid use in the multivariable model, if the association were not already null in this study.

Similarly, this study was not able to assess the role of race in opioid use. Estimates of opioid use may be confounded by race and ethnicity, which are not collected by the CSMD or Workers' Compensation databases. Studies in other states show that Whites tend to be prescribed opioids more frequently (Pensa et al., 2017) but non-Whites are more likely to be recipients of Workers' Compensation (Atlas, Tosteson, Hanscom, Blood, Pransky et al., 2007) In 2016, Tennessee's population was 74.2% White alone, 17.1% Black or African American alone, and 5.2% Hispanic or Latino (United States Census Bureau, 2016). As the racial makeup of the claimant sample is unknown, it is unknown how race may have affected this study's estimates.

This study likely underestimates the total burden of opioid use in injured workers as workers with more than one injury were not included. There is also evidence that, although reporting of workplace injuries is mandated by state law, many workplace injuries go unreported (Committee on Education and Labor, 2008). Workers with more injuries may have more contacts with medical care and residual pain or prescriptions from previous injuries resulting in more overall opioid use (Kowalski-McGraw et al., 2017b). However, if injuries are not reported because of their lack of severity then opioid use would not be expected.

Drug diversion is a well-known phenomenon for controlled substances that may bias estimates of use that are based on legally obtained drugs. This study only has data on prescription opioids purchased from dispensers. Similarly, this study measures only prescriptions that were filled, with no way to measure whether those prescriptions were consumed. However, in using the CSMD to identify and measure opioid use this study will substantially improve the accuracy of estimates made with WC records alone by including opioids paid for with cash and other forms of payment, regardless of claim approval.

Conclusions.

In conclusion, opioid use by injured workers in TN is widespread but generally within prescribing guidelines. This study is the first in TN to describe opioid use by injured workers, and among the first nationally to use a prescription drug monitoring program linked to WC records for this purpose, but more research is needed into what happens after opioids are initiated in injured workers. This work is built upon in the following two studies evaluating long-term opioid use and clinical events related to drug use after injury.

Chapter 3

Patterns of prescription opioid use associated with nonfatal opioid overdose: A case-control study using linked statewide databases in Tennessee.

Abstract

Background Opioid overdoses are now the leading cause of accidental death in Tennessee (TN). Although prescribing rates have begun to decrease since the enactment of prescribing controls intended to constrain the opioid epidemic, the burgeoning rate of overdoses shows no sign of decreasing. High opioid use by injured workers in TN raises concerns about overdose in this population, but this topic has not been studied before in TN.

Objective We conducted a nested case-control study to evaluate the frequency of nonfatal opioid overdose after injury and the prescription opioid use patterns associated with this outcome in workers who reported one injury to TN Workers' Compensation in 2013.

Methods Injured workers were linked to their prescription history in TN's prescription drug monitoring program and hospitalization and emergency department records in TN's Hospital Discharge Data Set and followed for three years after injury. Cases were workers who had a nonfatal opioid-related hospitalization or emergency department visit after injury. Controls were workers who did not have a nonfatal overdose during follow up and did not die before their matched case's date of overdose. Each case was matched to five controls on sex and age ± one year. Overdose characteristics were described and conditional logistic regression was used to evaluate risk factors.

Results From the cohort of 29,972 workers injured in 2013, 101 cases and 505 controls were included in this study. Among cases, 72.3% (n=72) overdosed on prescription opioids, 10.9% (n=11) on heroin, 9.9% (n=10) on opium, and 7.0% (n=7) on both prescription opioids and heroin. Over a quarter (n=29, 28.7%) of cases had no record of receiving a prescription opioid analgesic in the six months before overdose. Cases were significantly more likely ($p<0.05$) than controls to have knee injuries (67.3% vs. 9.1%), cancer (6.9% vs. 1.4%), depression (19.8% vs. 9.9%), a bipolar or psychotic disorder (9.9% vs. 2.4%), a positive Charlson comorbidity score (25.7% vs. 18.6% for a score of 1 and 26.7% vs. 7.5% for a score of ≥2), and receipt of a benzodiazepine (31.7% vs. 10.3%) or muscle relaxant (5.9% vs. 1.6%). After adjusting for Charlson comorbidity score, the only opioid use pattern strongly associated with overdose was receiving a benzodiazepine within one month of injury (odds ratio [OR]=3.9, 95% CI 1.75-8.52)

while the maximum received dose of morphine milligram equivalents received within one month of injury was weakly associated (OR=1.03, 95% CI 1.01-1.05). After surviving a nonfatal overdose, over half of cases (57.4%, n=58) received another prescription opioid within six months, and ten cases (9.9%) had subsequent nonfatal and/or fatal overdoses.

Conclusion This study provides a detailed description of the clinical and prescribing characteristics of opioid overdose by injured workers and sheds light on the complex relationship between opioid prescribing and overdose as well as what happens after overdose. Although most cases overdosed on prescription opioids, cases tended to have no prescription history prior to overdose or have a prescription history but not have any records for prescriptions within a month of overdose. Charlson comorbidity score confounded associations between opioid use and overdose except for benzodiazepine use.

Background

Opioid overdoses have increased in Tennessee (TN) every year since 2009 and are now the leading cause of accidental death in the state. In 2016, the TN mortality rate due to opioid overdoses was 24.5 per 100,000 (Tennessee Department of Health, Data Dashboard). In 2014, the overall United States opioid overdose mortality rate was 14.7 per 100,000. In TN and nationally, overdose rates are highest among people who are working aged, or 15-64 years old (Centers for Disease Control and Prevention, 2015).

In the general U.S. population, males, middle-aged adults, people living in rural areas, and Whites are more likely to fatally overdose on prescription painkillers than females, children, older adults, people living in urban areas, and Blacks or Hispanics (Rudd et al., 2016) . In a 2014 study of the National Inpatient Sample, urban residents were more likely to have a nonfatal overdose than rural residents (Centers for Disease Control and Prevention, 2011; Mosher, Zhou, Thurman, Sarrazin, & Ohl, 2017). Workers tend to have different characteristics and behaviors from the general population, however, and there may be uncertainty in applying risk factors observed in other groups to them (Dembe et al., 2012). Among people who had an opioid-related death in Utah, WC claimants were more likely than people in the overall population to have less education, have depression or anxiety, and use tobacco, alcohol, or other drugs, but less likely to use medications recreationally (Cheng, Sauer, Johnson, Porucznik, & Hegmann, 2013) or to use an unprescribed opioid (Fulton-Kehoe, Garg, Turner, Bauer, Sullivan et al., 2013).

In recent years, studies have shifted to opioid prescribing as a risk factor for overdose, and high opioid use by injured workers in TN (Durand, Krishnaswami, Nechuta, Hurwitz, & McPheeters, 2018) raises concerns. Dosage is one of the most well explored risk factors for overdose, with 100 mean daily morphine milligram equivalents (MMEs) commonly used as a threshold in prescribing guidelines (Tennessee Department of Health, 2014). Compared to receiving less than 20 mean daily MMEs, 100 mean daily MMEs has been linked to higher risk of overdose in the national Veteran Administration population (risk ratio [RR] = 4.1, 95% CI 2.6-6.5) (Zedler, Zie, Wang, Joyce, Vick et al., 2014) and in the general TN population (odds ratio [OR]=11.2, 95% CI 8.3-15.1) (Baumblatt et al., 2014). However, doses as low as 50 MMEs per day have been linked to increased odds of overdose in Colorado Medicaid beneficiaries (OR=1.99, 95% CI 1.51-2.61 compared to receiving less than 50 MMEs per day) (Dilokthornsakul, Moore, Campbell, Lodge, Traugott et al., 2016) and researchers point out that no dose is "safe" (Coyle, Pratt, Ocran-Appiah, Secora, Kornegay et al., 2017).

While dosage appears to be an important factor, it does not entirely explain the relationship between opioid use and overdose. Other high-risk patterns are emerging in the literature, including visiting multiple prescribers and dispensers (also called multiple provider episodes or doctor shopping), using more potent opioids, and using benzodiazepines combined with opioids (Bohnert, Logan, Ganoczy, & Dowell, 2016; Dilokthornsakul et al., 2016) A study of the overall state population by the TN Department of Health in 2014 found greatly increased odds of fatal overdose from visiting 4 or more prescribers (OR=6.5, 95% CI 4.4-8.3) and 4 or more pharmacies (OR=6.0, 95% CI 4.4-8.3) even after dosage was controlled for (Baumblatt et al., 2014).

In Washington WC claimants, more potent schedule II opioids and long-acting opioids appear more frequently in overdose cases than less potent schedule II and IV opioids and shorter-acting opioids (Franklin, Mai, Wickizer, Turner, Fulton-Kehoe et al., 2005; Fulton-Kehoe et al., 2013). In the Veterans Health Administration population, long-acting opioids are associated with greater risk of overdose (hazard ratio [HR] = 2.3), especially when given before trying other therapies (HR = 5.3) (Miller, Barber, Leatherman, Fonda, Hermos et al., 2015). The Veterans Administration population also shows an increased risk of overdose from concurrent receipt of opioids and benzodiazepines (HR = 3.9), which increases as benzodiazepine dosage increases

(Park, Lin, Hosanagar, Kogowski, Paige et al., 2016; Park, Saitz, Ganoczy, Ilgen, & Bohnert, 2015).

These studies' findings suggest that changes to opioid prescribing may be an opportunity to lower opioid-related overdoses in injured workers. Additionally, a recent qualitative study demonstrated optimistic bias, or an individual's belief that their risk of a particular outcome is lower than others in a similar risk group, amongst prescription opioid users (Frank, Mateu-Gelabert, Guarino, Bennett, Wendel et al., 2015), highlighting the importance of controlling opioid access at the prescriber and dispenser levels rather than depending on patients to self-regulate. A recent review has highlighted the connection between prescribing and overdose and called for better characterization of populations taking opioids in order to describe risk factors in greater detail (Park et al., 2016).

Several demographic characteristics and high-risk prescribing patterns have been linked to increased risk of overdose in WC claimants, Medicaid beneficiaries, and the Veterans' Administration population in other states, but research is scarce on the rate of overdose and other opioid use risk factors for overdose in injured workers and no research has been published for this population in TN. Previous studies may also have had insufficient follow up time: one study on WC claimants found that two-thirds of opioid poisonings in this population occurred over a year after the claim was opened (Fulton-Kehoe et al., 2013). This study will follow injured workers for three years and triangulate three large data sources to quantify the frequency and timing of opioid overdoses in injured workers, describe the relationship between prescribing and overdose, and identify demographic and prescription risk factors for overdose, with the following research questions and hypotheses:

RQ 3.1: How do the incidence rates of nonfatal opioid-involved overdose amongst injured workers compare to the incidence rates in the general population of Tennessee?

Hypothesis: Opioid-involved overdoses are less common in injured workers than in the general population (incidence rate ratios <1).

RQ 3.2: What are the associations of type of injury, early initiation of opioid therapy, prior history of opioid use, long-acting opioids, cash payment, combined opioid and benzodiazepine use, and multiple provider episodes with the odds of nonfatal overdose amongst injured workers with one or more opioid prescriptions?

Hypothesis: More traumatic injuries, early initiation of opioid therapy, prior history of opioid use, long-acting opioids, cash payment, combined opioid and benzodiazepine use, and multiple provider episodes are associated with nonfatal overdose (OR>1).

RQ 3.3: Is mean daily morphine milligram equivalents (MME) a mediator in the associations between type of injury, early initiation of opioid therapy, prior history of opioid use, long-acting opioids, cash payment, combined opioid and benzodiazepine use, and multiple provider episodes and the odds of nonfatal overdose amongst injured workers with one or more opioid prescriptions?

Hypothesis: Mean daily MME partially mediates the associations between more traumatic injuries, early initiation of opioid therapy, prior history of opioid use, long-acting opioids, cash payment, combined opioid and benzodiazepine use, and multiple provider episodes and the odds of nonfatal overdose (MME is associated with overdose with OR>1 and ORs of other variables decrease but do not reach null after the inclusion of MME in the model).

Methods

Data sources and linking

In this nested case-control study, cases and controls were sampled from a retrospective cohort of injured workers in TN. Eligibility was reporting only one injury to TN WC, reporting a physical injury, having complete name, date of birth, and sex information on the WC record, and being 15-99 years old at the time of injury. Worker names and dates of birth were standardized and cleaned to remove prefixes, suffixes, and titles and separate multiple names into separate fields (i.e. FirstName, FirstName2, etc.). Workers were linked to their prescription history in the CSMD by deterministic matching on any first name, any last name, and date of birth as in the first study. Workers were additionally linked to their hospitalization and emergency room visits in HDDS and death certificate in Vital Statistics by deterministic matching on social security number. No workers had missing social security number. Prescription records, hospitalizations, and deaths were tracked for two years after injury.

Case and control selection

Injured workers who had a record of an emergency department visit or hospitalization (both referred to hereafter as hospitalizations) for a nonfatal opioid-involved overdose during the three year follow up period after injury were defined as cases. Overdose was defined using ICD-9 and ICD-10 codes: ICD-9 codes 965.02, 965.09, E850.1, E850.2 and ICD-10 codes T40.2, T40.3, T40.4 for prescription opioids, ICD-9 codes 965.01, E850.0 and ICD-10 code T40.1 for heroin, and ICD-9 code 965.00 and ICD-10 code T40.0 for opium (Centers for Disease Control and Prevention Prescription Drug Overdose Team, 2013). Overdoses were considered to be nonfatal if the patient was not deceased at the time of discharge or transfer. The case's overdose date was the date of the first overdose that occurred during follow-up period.

Controls were matched to cases on sex, age ± 1 year, and overdose status. To begin matching, a control pool of all eligible controls was assembled for each case. Cases were ordered so that those with smaller control pools were matched first, and then simple random sampling was used to match five controls to each case. A 5:1 ratio was chosen to allow for 82% power to detect an odds ratio of 2.5 or greater at $\alpha=0.05$ without reusing controls for more than one case. After being matched, that control was withdrawn from the control pools of all other cases so that each control was only matched to one case. The control index date was the date of the matched case's overdose. Controls did not have a nonfatal overdose during the study period and were alive at the time of their index date.

Covariates

Age at the time of injury, sex, type of injury, part of body injured, and address were obtained from WC records. County of residence was obtained by geocoding from address, and residence was categorized as urban (belonging to one of TN's six metro regions) or rural (not in a metro region) based on TN Department of Health classifications (Tennessee Department of Health, Local and regional health departments). Marital status and industry were considered as demographic covariates, but were dropped from analyses when high missing values (45% for marital status and 97% for industry) were found.

Variables for opioid use in the six months before overdose or index date and the month after injury were obtained from the CSMD and were measured in the six months before overdose or index date as well as the month after injury. Variables included maximum dose in morphine milligram equivalents (MME), receiving a long-acting opioid, visiting ≥2 prescribers or ≥2 dispensers for opioids (6 months before overdose or index date, only), paying for an opioid with cash, receiving an opioid indicated for medically assisted treatment (MAT), and receiving a benzodiazepine. Opioids were included if they were for schedule II, III, or IV analgesics, and not dispensed from a veterinary or Veterans Affairs pharmacy to restrict prescriptions to a human, nonmilitary population. Receiving an opioid indicated for MAT was correlated with having a hospitalization for a substance use disorder, so the MAT flag was incorporated into the substance use hospitalization variable.

The maximum dose in MMEs was included to measure the received dose of prescription opioids. Receipt of a long-acting opioid and receipt of a benzodiazepine were included due to the direct biological link between these variables and overdose: long-acting opioids stay in the body longer and increase the risk of overdose if another opioid is taken before the first dose has left the body (Braden, Russo, Fan, Edlund, Martin et al., 2010; Miller et al., 2015) and benzodiazepines depress respiration, especially in combination with opioids (Jann, Kennedy, & Lopez, 2014; Park et al., 2015). Visiting multiple prescribers and dispensers is included as a measure of high healthcare usage. Paying for an opioid with cash is included as a measure of doctor shopping. Receiving an opioid indicated for medically assisted treatment is a measure of an opioid use disorder. Receipt of muscle relaxants and stimulants in the six months before overdose or index date were measured to assess prescribing of controlled substances for other medical conditions close to overdose.

Hospitalization and comorbidity variables were taken from HDDS. In addition to overdoses, ICD-9 and ICD-10 codes were used to identify hospitalizations and emergency department visits involving cancer, substance use disorders, anxiety disorders, depressive disorders, and bipolar or psychotic disorders (see Appendix 3, Table S3.1 for ICD codes). The Charlson Comorbidity Index, a 19-category weighted measure, was used to assign a composite comorbidity score (Quan, Sundararajan, Halfon, Fong, Burnand et al., 2005).

Statistical analysis

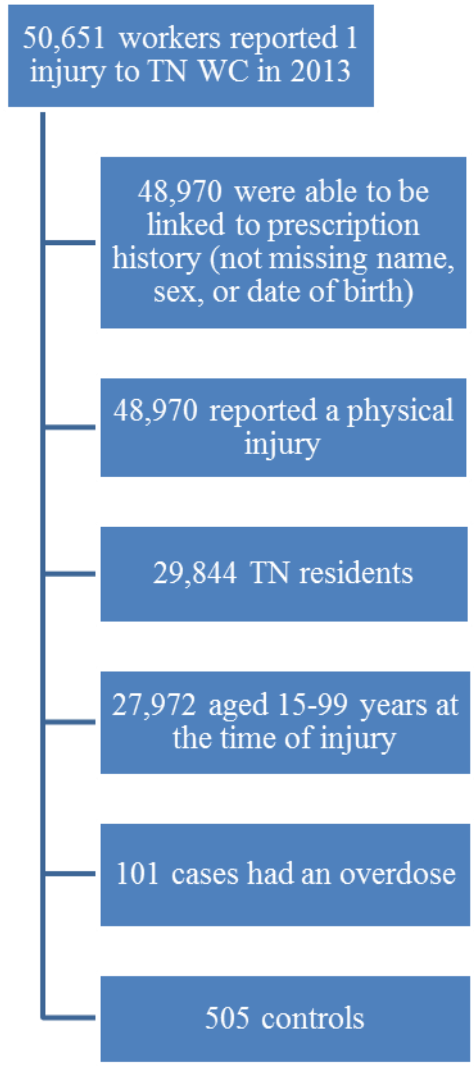
Among cases, type of overdose and prescription history prior to overdose was described with frequencies, percentages, means, and standard deviations (SD). To compare demographic, injury, and prescription risk factors between cases and controls, the two groups were compared with frequencies, percentages, means, standard deviations, t-tests, chi square test (where cell sizes >5), Fisher’s exact test (where cell sizes ≤5). Statistical significance was defined in t-tests, chi square tests, and Fisher’s exact tests as $p<0.05$. Conditional logistic regression was used to calculate matched odds ratios (ORs) in bivariable models and in multivariable models while controlling for demographic characteristics, injury characteristics, and Charlson Comorbidity Score. An analysis of MME as a potential mediator was planned, but MME was very weakly associated with overdose and the study did not have enough statistical power to detect low odds ratios. Instead, other hospitalizations occurring during the study period were identified and described by age group to shed light on common morbidities in injured workers.

This study was approved by the Institutional Review Boards at the Tennessee Department of Health and University of Hawaii. SAS 9.4 was used for all analyses.

Results

The retrospective cohort included 50,651 injured workers who reported one injury to TN WC in 2013. Among these, 48,970 reported a physical injury and were able to be linked to their prescription history, 29,844 were TN residents, and 29,972 were 15-99 years old. These injured workers were matched to 323,873 hospital and emergency room visits, and 114 nonfatal overdoses among 101 workers were identified. The 101 cases were matched with 505 controls for a total sample size of 606 (Figure 3.1).

Figure 3.1: Study population flowchart



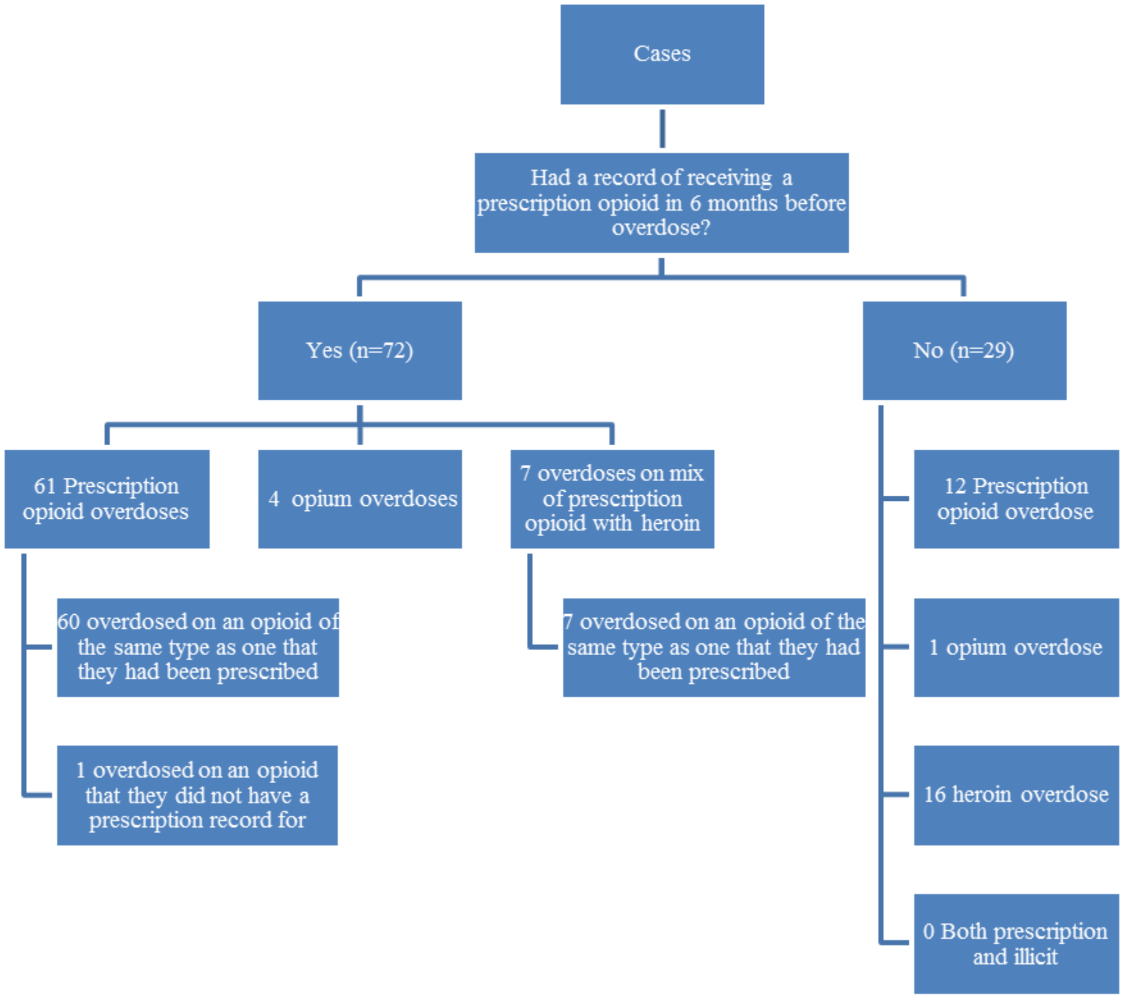
Among workers who overdosed, 72.3% (n=72) overdosed on prescription opioids, 10.9% (n=11) on heroin, 9.9% (n=10) on opium, and 7.0% (n=7) on both prescription opioids and heroin (Figure 3.2). Among prescription opioid overdoses, 9 (11.3%) overdoses identified methadone. Half (n=5) of the opium overdoses included medical procedures (3 dental work, 2 surgery) as co-diagnoses. The most common co-diagnoses for overdoses were acute respiratory failure (33.7%, n=34), toxic encephalopathy (21.8%, n=22) and cerebral edema (8.9%, n=9). The mean amount of time between injury and overdose was 1.8 years ± 1.1 SD.

Cases ranged in age from 18.1-73.6 years (mean 39.0 ± 12.64 SD) and controls ranged from 17.5-74.5 years (mean 39.0 ± 12.58 SD). Cases and controls were both 50.5% female. Cases were more likely than controls to have knee injuries (67.3% vs. 9.1%), cancer (6.9% vs. 1.4%), a substance use disorder (48.5% vs. 29.7%), depression (19.8% vs. 9.9%), bipolar/psychotic disorder (9.9% vs. 2.4%), a positive Charlson comorbidity score (25.7% vs. 18.6% for a score of 1 and 26.7% vs. 7.5% for a score of ≥2), a history of benzodiazepine prescriptions (31.7 vs. 10.3), and a history of muscle relaxant prescriptions (5.9% vs. 1.6%). Type of injury did not differ statistically between cases and controls, with strains, sprains, or tears being the most common (36.6% cases and 40.6% controls), followed by contusions (17.8% cases vs. 17.2% controls) and lacerations (13.9% cases and 12.1% controls) (Table 3.1).

Table 3.1: Comparison of demographic and clinical characteristics between nonfatal opioid overdose cases and controls (N=606)				
	Cases (n=101)		Controls (n=505)	
Characteristic	n	%	n	%
Type of injury				
Other	32	31.7	152	30.1
Strain, sprain, or tear	37	36.6	205	40.6
Contusion	18	17.8	87	17.2
Laceration	14	13.9	61	12.1
Part of body injured				
Other *	13	12.9	348	68.9
Lower back	12	11.9	62	12.3
Finger(s)	8	7.9	49	9.7
Knee *	68	67.3	46	9.1
Region				
Rural	60	59.4	330	65.4
Urban	41	40.6	175	34.6
Comorbidities during 3 year follow-up				
Cancer*	7	6.9	7	1.4
Substance use disorder (SUD)*	49	48.5	150	29.7
Anxiety disorder	14	13.9	62	12.3
Depression*	20	19.8	50	9.9
Bipolar/psychotic disorder*	10	9.9	12	2.4
Charlson comorbidity score during 3 year follow-up				
0*	48	47.5	373	73.9
1*	26	25.7	94	18.6
≥2*	27	26.7	38	7.5
Receipt of other drugs in 6 months before index date				
Benzodiazepine*	32	31.7	52	10.3
Muscle relaxant*	6	5.9	8	1.6
Stimulant	2	2.0	13	2.6
* p<0.05				

Only 56 cases (55.4%) had a record of an opioid prescription within one month of overdose, 64 (64.6%) had a record within three months, and 72 (71.3%) had a record within six months. Among 72 cases who had a record for a prescription opioid within six months of overdose, 67 (66.3%) overdosed on a prescription opioid that was the same type as one that they had been prescribed, including seven who overdosed on a mix of a prescribed opioid and heroin. One worker overdosed on a prescription opioid that they did not have a prescription record for, and 12 workers overdosed on prescription opioids without having any history of having received any opioid legally within six months. An additional four workers overdosed on opium and had a corresponding prescription for opium (Figure 3.2).

Figure 3.2: Overdose type by prescription history



Among cases that had a prescription history in the six months prior to overdose, the mean of the largest daily dose received was 86.7 MMEs ± 60.27 SD and the mean of the largest day's supply received was 32.1 ± 23.09 SD days. Over half of cases with a prescription record visited ≥2 prescribers (n=43) or ≥2 dispensers (n=37) for opioids, a quarter received a long-acting opioid (n=18), and a third paid for an opioid with cash (n=24). Thirty-two received a benzodiazepine, a significantly greater proportion than that of controls (31.7% vs. 10.5%) (Table 3.2).

Table 3.2: Estimated associations (odds ratios [ORs] and 95% confidence intervals [CIs] of demographic characteristics and type of injury with having an opioid-related overdose within 2 years of injury in injured workers who reported one injury to TN Workers' Compensation 2013-2015 (N=606): Results from conditional logistic regression analyses.

Opioid use pattern	Cases (n=101)		Controls (n=505)		Unadjusted OR (95% CI)	Adjusted† matched OR (95% CI)
	n	%	n	%		
Opioid analgesic use pattern in 6 months before overdose or index date	72	71.3	0	0.0	Not included	Not included
Max MME received mean (SD),	86.7	60.27	0.0	0.00	Not included	Not included
Days' supply received (SD)	32.1	23.09	0.0	0.00	Not included	Not included
Received a long-acting opioid	18	17.8	0	0.0	Not included	Not included
Visited ≥2 prescribers for opioids	43	42.6	0	0.0	Not included	Not included
Visited ≥2 dispensers for opioids	37	36.6	0	0.0	Not included	Not included
Paid for an opioid with cash	24	23.8	0	0.0	Not included	Not included
Received benzodiazepine*	32	31.7	53	10.5	Not included	Not included
Opioid use in the month after injury*	56	55.5	199	39.4	2.1 (1.33-3.28)	Not included
Early receipt of opioid (≤1 week after injury)	34	33.7	156	30.9	1.2 (0.74-1.85)	1.02 (1.00-1.04)
Max MME received mean (SD), units=20*	61.9	62.50	38.7	28.95	1.02 (1.01-1.04)	1.03 (1.01-1.05)*
Days' supply received (SD), units=7*	9.6	12.4	3.8	7.33	1.01 (1.01-1.03)	1.9 (0.19-19.19)
Received a long-acting opioid *	10	9.9	7	1.4	8.1 (2.94-22.47)	1.0 (0.30-3.07)
Paid for an opioid with cash*	13	12.9	34	6.7	2.2 (1.08-4.42)	5.5 (0.87-35.21)
Received benzodiazepine*	15	14.9	13	2.6	8.2 (3.42-19.52)	3.9 (1.75-8.52)*

Definitions: TN=Tennessee; OR=odds ratio; CI=confidence interval; SD=standard deviation; MME=morphine milligram equivalents

* $p<0.05$

† Adjusted odds ratios control for Charlson comorbidity score and receipt of an opioid in the six months before overdose or index date

Because no controls received an opioid analgesic in the 6 months before their index date, the month after injury was chosen as the time frame for measuring prescriptions for the multivariable analysis. Cases had significantly more opioid use in the month after injury (33.7% vs. 30.9%, left out of the multivariable to avoid confounding with other opioid variables) than controls. In bivariable models, overdose was associated with receiving a long-acting opioid (OR=8.1, 95% CI 2.94-22.47), paying for an opioid with cash (OR=2.2, 95% CI 1.08-4.42), and receiving a benzodiazepine (OR=8.2, 95% CI 3.42-19.52) while day's supply (OR=1.01, 95% CI 1.01-1.03 for every increase in 7 days' supply) and the maximum received daily MME (OR=1.02, 95% CI 1.01-1.04 for every increase in 20 MME) were weakly associated. After adjusting for Charlson comorbidity score, associations were no longer significant except for daily MME (OR=1.03, 95% CI 1.01-1.05 for every increase in 20 MME) and benzodiazepines (OR=3.9, 95% CI 1.75-8.52). When MME was classified as a dichotomous variable with values ≥100 MME or <100 MME, it was no longer associated with overdose. Paying for an opioid with cash was not associated.

After surviving a nonfatal overdose, 58 cases had a record of receiving a prescription opioid within six months after injury. This included 54 cases who had a prescription record in the month before injury. All but six cases (n=52) received an opioid of the same type that they had been prescribed before, and only three cases had decreased dosage after overdose (mean -11.7 MMEs ± 10.23 SD). The remaining 49 cases continued receiving the same type and dosage of opioid as they had received before overdose.

Although only the first overdose was analyzed, 8.9% of cases (n=9) had a subsequent overdose during the study period. The mean amount of time between the first and second overdoses was 18.9 weeks ± 20.00 sd. Seven people had two overdoses during the study period, one person had three overdoses, and one person had five overdoses. This person experienced 2 heroin overdoses and 3 prescription opioid overdoses over 11 months.

Nine cases had fatal drug overdoses during the study period (eight had ≥2 nonfatal overdoses before a fatal overdose and one had a single nonfatal overdose before a fatal overdose). Four died from prescription opioids, 1 died from heroin, 2 died from non-opioid narcotics, 1 died from antidepressants, and 1 died from chronic viral hepatitis C and psychoactive substance abuse. Two controls died: 1 from nonrheumatic (aortic) valve stenosis and 1 from acute myocardial infarction. Both controls died after their corresponding case's date of overdose (index date) and were not removed from the study.

In the parent cohort, the most common injuries for 15-29 year olds were abdominal pain (2.8% of hospitalizations), chest pain (2.2%), and urinary tract infection (1.2%). The most common injuries for 30-59 year olds were chest pain (4.5%), abdominal pain, (2.3%), and headache (1.9%). The most common injuries for workers aged 60 years and older were chest pain (3.3%), screening for malignant neoplasms of colon (2.3%), and atherosclerotic heart disease (1.2%) (Supplement Table S3.2)

Discussion

In this case-control study of 27,972 injured workers, 101 workers with a nonfatal overdose were found over a three year follow-up period and almost half of cases (44.6%) did not have a record for an opioid prescription in the month before overdose. The overdose rate appears to be lower than the overdose rate in the overall TN population. The most recently available data show that TN had 7,092 inpatient stays (rate of 107.4 per 100,000 persons) and 13,034 outpatient visits (rate of 197.5 per 100,000 persons) for nonfatal opioid overdoses in 2015 (i.e. over a one year period) (Tennessee Department of Health, Data Dashboard). In the parent cohort of this study, the cumulative incidence of nonfatal overdose was 380 cases per 100,000 persons over a three year period. WC populations in other states show similarly low rates of overdose. In a cohort study of Washington State WC, 92 deaths and 312 adverse events due to opioids were found over six years of observation, although this study was held in 2004-2010 when the opioid epidemic was less severe in all states (Fulton-Kehoe et al., 2013).

Opioid prescribing and hospitalization patterns prior to overdose show three main groups of workers who overdosed: people with a prescription history (including people with cancer, mental health diagnoses, and/or high healthcare usage) and people without a prescription history and possibly involved in drug diversion.

This study supports a link between prescribing and overdose. Risk factors such as higher dose and use of benzodiazepines come as no surprise due to increasing drug toxicity and the combined depressive effect of opioids and benzodiazepines on the cardiovascular system (Chen & Ashburn, 2015). Compared to controls who received virtually no opioids before their index date, prescribing to cases was characterized by dangerously high doses and days' supplies. Among cases with a history of opioid prescriptions before overdose, 40% received a dose over the 90 MME threshold designated by the TN chronic pain guidelines as indicating referral to a pain specialist, and 55% received a days' supply that was over the 30 day legal limit in TN ("Prescription Safety Act of 2012," 2012). Almost all of the cases who had a record for an opioid prescription in the month before overdose received another opioid prescription within six months after overdose. The high post-overdose prescribing in this study has been shown in other populations, such as in a large U.S. health insurer population where 91% of nonfatal overdose patients received another prescribed opioid within two years (Larochelle, Liebschutz, Zhang, Ross-Degnan, & Wharam, 2016). Automatic alerts to prescribers when one of their patients is hospitalized for an overdose (under development by the TN Department of Health) may help alert prescribers when a patient needs increased attention or a change in treatment.

For the nine cases who died of an overdose after surviving a nonfatal overdose, this supports suggestions that the encounter with healthcare that occurs during an overdose is not being effectively utilized as an intervention point (Frazier, Cochran, Lo-Ciganic, Gellad, Gordon et al., 2017). By one recent study's estimate, injection drug users in Vancouver who are brought to the hospital for a nonfatal overdose have 95% higher hazards of having a later fatal overdose than drug users who do not have a documented nonfatal overdose (HR= 1.95, 95% CI 1.17-3.27) (Caudarella, Dong, Milloy, Kerr, Wood et al., 2016), indicating that this is a particularly vulnerable group. Additionally, although HDDS records do not contain enough information to identify the place that an overdose occurred or what circumstances surround it, the five opium overdoses that were accompanied with medical procedure co-diagnoses raise the question of whether these overdoses occurred in medical settings, perhaps through human error during or after procedures. In-hospital opioid overdose have also been noted elsewhere (Cauley, Anderson, Haynes, Menendez, Bateman et al., 2017).

For cases with a prescription history, it is easy to call for a crackdown on prescribers who supply the drugs and regulating prescribing to prevent overdose has been a common approach ("Prescription Safety Act of 2012," 2012), with demonstrated success on a population level (Al Achkar, Grannis, Revere, MacKie, Howard et al., 2018). However, many cases in this study had a prescription history but disappeared from the dataset a few months before overdose. It is unknown what happened to these cases between their last prescription and their date of overdose, especially since many of them overdosed on a prescription opioid, but others have suggested that patients may turn to more dangerous illicit supplies of opioids when they are cut off by their prescribers (Tedesco, Asch, Curtin, Hah, McDonald et al., 2017). Opioids available on illicit markets are often counterfeit or cut with fentanyl, making it difficult to judge their potency before they are consumed (Pergolizzi, LeQuang, Taylor, & Raffa, 2018). Improving naloxone distribution, safe injection sites, and other harm reduction approaches is needed (Rudd et al., 2016), and this study provides support for arguments that access to prescription opioids should be maintained in certain cases of dependence (Compton, Jones, & Baldwin, 2016).

Charlson comorbidity score was a confounder in the association between several opioid use patterns and overdose, suggesting that overall healthcare usage, especially for cancer and mental health diagnoses, is a key variable associated with overdose. This association is repeated in other studies, notably in a recent meta-analysis where drug overdose death in the United States was most strongly associated with a history of substance use disorders (OR=5.24, 95% CI 3.53-7.76) and psychiatric disorders (OR=3.94, 95% CI 3.09-5.01) (Brady, McCauley, & Back, 2016).

This study provides a detailed description of the clinical and prescribing characteristics of opioid overdose by injured workers and sheds light on the complex relationship between opioid prescribing and overdose as well as what happens after overdose. Workers who experienced an opioid overdose often had no prescription history prior to overdose or had a prescription history but no records for prescriptions within a month of overdose. Charlson comorbidity score confounded associations between opioid use and overdose except for benzodiazepine use and MME, which was weakly associated at an OR below that which the study had 80% power to calculate. There was a high rate of repeat overdoses with ten cases (9.9%) suffering a subsequent nonfatal and/or fatal overdose. The results of this study have high applicability to TN but may not be generalizable to other states.

Limitations

Several of the major insurance companies in TN exclude drug overdose hospitalizations from coverage (Liveoak, 2017) so hospitals have an incentive to underreport overdose and it is likely underestimated by using HDDS, a dataset intended for billing, to define cases in this study. Other states have noted suspected overdoses being coded as cardiac arrest in hospital discharge records (Slavova, Bunn, & Talbert, 2014). Chest pain, the most frequent cause of hospitalization in ages 30-59 and 60-99 years old of the parent cohort and the second most frequent in ages 15-29 years, may include some overdose cases that were not captured by the overdose definition. Effect estimates are not expected to be biased as misclassification error for overdoses is nondifferential between opioid use groups. However, effect sizes of opioid use variables, especially MME and days' supply, may be biased towards the null by failing to account for opioids that were obtained through illicit markets. There is particularly concern about opioids on illicit markets being cut with fentanyl, a cheaply manufactured synthetic opioid that is 80 times more powerful than morphine (National Institute on Drug Abuse, 2017).

Survival bias is introduced by excluding controls who died of another cause during the study period and requiring cases to have survived long enough to have an overdose, and is expected to affect odds ratios by causing underestimates. With a long follow up period, results are also more vulnerable to confounding by chronic opioid use. For example, increasing drug tolerance is a side effect of chronic opioid use, so while high doses are characteristic of overdoses in chronic users, the overdose may be more attributable to the introduction of another drug or sudden modulations in substance use rather than the size of the prescribed dose (Glanz, Narwaney, Mueller, Gardner, Calcaterra et al., 2018; Witkiewitz & Vowles, 2018), decreasing the effect size of MME on overdose.

Conclusions

A healthy worker effect was found in injured workers in TN, who had a lower incidence of nonfatal opioid-involved overdose than the overall TN population. Among injured workers who overdosed, most had received a prescription opioid within six months of overdose (compared to 0% of controls). A concerning trend of "disappearing" from the prescription opioid database in the months before overdose was noted, possibly indicating migration to illicit markets when prescriptions can no longer be obtained. Increasing odds of overdose were found with increasing dose received in the month after injury, implying that opioids prescribed after injury may lay the groundwork for future outcomes. Caution is needed in initiating new patients to opioid use and discontinuation of opioid use should be treated thoughtfully, with treatment and harm reduction options available for patients with suspected opioid use disorder.

Chapter 4

A predictive model for injury as a gateway to long-term opioid use: A retrospective cohort study using linked statewide databases in Tennessee.

Abstract

Background Opioids are unsurpassed at treating acute pain, but become increasingly harmful when used for long periods. Injury has been documented as a gateway to opioid use in some populations but not injured workers in Tennessee (TN).

Objective A retrospective cohort study was conducted to evaluate the prevalence of and risk factors for developing long-term opioid use after injury among workers who were opioid-free before injury and reported an injury to the TN Bureau of Workers' Compensation (WC) March 2013 – December 2015.

Methods Injured workers who reported only one injury to TN WC 2013-2015 were identified in WC records and matched to their prescription history in TN's prescription drug monitoring program. Injured workers who were opioid-free at the time of injury and between the ages of 15 and 99 years were included in analyses. Long-term opioid use was defined as receiving opioids on greater than or equal to 45 days in the 90 days after injury, and associations between long-term use and demographic, injury, and opioid use variables were calculated with bivariable and multivariable unconditional logistic regression yielding odds ratios (ORs) and 95% confidence intervals (CIs). A derivation model (including workers injured March 2, 2013 – December 31, 2014) was used in model development and a validation model (including workers injured January 1, 2015 – December 31, 2015) was used in testing the model's predictive ability.

Results The final sample was 46,399 injured workers who were opioid-free at the time of injury and received opioids after injury, 1,843 (4%) of whom became long-term opioid users after injury. The odds of long-term opioid use increased 30% when 5-9 days' supply was given in the initial prescription compared to <5 day's supply (95% CI 1.18-1.47). However, long-term use was most strongly associated with receiving ≥20 days' supply in the initial opioid prescription (odds ratio [OR]=32.2, 95% confidence interval [CI] 28.91-35.85), followed by receiving a long acting opioid within 30 days of injury (OR=6.6, 95% CI 5.34-8.08), visiting ≥3 prescribers (OR=6.9, 95% CI 5.82-8.23), and visiting ≥3 pharmacies (OR=6.0, 95% CI 4.67-7.70) after part of body injured, overlapping opioid and benzodiazepine prescriptions, and maximum MME received within 30 days of injury were controlled for.

Conclusion Injury is a gateway to long-term opioid use in a vulnerable set of injured workers. Risk for developing long-term use appears to be more tied to opioid prescribing than demographic characteristics.

Background

Long-term opioid use is about more than the number of days on which someone takes an opioid: it is about the threshold at which the costs of opioid use begin to outweigh the advantages. While opioids are unsurpassed at treating acute pain, evidence increasingly indicates that opioids are not effective at managing chronic pain (Turk, 2002). In some studies, long-term opioid use is associated with increased or equivalent reports of pain compared to baseline, possibly due to a developing tolerance to the opioid (Eriksen et al., 2006; Trang et al., 2015) or increased pain sensitivity (Angst & Clark, 2006; Mao, Sung, Ji, & Lim, 2002). Most concerning, however, is that long-term opioid use has been documented as a precursor to the use of heroin and other illicit opioids, possibly because of illicit drugs' greater affordability and availability (Palamar et al., 2016). In injured workers, chronic opioid therapy is associated with higher healthcare costs (Johnston, Alexander, Masters, Mardekian, Semel et al., 2016) and poor return to work rates (Anderson, Haas, Percy, Woods, Ahn et al., 2016).

The most rigorous recent research on long-term opioid use was summarized in a systematic review for a National Institutes of Health workshop. This review found no evidence of effectiveness for opioid use of greater than three months, but increased risk of harms including overdose, drug abuse, fractures, myocardial infarction, and use of drugs used to treat sexual dysfunction (Chou, Turner, Devine, Hansen, Sullivan et al., 2015) and is supported by an earlier review showing that evidence linking long-term opioid use to improvements in pain and function is weak (Manchikanti, Vallejo, Manchikanti, Benyamin, Datta et al., 2011). The workshop review may have concluded even greater harms from long-term opioid use had it included non-controlled studies, which show that long-term opioid use is associated with dependence and addiction, poor self-rated health, inactivity, unemployment, higher healthcare utilization, and poor self-rated quality of life (Eriksen et al., 2006). Some non-opioid treatments, in contrast, have been shown to be effective in managing chronic pain without the side effects associated with analgesic treatment (Gatchel & Okifuji, 2006) and with the same or better pain outcomes as opioids (Eriksen et al., 2006).

In previous research, injury has been documented as a gateway to opioid use in athletes (Cottler, Ben Abdallah, Cummings, Barr, Banks et al., 2011; Veliz, Epstein-Ngo, Meier, Ross-Durow, McCabe et al., 2014) and people who have experienced car crashes (Berecki-Gisolf, Hassani-Mahmooei, Collie, & McClure, 2016). Surgery has similarly been documented as a gateway to long-term opioid use (Alam, Gomes, & Zheng, 2012; Johnson, Chung, Zhong, Shauver, Engelsbe et al., 2016a) but also identified as an opportunity for opioid weaning (Inacio et al., 2016). Research on risk factors shows strong evidence that pre-existing substance use and mental health disorders increase the likelihood of developing long-term opioid use (odds ratio [OR]=1.46, 95% confidence interval [CI] 1.12-1.91 for mental health diagnoses and (OR=2.34, 95% CI 1.75-3.14), for substance abuse vs. no diagnosis in Veterans Affairs patients), (Brummett, Waljee, Goesling, Moser, Lin et al., 2017; Sun, Darnall, Baker, & Mackey, 2016).

Evidence on demographic risk factors, however, has not reached consensus and at times is directly contradictory. For example, in two studies of opioid use after surgery in previously opioid-free patients, one found that males and people older than 50 years were at highest risk of long-term opioid use while the other showed females and younger age groups at highest risk (Johnson et al., 2016a; Sun et al., 2016). In veterans, which may be a more comparable population to injured workers, males, younger age groups, and people with mental health disorders are most vulnerable to developing long-term opioid use (Edlund, Steffick, Hudson, Harris, & Sullivan, 2007), and in Oregon, rural residents have higher odds of long-term opioid use than urban residents (OR=1.37, 95 % CI 1.34-1.41) (Deyo, Hallvik, Hildebran, Marino, Dexter et al., 2017).

In workers, patterns of prescribing soon after injury have been linked to later long-term opioid use (Fritz, King, & McAdams-Marx, 2017). A recent MMWR article pointed to the days' supply of the initial prescription as the single largest factor in later long-term opioid use after dose was controlled for (Shah, Hayes, & Martin, 2017). Two other cohort studies of injured workers with back injuries found that higher daily dose, measured in morphine milligram equivalents (MME), in the first three months after injury is strongly predictive of long-term opioid use after baseline pain and injury severity is controlled for (Franklin et al., 2009; Webster et al., 2007). Links between long-term opioid use and dose escalation have also been noted (Cifuentes et al., 2010; Franklin et al., 2009).

There are several definitions for long-term opioid use. The Centers for Disease Control and Prevention (CDC) defines long-term opioid use as receiving opioids on most days for greater than or equal to 3 months (Dowell et al., 2016). In contrast, previous research on injured workers, including WC claimants, has defined long-term opioid use as receiving an opioid in each quarter for a year after injury (Franklin et al., 2009), receiving greater than or equal to five opioid prescriptions from 30 to 730 days after injury (Webster et al., 2007), and receiving an opioid for greater than three months (Heins, Feldman, Bodycombe, Wegener, & Castillo, 2016).

The CDC's definition, referred here as "3-month continuous use," is consistent with definitions of chronic pain in the Tennessee Chronic Pain Guidelines and CDC Chronic Pain Guidelines, which define chronic pain as pain lasting longer than 90 days (Dowell et al., 2016; Tennessee Department of Health, 2014). However, this definition may have less clinical applicability in a WC setting than in the surgical settings for which it was derived. In a surgical setting, the extent of tissue damage is controlled and anti-infection measures are taken to minimize recovery time. In a WC setting, the extent of tissue damage is uncontrolled and often involves longer-healing injuries such as tears and breakages. Additionally, infection and the introduction of foreign bodies to a wound may additionally increase recovery time, and surgery scheduled in the weeks and months after an injury may additionally increase the time that a patient spends on opioids. In this context, we anticipate that a 90-day threshold after injury will be too conservative and will capture fewer cases than a threshold further after injury.

The definitions used in occupational medicine research are unstandardized but are often longer than 3 months. These definitions accommodate the protracted treatment of acute pain after injury and encapsulate the continuity of therapy which is an essential feature of long-term opioid use. However, a common definition is needed to allow comparability between studies. This study will evaluate the appropriateness of different definitions and construct a predictive model for long-term opioid use in previously opioid-free injured workers with the following research questions and hypotheses:

RQ 4.1: What percentage of injured workers are opioid-free at the time of their injury?

Hypothesis: More than half (>50%) of injured workers are opioid-free at the time of their injury.

RQ 4.2: Among injured workers who were opioid-free at the time of injury but who received an opioid in the month after injury, does a three or four month follow-up period capture more cases of long-term opioid use?

Hypothesis: Measuring opioid use as receiving an opioid on most days in a four month period captures more cases than measuring opioid use as receiving an opioid on most days in a three month period.

RQ 4.3: What demographic factors (sex, age, residence area, injury type, and part of body injured) and opioid use patterns (early initiation of opioid therapy, combined opioid and benzodiazepine use, long-acting opioids, higher mean daily MME, higher day's supply, multiple prescribers and pharmacies, cash payment) predict a previously opioid-free injured worker developing long-term opioid use after injury?

Hypothesis: Female sex, middle age group, residence in east TN, more traumatic injuries, early initiation of opioid therapy, long-acting opioids, higher mean daily MME, using multiple prescribers and pharmacies, and cash payment predict long-term opioid use (ORs>1). Part of body injured does not predict long-term opioid use (OR=1).

Methods

We used data from TN WC and CSMD records, cleaned and linked as described in Chapters 2 and 3. To allow for prescriptions to be measured from 60 days prior to injury through 180 days after injury, prescription records were accessed from January 1, 2013 – April 30, 2016 and WC records were accessed from March 2, 2013 – December 31, 2015.

Study population

The main study population was injured workers who were opioid-free at the time of injury, defined as having no record of receiving an opioid prescription for 60 days prior to injury. As in Study 1, eligibility was having complete name, date of birth, and sex data in the WC record to enable matching to the CSMD, having a physical injury, and being aged 15-99 years. To avoid the confounding effect of multiple injuries, eligibility was restricted to injured workers who reported no more than one injury during the study period. Opioid prescriptions were included if they were class "opioid" and schedule 2-4, and excluded if they were indicated for medication-assisted therapy, or dispensed by a veterinarian or Veterans Affairs pharmacy. Opioid prescriptions were measured from 60 days prior to each person's date of injury (earliest January

1, 2013) to 120 days after each person's injury (latest April 30, 2016). Injured workers who received opioids after injury but were opioid-free before injury were selected for analysis.

Demographics and clinical information

Age at the time of injury, sex, marital status, type of injury, part of body injured, and residence type were selected from WC records based on availability, completeness, and previous literature. Type of injury was categorized into strains, sprains, and tears, fractures, and other based on frequency and association with long-term opioid use. Part of body injured was lower back, finger(s), knee, and other based on frequency and association with long-term use. Residence type was identified from zip codes and classified as urban (residing in a county with one of TN's 6 largest cities) or rural (residing in one of the other 89 counties).

After linking to the CSMD, opioids and benzodiazepines received in the 60 days prior to injury were flagged. Post-injury opioids were flagged for long-acting opioids, cash payment, and overlapping opioid and benzodiazepine prescriptions, maximum daily dose in morphine milligram equivalents (MMEs), and maximum days' supply were noted. Each prescription flag, dose, and days' supply was completed for 7, 30, and 90 days after injury. Additionally, the dose in MMEs and days' supply of the first prescription were identified, receiving a benzodiazepine in the 60 days prior to injury was flagged, and the number of prescribers and pharmacies visited within the first 90 days of injury were calculated. For workers with ties for the first prescription received, MME and days' supply were summed for all eligible opioid prescriptions received on that day. Opioid use variables were chosen based on availability.

Primary outcome

The primary outcome of this study was long-term opioid use. Long-term opioid use was measured with prescription days, i.e. the days' supply of an opioid added to the date on which the opioid was received. For example, a prescription received on January 1 with 10 days' supply has prescription days on January 1 – 10. For overlapping prescriptions, prescription days were only counted once. Two definitions were assessed: 1) the CDC definition of receiving an opioid on most days for a 90 day period, measured as ≥45 prescription days in the 90 days after injury, and 2) a novel definition of receiving an opioid on most days in a 120 day period, measured as ≥60 prescription days in the 120 days after injury, to account for opioids received after a delay.

Statistical analysis

The sample of opioid-free injured workers was split so that people with injuries occurring in 2013 and 2014 were used for the derivation model and the last year was kept separate for use in validating the derivation model. Frequencies and percentages were used to describe the distribution of demographic and clinical characteristics in the population. Opioid-free injured workers were compared with non opioid-free injured workers.

The two definitions of long-term opioid use were compared by calculating the number of injured workers identified as cases by each time frame, and the definition that captured the greatest number of cases was chosen for use in analyses. To identify associations with long-term opioid use, we used chi squared test to compare sample percentages and unconditional logistic regression to compute unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs).

To build the derivation model, demographic and clinical variables that showed an association (CIs do not overlap 1) with long-term opioid use in unadjusted models were selected for inclusion in a multivariable model. Where different time frames had been considered for opioid-use measures (e.g. long-acting opioid received within 7 vs. 30 vs. 90 days of injury), the time-frame with the highest associated point estimate was included in the starting multivariable model. The multivariable model was refined with feedback from ROC curves to maximize model fit, systematically changing variables and time frames to maximize ROC curve. After the best-fitting derivation model had been achieved, the model parameters were applied to the validation group to form the validation model, and the validation model fit and associations were compared to the derivation model. SAS 9.4 was used for all analyses. This study was approved by the Institutional Review Boards at the Tennessee Department of Health and University of Hawaii.

Results

Demographics and opioid-free status

Of 205,798 injured workers who reported one injury to TN WC, 128,885 met eligibility criteria, and 58,278 received opioids in the 90 days after injury. Among injured workers who received opioids, 79.6% (n=46,399) were opioid-free at the time of injury (Table 4.1). Most (82.1%, n=38,080) received their first opioid within a month of injury, but 17.9% received their first opioid 30-90 days after injury. Approximately 4% of the opioid-free group (n=1,834) became long-term users, and 653 (1.7%) had sustained opioid use throughout the 90 days after injury (i.e. received an opioid on most days for each of the three months).

Compared to injured workers with a recent history of opioid use before injury, opioid-free injured workers were more likely to be less than 35 years old (34.8% vs. 24.0% in the derivation model), male (57.8% vs. 48.8%), injured with fractures (9.0% vs. 5.5%), injured on the fingers (10.2% vs. 7.5%), and from urban areas (38.2% vs. 31.7%) (Table 4.2).

Table 4.1: Sample selection methodology and description of sample size, by model		
Study selection criteria	Derivation model (March 2, 2013- December 31, 2014)	Validation model (January 1, 2015 – December 31, 2015)
Injured workers who reported only one injury to TN Workers' Compensation 2013-2015	133,542	72,256
Injury type indicates a physical injury	132,112	71,672
Able to be linked to prescription history (not missing name, sex, or date of birth)	132,112	71,672
15-99 years of age	83,853	45,032
Received an opioid within 90 days of injury	38,646	19,632
Opioid-free at the time of injury and included in analysis	30,608	15,791
Definitions: TN=Tennessee		

Table 4.2: Demographic and clinical characteristics of injured workers who reported one injury to TN Workers' Compensation from March 2 2013 – December 31, 2015 and received opioids within 90 days of injury (N=58,278), by model and opioid-free status at time of injury

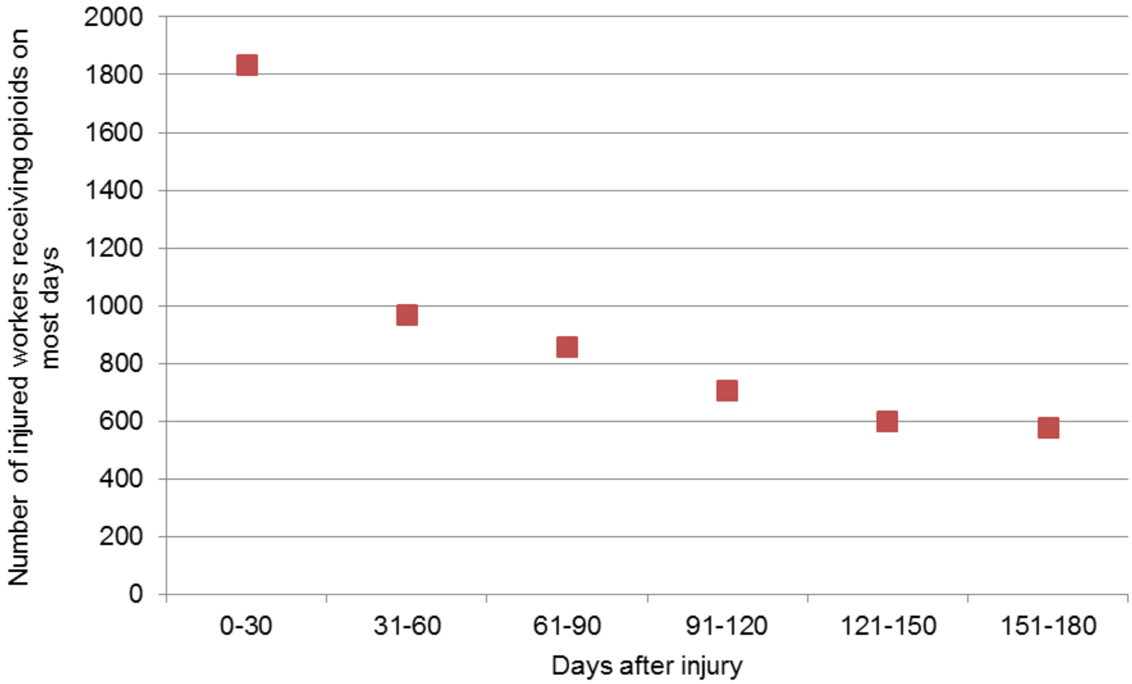
	Derivation Model				Validation model			
	Opioid free				Opioid free			
	No (n=8038)		Yes (n=30608)		No (n=3841)		Yes (n=15791)	
Characteristic	n	%	n	%	n	%	n	%
Age (years)								
15 – 34	1925	24.0	10663	34.8	839	21.8	5550	35.2
35-54	4278	53.2	14121	46.1	2041	53.1	7074	44.8
55-99	1835	22.8	5824	19.0	961	25.0	3167	20.1
Sex								
Female	4117	51.2	12921	42.2	2015	52.5	6618	41.9
Male	3921	48.8	17687	57.8	1826	47.5	9173	58.1
Marital status								
Single	188	2.3	694	2.3	88	2.3	303	1.9
Married	2403	29.9	8749	28.6	1079	28.1	4240	26.9
Widowed, separated, or divorced*	1796	22.3	6561	21.4	1012	26.4	3841	24.3
Missing / unknown	3651	45.4	14604	47.7	1662	43.3	7407	46.9
Type of injury								
Strain, sprain, or tear	3193	39.7	11994	39.2	1480	38.5	5839	37.0
Fracture	439	5.5	2755	9.0	214	5.6	1596	10.1
Other	4406	54.8	15859	51.8	2147	55.9	8356	52.9
Part of body injured								
Lower back	965	12.0	3723	12.2	458	11.9	1791	11.3
Finger(s)	603	7.5	3118	10.2	279	7.3	1524	9.7
Knee	635	7.9	2465	8.1	309	8.0	1246	7.9
Other	5835	72.6	21302	69.6	2795	72.8	11230	71.1
Residence type								
Rural	5490	68.3	18927	61.8	2627	68.4	9847	62.4
Urban	2548	31.7	11681	38.2	1214	31.6	5944	37.6

Definitions: Opioid-free at the time of injury=no record of opioid use in the 60 days prior to injury; Long-term use=receiving an opioid on most days in the 90 day period after injury; TN=Tennessee
*All comparisons between non opioid free and opioid free injured workers were significantly different at $p<0.05$

Long-term opioid use

Of the two definitions of long-term opioid use that were tested, the definition of receiving an opioid for most days in a 90 day period captured the most cases (1,834 vs 1,612 captured by the definition of receiving an opioid for most days in a 120 day period) and was selected for use throughout remaining analyses (Appendix 4, Table S4.1). The number of injured workers who received an opioid on most days decreased sharply between the first and second month after injury, decreased between 31 and 150 days after injury with a slight slowing in the rate of decrease in the 61-90 day period, and plateaued around 150-180 days after injury (Chart 4.1). Expanding the definition to receiving an opioid for most days in a 120 day lost 824 people whose opioid use waned after 90 days, even as it added 684 cases who did not have enough opioid use in the first 90 days to qualify for the 90-day definition (Appendix 4, Table S4.1).

Figure 4.1: Number of injured workers receiving opioids on most days, by 30-day time period after injury among workers who were opioid-free at the time of injury and received opioids within 90 days of injury (n=46,399)



The derivation model included 30,608 injured workers and the validation model included 15,789. Because of small cell size, categories for days' supply and daily MME were collapsed and marital status was not included in the models.

The derivation model and validation model found similar effects for all variables except that finger injuries were not significantly associated (CI overlapped 1) in the validation model and receiving ≥20 days' supply in the initial opioid prescription was associated at reduced magnitude in the validation model (OR=18.4, 95% CI 15.95-21.23) compared to the derivation model (OR=32.2 95% CI 28.91-35.85) (Table 4.3). Long-term opioid use was most strongly predicted by receiving ≥20 days' supply in the initial opioid prescription, followed by receiving a long acting opioid within 30 days of injury (OR=6.6, 95% CI 5.34-8.08), visiting ≥3 prescribers (OR=6.9, 95% CI 5.82-8.23), visiting ≥3 pharmacies (OR=6.0, 95% CI 4.67-7.70) after part of body injured, overlapping opioid and benzodiazepine prescriptions, and maximum MME received within 30 days of injury were controlled for. Cash payment was not associated with long-term use. Lower odds of long-term opioid use were found in finger injuries compared to other body parts (OR=0.7, 95% CI 0.60-0.82), urban residence compared to rural residence (OR=0.6, 95% CI 0.58-0.69), and receipt of an opioid within 7 days of injury compared with not receiving an opioid within 7 days (OR=0.5, 95% CI 0.45-0.53). See Appendix 4, Table S4.2 for cell sizes and Appendix 4, Table S4.3 for derivation model unadjusted odds ratios.

Although long-term opioid use was associated with sex in bivariable analyses (OR=1.4, 95% CI 1.26-1.60 for males vs. females), sex had an inconsequential effect on derivation model fit and its inclusion did not change associations with other variables. Ages 55-99 years were associated with long-term use in bivariable models (OR=1.9, 95% CI 1.63-2.27) but the association decreased (to OR=1.2, 95% CI 1.11-1.43) in multivariable models. The derivation model fit improved when age was removed while associations between other variables and opioid use were unchanged. Although type of injury was associated with long-term opioid use in bivariable models (OR=1.14, 95% CI 1.04-1.24 vs. for strains, sprains, and tears vs. "Other" injuries and OR=0.78, 95% CI 0.68-0.90 for fractures vs. "Other" injuries), its inclusion in the derivation model resulted in changing the model fit from 0.895 to 0.896. This was deemed to be an inconsequential change and type of injury was removed from the model for the sake of parsimony. Benzodiazepine use before injury was not included in multivariable models because it was correlated with overlapping opioid and benzodiazepine prescriptions after injury.

Table 4.3: Estimated adjusted associations (odds ratios [ORs] and 95% confidence intervals [CIs] of demographic, injury, and opioid use variables with long-term opioid use after injury in injured workers who reported one injury to TN Workers' Compensation and were opioid-free at the time of injury: Results from unconditional logistic regression analyses.						
	Derivation model (n=30,608; c=0.91)			Validation model (n=15,791; c=0.89)		
	Adjusted† OR	95% CI		Adjusted† OR	95% CI	
Characteristic		lower	upper		lower	upper
Part of body injured						
Other	ref			ref		
Lower back	1.1*	1.02*	1.29	1.4**	1.16	1.59
Finger(s)	0.7**	0.60	0.82	0.8	0.58	2.04
Knee	1.0	0.83	1.11	1.1	0.78	2.30
Residence type						
Urban	ref			ref		
Rural	1.3**	1.26	1.37	1.3**	1.22	1.41
Receipt of an opioid within 7 days of injury	0.5**	0.45	0.53	0.4**	0.36	0.45
Days' supply of first prescription						
<5	ref			ref		
5-9	1.3**	1.18	1.47	1.3**	1.13	1.51
10-19	3.0**	2.60	3.50	2.5**	2.06	3.15
≥20	32.2**	28.91	35.85	18.4**	15.95	21.23
Long-acting opioid within 30 days of injury	6.6**	5.34	8.08	3.4**	2.93	3.95
Overlapping opioid and benzodiazepine prescription days within 30 days of injury	3.9**	3.49	4.34	1.3**	1.13	1.51
Number of prescribers visited for opioids within 90 days of injury						
1	ref			ref		
2	2.1**	1.90	2.33	1.9**	1.69	2.23
≥3	6.9**	5.82	8.23	6.1**	4.80	7.69
Number of pharmacies visited for opioids within 90 days of injury						
1	ref			ref		
2	1.6**	1.47	1.81	1.8**	1.57	2.08
≥3	6.0**	4.67	7.70	3.0**	1.98	4.54
Maximum MME received within 30 days of injury						
<40	ref			ref		
40-99	1.9**	1.77	2.12	2.0**	1.74	2.21
100-159	1.5**	1.26	1.89	1.6**	1.22	2.14
≥160	3.7**	2.74	4.92	3.0**	1.95	4.77

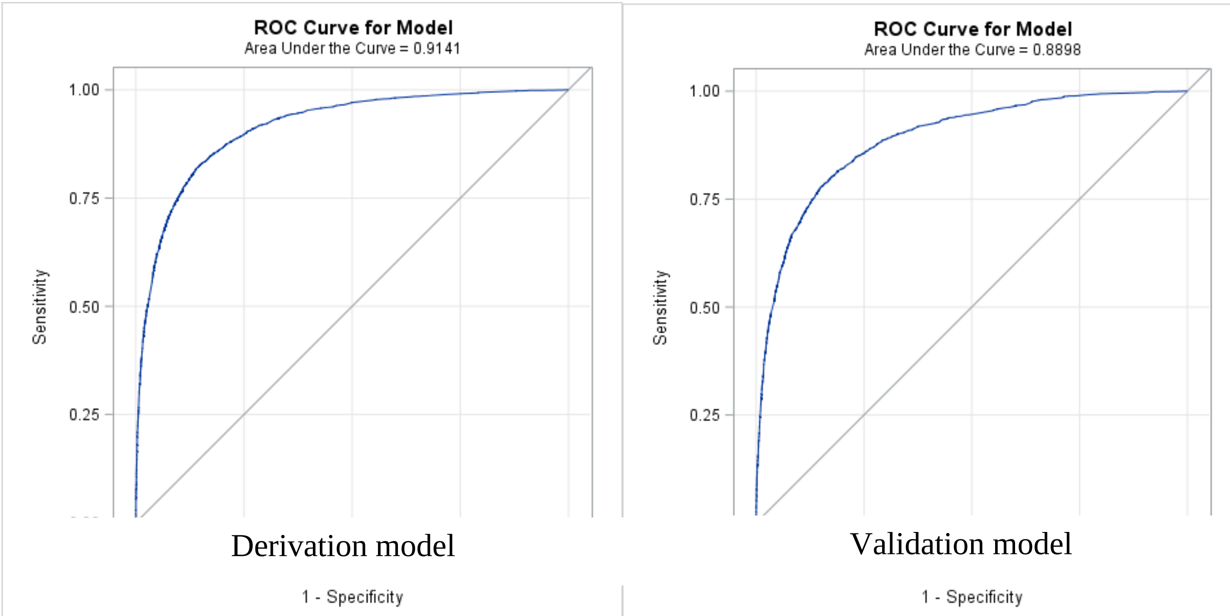
Definitions: Opioid-free at the time of injury=no record of opioid use in the 60 days prior to injury; Long-term use=receiving an opioid on most days in the 90 day period after injury; TN=Tennessee; MME=morphine milligram equivalents

† Adjusted for all variables in table

* p<0.05

** p<0.01

Figure 4.2: Receiver operating characteristic (ROC) curves of the multivariable unconditional logistic regression derivation and validation models.



A sensitivity analysis conducted by restricting the model to people with the most common injury, strains, sprains, and tears, lowered the model fit to 0.885 while associations were unchanged except that receiving a long acting opioid within 30 days of injury in the validation group was higher (OR=15.7, 95% CI 9.33-26.31) than in the full sample validation group (OR= 3.4, 95% CI 2.93-3.95) (Supplement Table S1). However, cell sizes for long-acting opioid use were low in the restricted analysis (n=9 with no long-term use and 58 with long-term use). Additional sensitivity analyses were performed by treating MME and days' supply of the first prescription as continuous variables, but they were found to have non-linear associations with long-term opioid use.

Dose escalation was observed in 23.5% (n=431) of people who became long-term opioid users. The mean increase between the first and third months after injury was 34.04 daily MMEs (standard deviation 45.23, range 0.22 – 1171.43 daily MMEs). Among injured workers who qualified as long-term users in the first 90 days after injury, 31.5% (n=577) were still using opioids on most days 6 months after injury.

Discussion

Defining long-term opioid use as receiving an opioid for most days in a 90-day period captured more cases than using a 120-day period. Since TN law designates 30-day supply as the maximum that can be dispensed ("Prescription Safety Act of 2012," 2012), opioid users had to have received at least two opioid prescriptions over at least two months to surpass 45 prescription days and meet the definition of a long-term user.

Most (79.6%) injured workers who received opioids after injury were opioid-free at the time of injury, and 4% of these became long-term users. One hundred thirty-two of the long-term users received their first opioid more than 30 days after injury, indicating that even people who go a month after injury without any opioid use may still be vulnerable to opioid use or other injuries that may require opioid use. Notably, a third of people who qualified as long-term opioid users in the 90 days after injury continued to use opioids 180 days after injury. Although dose escalation was noted in only a quarter of long-term users, even surpassing 50 MME/day can increase the risk of overdose by 30% (Dowell et al., 2016).

Initial days' supply was more strongly associated with long-term opioid use than MME in bivariable models, and continued to be a strong predictor after MME, demographic variables, and other opioid use patterns were controlled for. Even receiving 5-9 days' supply compared to <5 days increased the odds of long-term opioid use by 30%. Current TN prescribing guidelines set 7 days' supply as a cut point for caution (Tennessee Department of Health, 2014), a threshold which may be too low in light of this study's findings. This finding supports a nationwide study's findings that initial days' supply was the strongest predictor of continued opioid use (Shah et al., 2017). MME was associated with long-term opioid use at a lower magnitude, and this study showed a dose-response relationship between higher opioid doses and higher odds of long-term opioid use similar to that demonstrated in other research (Deyo et al., 2017).

Six opioid use characteristics (days' supply of first prescription, receipt of a long-acting opioid within 30 days of injury, overlapping opioid and benzodiazepine prescription, number of prescribers and pharmacies visited within 90 days of injury, and maximum MME received within 30 days of injury) were associated with long-term opioid use in previously opioid-free injured workers. The strongest associations were receiving ≥20 days' supply in the initial prescription (OR=10.1, 95% CI 8.21-12.47), receiving a long-acting opioid within 30 days of injury (OR=6.6, 95% CI 5.34-8.08), visiting ≥3 prescribers (OR=6.9, 95% CI 5.82-8.23) or ≥3 pharmacies (OR=6.0, 95% CI 4.67-7.70) within 90 days of injury, associations which have been demonstrated in other populations. Injured workers who received an opioid within 7 days of injury had 50% lower odds (95% CI 0.45-0.53) of developing long-term opioid use than workers who received their first opioid more than 7 days after injury, possibly because delayed seeking of care may worsen injuries or treatment may be given for a subsequent, undocumented injury.

This study identified one demographic characteristic (rural residence) associated with long-term use at a similar magnitude to the association demonstrated in a group of Oregon residents (OR=1.4, 95 % CI 1.34-1.41 for rural vs. urban) (Deyo et al., 2017). Associations between sex and long-term opioid use after surgery have been mixed in previous research (Johnson et al., 2016a; Sun et al., 2016), male sex has been shown to be associated with prescription opioid abuse (Rice, White, Birnbaum, Schiller, Brown et al., 2012; A. G. White, Birnbaum, Schiller, Tang, & Katz, 2009), and sex disparities have also been observed in drug treatment programs (Welty, Harrison, Abram, Olson, Aaby et al., 2016) in national samples. This study, however, found no association between sex and long-term opioid use and, unlike the other studies, did not use diagnostic records to define cases. The findings of a sex association in other studies may be the result of diagnostic bias for opioid misuse.

Previously researched associations between age and long-term opioid use have been similarly mixed (Edlund et al., 2007; Johnson, Chung, Zhong, Shauver, Engelsbe et al., 2016b; Sun et al., 2016), and this study found a positive association between middle age groups in bivariable analyses that nonetheless diminished model fit in multivariable analyses. This decrease, and the decrease observed when injury type were added, were likely the result of overfitting where the increase in model fit did not make up for the loss of degrees of freedom. Type of injury was included as a proxy for injury severity, but unchanged associations in the analysis of workers with strains, sprains, and tears indicate that this was not an important factor. Other injury groups may have more of an association, but group sizes were too small to test. Lower back injuries were associated with long-term opioid use.

Addressing injury as a gateway to long-term opioid use is an important step towards curbing the opioid epidemic. Although previous studies have identified risk factors for the development of long-term opioid use, this is the first to comprehensively measure all opioid prescriptions, regardless of insurance or other payer source, for long-term use in injured workers. Additionally, this study measures long-term opioid use through prescription history, capturing more cases than the ICD codes used in previous research. The results of this study have high applicability to TN but may not be generalizable to other states.

Limitations

Survival bias may be present in limiting the study population to people who were opioid-free at the time of injury. That is, people who were more likely to develop long-term opioid use or an opioid use disorder may have already had that outcome before the study began. As a result, this study measures incident cases and does not quantify how widespread long-term use is in this population. Effect measures apply to opioid-naïve injured workers who may develop long-term opioid use, not injured workers who may have long-term opioid use.

Some people may have been classified as opioid-free due to drug diversion, i.e., taking opioids that were not prescribed to them. Misclassification of opioid-naivety may cause someone to be wrongly considered to have developed long-term opioid use after injury when in fact they merely switched their mechanism of obtaining opioids. In considering only new prescriptions, this study also misses opioids and benzodiazepines that people were previously prescribed and take from storage in their own medicine cabinets. Men and people with lower than $50,000 annual income are more likely to be involved in drug diversion, which may mean that these groups are more likely to be misclassified in this study and more likely to be associated with the development of long-term opioid use (Jones, Paulozzi, & Mack, 2014). However, research in other states shows that adults generally start on prescription opioids and then move to drug diversion when their legal supply is constrained, not vice-versa (Tedesco et al., 2017). If workers in this study tend to move from diverted drug sources to prescription sources, then the prevalence of opioid-free status would be overestimated and effect measures for opioid use variables would likely be underestimates. If workers tend to move from prescription drug sources to diverted sources, then the prevalence of long-term use would be underestimated and effect measures for opioid use variables would likely be underestimates. In using the CSMD to identify and measure opioid use this study substantially improves the accuracy of estimates made with WC records alone by including opioids paid for with cash and other forms of payment, regardless of claim approval.

Due to limitations of the data sources, this study is not able to include several major predictors of opioid use disorders: mental illness, other drug use, and race and ethnicity. Due to a healthy worker effect, mental illness and other drug use may not cause much confounding in the model (Cheng et al., 2013). The effect of race and ethnicity may be a larger concern: studies in other states show that Whites tend to be prescribed opioids more frequently (Morden, Munson, Colla, Skinner, Bynum et al., 2014) and are more likely to overdose on opioids than Blacks (Centers for Disease Control and Prevention, 2011) but non-Whites are more likely to be recipients of WC (Atlas et al., 2007). Stratifying by race/ethnicity would improve the precision of estimates and provide more granular detail towards understanding the trends in the epidemic and directing resources towards groups that would benefit from increased attention, and may decrease the association between residence type and opioid use as Whites are more concentrated in rural areas of TN.

Conclusion

This is the first study to examine long-term opioid use in Tennessee, and among the first nationally to use a prescription drug monitoring program to measure long-term opioid use in injured workers with prescription records instead of clinical records. The development of long-term opioid use is rare in opioid-free injured workers, but opioid use tends to be pernicious once established. Injury is a gateway to long-term opioid use in a vulnerable set of injured workers. Developing long-term use appears to be more tied to opioid prescribing than demographic characteristics, especially days' supply. This finding suggests that something about the habit or normalization of opioid use early in treatment sets the stage for long-term use, and that care should be taken to providing only a "necessary and sufficient" opioid course, if at all.

Chapter 5

Commentary on TN's response to the opioid epidemic through the lens of these findings

These studies provide a previously unknown picture of the prevalence, patterns, and outcomes of opioid use by injured workers in TN, and are among the first nationally to use a prescription drug monitoring program to measure opioid use in injured workers. This research used a novel cleaning and linkage approach to connecting statewide databases for monitoring of opioid use on a population level, which may be of interest to other states working with prescription drug monitoring programs using sources of big data that lack a unique identifier. The results presented here provide data-driven recommendations for vulnerable groups within the injured worker population as well as commentary on how opioid use in injured workers compares to the overall population of TN. These studies are being finalized and shared with stakeholders shortly after TN's governor proposed a budget with an aggressive new plan to target the opioid epidemic with funding of $30 million (Tennessee Office of the Governor, January 22, 2018).

These findings show that while opioid use is high in TN workers after injury, high-risk opioid use patterns, overdose, and long-term use are low. In light of these findings, injured workers overall are not a population of particular concern for opioid use. Subgroups of injured workers receiving overlapping benzodiazepine and opioid prescriptions and prescriptions with long days' supply, and chronic users who have had their prescription opioid supply constrained are at high risk, as are those in the U.S. population at large who have these characteristics (Rudd et al., 2016). If the healthy worker effect observed for opioid use and opioid outcomes extends to high-risk prescribing patterns, then the subgroups described above may be more prevalent in the general population than they are in injured workers.

TN has made progress in reducing opioid prescribing in recent years (Tennessee Department of Health, Data Dashboard, also see Appendix 5: Overview of opioid-related policy milestones) and these studies reflect general adherence to guidelines for dose and days' supply in injured workers. However, the high percentage of injured workers receiving benzodiazepines with opioids is cause for concern. TN chronic pain guidelines states that "benzodiazepines should be generally avoided in combination with chronic therapy" and advises that "when the opioid dose reaches 120 [MMEs] and the benzodiazepines are being used for mental health purposes, the provider shall refer to a mental health professional to assess the necessity of benzodiazepine medication" (Tennessee Department of Health, 2014). The prescribing guidelines approach concurrent use as chronic opioid use with an introduction of benzodiazepines, but these studies found that chronic benzodiazepine use with the introduction of acute opioids was more common. Attention towards this pathway may be warranted.

TN's Bureau of Workers' Compensation has contributed to controls on prescribing through a drug formulary implemented in 2016. The formulary is more driven towards substituting lower cost opioids for higher cost ones than demanding non-opioid therapies, although it does encourage the use of short-acting formulas over long-acting. The TN Department of Labor also offers a discount on WC insurance to employers who are certified as drug free workplaces, achieved through employer-sponsored drug testing (including opioids with a cutoff level of >2000 ng/ml in urine) and a zero tolerance policy towards drug use in the workplace (Tennessee Department of Labor). Drug testing is associated with fewer workplace injuries (Pidd & Roche, 2014) but may also exclude people with a drug use problem from participation in the workforce (Pinsker, 2015), reinforcing the healthy worker effect.

TN's Medicaid program has taken another approach with a pharmacy "lock in" program, where suspected doctor shoppers are only permitted to fill prescriptions at one pharmacy. Lock-in programs in other states have shown that they decrease the amount of opioids that people receive through Medicaid, which appears to be a success until bias from migration to opioids paid for with cash and private insurance is considered (Dreyer, Michalski, & Williams, 2015; Kesselheim, Huybrechts, Choudhry, Fulchino, Isaman et al., 2015). Lock-in programs may also be contributing to increases in overdoses of non-prescribed opioids as opioid users turn to illicit markets when their legal supplies are constrained. Controls on prescribing are important to prevent new cases of opioid dependence, but evidence increasingly shows that this is not an effective solution for people who are already addicted.

On a state population level, recent legislation has aimed at getting opioid users into treatment. A "Good Samaritan Law" enacted in 2014 gives civil immunity to people who administer naloxone (an overdose reversal drug) to another in good faith. The law also grants immunity from being charged with drug crimes to people who call 911 for an overdose or seek treatment for drug addiction. Despite these measures, overdose data show that heroin use is increasing, which leads to concerns about the spread of blood borne illness such as the 2016 HIV outbreak in Scott County Indiana fueled by injected heroin use. Syringe exchange programs were legalized in TN in 2017 (T.C.A. § 68-1-136, 2017), but only two such programs have been established statewide since: one at a nonprofit in Nashville and one at the local Department of Health in Memphis (Detox local). Having exchanges at all Departments of Health throughout the state would increase their accessibility, make them convenient to maintain and track their usage, and serve as points of contact in case of an outbreak of blood borne illness. Other harm reduction approaches such as safe injection sites are completely absent from TN.

Governor Haslam's budget focuses on expanding access to narcotics treatment programs, which are currently inaccessible to much of the state's population. As of spring 2018, only ten counties out of 95 had narcotic treatment clinics (Tennessee Department of Mental Health, 2018). In contrast, TN had 185 registered pain clinics in 2016 (Tennessee Department of Health, 2017). Even if treatment is accessible and affordable, however, pharmaceutical opioid treatment is not very effective at producing long-term abstinence. A randomized controlled trial of eight community-based opioid treatment centers in the U.S. found relapse rates of 57% for partial opioid agonist buprenorphine/naloxone to 65% for opioid antagonist naltrexone (Lee, Nunes, Novo, Bachrach, Bailey et al., 2018) within 24 weeks alone. Another study of outcomes following treatment at a residential detox clinic in Ireland found 91% of patients relapsed at some point after treatment, and 59% of these relapsed within the first week after discharge (Smyth, Barry, Keenan, & Ducray, 2010). Policy makers and funders should recognize that opioid use disorder, like other forms of addiction, is a chronic and relapsing disease. Improving access to treatment is an important part of providing people with agency and opportunities for healing, but relapses and non-use of treatment are facts of addiction that should be acknowledged and planned for.

An overdose reversal drug, opioid-agonist naloxone that goes by the brand name Narcan, has been available and carried by medics for decades but only recently come into mainstream use. Police officers began carrying naloxone in their kits beginning in 2016 in Knoxville and 2017 in Nashville (Allison, 2017; Naloxone Community Collaborative, 2018). Knoxville began tracking naloxone administration by first responders in 2017, and found that 1,200 doses of the lifesaving drug were given by medics, fire fighters, and police officers in the first year (Naloxone Community Collaborative, 2018). Naloxone is available as an over-the-counter drug and is held in several large chain pharmacies, but its high cost diminishes its accessibility to lay persons. When paid for in cash, naloxone costs $20-$40 per dose (Crowe, 2016) and multiple doses are often needed to stop a single overdose (Faul, Lurie, Kinsman, Dailey, Crabaugh et al., 2017). Subsidizing and distributing naloxone may be an effective way for TN to apply funds towards lives saved.

The studies in this dissertation support an argument that prescribing controls are working in TN, highlighting the importance of primary prevention. No silver bullet has been found for secondary and tertiary prevention of opioid substance use disorder and its effects, either for injured workers or the overall state population. On a population level, current best practices have limited effectiveness. TN has room to update prescribing guidelines with regards to overlapping opioid and benzodiazepine use and to improve evidence-based solutions outside of prescribing guidelines towards fighting the epidemic and preventing lost lives and livelihoods.

Appendix 1 – Forms supplying datasets used in this research

First Report of Injury Form – Workers' Compensation dataset

TENNESSEE DEPARTMENT OF LABOR AND WORKFORCE DEVELOPMENT
EMPLOYER'S FIRST REPORT OF WORK INJURY OR ILLNESS

CLAIMS ADM/CARRIER

JURISDICTION CLAIM # (STATE FILE #)
CLAIMS ADM CLAIM # (INSURER CLAIM #)
OSHA LOG CASE #
NAME OF INSURANCE CARRIER
CLAIMS ADMIN FIRM NAME (IF DIFFERENT FROM CARRIER)
CLAIMS ADJUSTER NAME
CLAIM HANDLING OFFICE ADDRESS LINE 1 AND LINE 2

CLAIM TYPE CODE
☐ MED ONLY
☐ INDEMNITY
☐ BECAME LOST TIME
☐ BECAME MED ONLY
☐ NOTIFY ONLY
☐ TRANSFER
CARRIER FEIN
FEIN OF CLMS ADM
CLMS ADJ PHONE #

THE USE OF THIS FORM IS REQUIRED UNDER THE PROVISIONS OF THE TENNESSEE WORKERS' COMPENSATION LAW AND MUST BE COMPLETED AND FILED WITH YOUR INSURANCE CARRIER IMMEDIATELY AFTER NOTICE OF INJURY.

IT IS A CRIME TO KNOWINGLY PROVIDE FALSE, INCOMPLETE OR MISLEADING INFORMATION TO ANY PARTY TO A WORKERS' COMPENSATION TRANSACTION FOR THE PURPOSE OF COMMITTING FRAUD. PENALTIES INCLUDE IMPRISONMENT, FINES AND DENIAL OF INSURANCE BENEFITS.

IF YOU HAVE QUESTIONS, THE STATE NOW HAS A BENEFIT REVIEW SYSTEM WHERE A WORKERS' COMPENSATION SPECIALIST CAN PROVIDE ASSISTANCE. CALL 1-800-332-2667 (TDD).

CITY | STATE | ZIP

EMPLOYER

EMPLOYER NAME | EMPLOYER FEIN | SIC CODE | PHONE NUMBER
EMPLOYER ADDRESS LINE 1 AND LINE 2 | NATURE OF BUSINESS
CITY | STATE | ZIP | INSURED REPORT # | EMPLOYER LOCATION

POLICY

INSURED NAME (PARENT CO. IF DIFFERENT THAN EMPLOYER)
POLICY NUMBER
SELF INSURED? ☐ YES ☐ NO
EFF DATE
EXP DATE

EMPLOYMENT STATUS CODE
☐ FULL TIME/REGULAR
☐ PART TIME
☐ PIECE WORKER
☐ SEASONAL
☐ VOLUNTEER
☐ APPRENTICE FULL TIME
☐ APPRENTICE PART TIME

EMPLOYEE

EMPLOYEE LAST NAME | PHONE INCL AREA CODE
FIRST | MI | DEPARTMENT REGULARLY WORKED
ADRRESS LINE 1 & 2
CITY | STATE | ZIP
SSN | DATE OF BIRTH | DATE OF HIRE

GENDER
☐ MALE
☐ FEMALE
☐ UNKNOWN

OCCUPATION DESCRIPTION

MARITAL STATUS
☐ UNMARRIED, SINGLE, DIVORCED
☐ MARRIED
☐ SEPARATED
☐ UNKNOWN

NCCI CLASS CODE

WAGE

WAGE $
PERIOD ☐ HOURLY ☐ DAILY ☐ WEEKLY ☐ BI-WEEKLY ☐ MONTHLY
NUMBER OF DAYS WORKED PER WEEK
SALARY CONTINUED IN LIEU OF COMPENSATION ☐ YES ☐ NO
FULL WAGES PAID FOR DATE OF INJURY ☐ YES ☐ NO

ACCIDENT/INJURY

DATE OF INJURY
TIME OF INJURY ☐ AM ☐ PM ☐ COULD NOT BE DETERMINED
TIME EMPLOYEE BEGAN WORK ON INJURY DATE ☐ AM ☐ PM
DATE EMPLOYER NOTIFIED OF INJURY
BODY PART AFFECTED CODE
NATURE OF INJURY CODE
CAUSE OF INJURY CODE
DATE CLAIM ADM NOTIFIED OF INJURY
DATE LAST DAY WORKED
DATE DISABILITY BEGAN
RETURN TO WORK DATE (IF APPLICABLE)

HOW INJURY OR ILLNESS OCCURRED. DESCRIBE THE INCIDENT INCLUDING WHAT THE EMPLOYEE WAS DOING JUST BEFORE, THE PART OF THE BODY AFFECTED AND HOW, AND OBJECT OR SUBSTANCE THAT DIRECTLY HARMED THE EMPLOYEE.

DATE OF DEATH (IF APPLICABLE)
DID INJURY/ILLNESS OCCUR ON EMPLOYER'S PREMISES? ☐ YES ☐ NO

IF DEATH CLAIM, GIVE # DEPENDENTS FOR EACH RELATIONSHIP
☐ WIDOW ☐ FATHER ___ SISTER
☐ WIDOWER ___ DAUGHTER ___ BROTHER
☐ MOTHER ___ SON ___ HANDICAPPED CHILD
TOTAL # DEPENDENTS

ADDRESS WHERE INJURY OCCURRED (IF OTHER THAN EMPLOYER'S PREMISES)
CITY | STATE | ZIP
COUNTY OF INJURY

TREATMENT

PHYSICIAN NAME | HOSPITAL OR OFF SITE TREATMENT NAME
ADDRESS LINE 1 AND 2 | ADDRESS LINE 1 AND 2
CITY | STATE | ZIP | CITY | STATE | ZIP

INITIAL TREATMENT
☐ NO MEDICAL TREATMENT
☐ MINOR BY EMPLOYER
☐ MINOR BY CLINIC/HOSPITAL
☐ HOSPITALIZED > 24 HRS
☐ EMERGENCY CARE
☐ FUTURE MAJOR MEDICAL/LOST TIME ANTICIPATED

OTHER

DATE PREPARED | PREPARER'S NAME & TITLE | PREPARER'S COMPANY NAME | PHONE NUMBER

LB-0021 (REV. 12/07) RDA 10183

State of Tennessee Certificate of Death Form – Vital Statistics death certificate dataset

Data Collection Form

TENNESSEE DEPARTMENT OF HEALTH
CERTIFICATE OF DEATH
STATE FILE NUMBER

DECEDENT

1. **DECEDENT'S LEGAL NAME** (First, Middle, Last, Suffix)
2. **SEX**
3. **DATE OF DEATH** (Month, Day, Year)
4. **TIME OF DEATH** (Approx.)
5a. **AGE-Last Birthday** (Years)
5b. **UNDER 1 YEAR** Months / Days
5c. **UNDER 1 DAY** Hours / Minutes
6. **DATE OF BIRTH** (Month, Day, Year)
7. **BIRTHPLACE** (City and State or Foreign Country)

TYPE/PRINT IN PERMANENT BLACK INK

8a. **PLACE OF DEATH** (Check only one)
IF DEATH OCCURRED IN A HOSPITAL: ☐ Inpatient ☐ ER/Outpatient ☐ DOA
IF DEATH OCCURRED SOMEWHERE OTHER THAN A HOSPITAL: ☐ Hospice facility ☐ Nursing home/Long term care facility ☐ Decedent's home ☐ Other residence ☐ Other (Specify) ____________
8b. **FACILITY NAME** (If not institution, give street and number)
8c. **CITY OR TOWN**
8d. **COUNTY OF DEATH**

NAME OF DECEDENT (For use by Physician or Institution)

9. **MARITAL STATUS** ☐ Married ☐ Married, but separated ☐ Widowed ☐ Divorced ☐ Never married ☐ Unknown
10. **SURVIVING SPOUSE** (If wife, give name prior to first marriage)
11a. **DECEDENT'S USUAL OCCUPATION**
11b. **KIND OF BUSINESS/INDUSTRY**
12. **SOCIAL SECURITY NUMBER**
13a. **RESIDENCE-STATE OR FOREIGN COUNTRY**
13b. **COUNTY**
13c. **CITY OR TOWN**
13d. **STREET AND NUMBER**
13e. **INSIDE CITY LIMITS** ☐ Yes ☐ No
13f. **ZIP CODE**
14. **WAS DECEDENT EVER IN US ARMED FORCES?** ☐ Yes ☐ No

15. **DECEDENT'S EDUCATION** (Check the box that best describes the highest degree or level of school completed at the time of death)
☐ 8th grade or less
☐ 9th – 12th grade; no diploma
☐ High school graduate or GED completed
☐ Some college credit, but no degree
☐ Associate degree (e.g., AA, AS)
☐ Bachelor's degree (e.g., BA, AB, BS)
☐ Master's degree (e.g. MA,MS,MEng,MEd,MSW,MBA)
☐ Doctorate (e.g., PhD, EdD) or Professional degree (e.g., MD, DDS, DVM, LLB, JD)
☐ Unknown

16. **DECEDENT OF HISPANIC ORIGIN?** (Check the box that best describes whether the decedent is Spanish/Hispanic/Latino. Check the "No" box if decedent is not Spanish/Hispanic/Latino)
☐ No, not Spanish/Hispanic/Latino
☐ Yes, Mexican, Mexican American, Chicano
☐ Yes, Puerto Rican
☐ Yes, Cuban
☐ Yes, other Spanish/Hispanic/Latino (Specify) ____________
☐ Unknown

17. **DECEDENT'S RACE** (Check one or more races to indicate what the decedent considered himself or herself to be)
☐ White
☐ Black or African American
☐ American Indian or Alaska Native (Name of the enrolled or principal tribe) ____________
☐ Asian Indian
☐ Chinese
☐ Filipino
☐ Japanese
☐ Korean
☐ Vietnamese
☐ Other Asian (Specify) ____________
☐ Native Hawaiian
☐ Guamanian or Chamorro
☐ Samoan
☐ Other Pacific Islander (Specify) ____________
☐ Other (Specify) ____________
☐ Unknown

PARENTS

18. **FATHER'S NAME** (First, Middle, Last)
19. **MOTHER'S NAME PRIOR TO FIRST MARRIAGE** (First, Middle, Last)
20a. **INFORMANT'S NAME**
20b. **RELATIONSHIP TO DECEDENT**
20c. **MAILING ADDRESS** (Street and Number, City, State, Zip Code)

DISPOSITION

21a. **METHOD OF DISPOSITION** ☐ Burial ☐ Cremation ☐ Donation ☐ Entombment ☐ Removal from State ☐ Other (Specify) ____________
21b. **PLACE OF DISPOSITION** (Name of cemetery, crematory, other place)
21c. **LOCATION** - City or Town and State
22a. **SIGNATURE OF FUNERAL DIRECTOR** ▶
22b. **LICENSE NUMBER**
22c. **SIGNATURE OF EMBALMER** ▶
22d. **LICENSE NUMBER**
23a. **NAME AND ADDRESS OF FUNERAL HOME**
23b. **LICENSE NUMBER OF FUNERAL HOME**

REGISTRAR

24. **REGISTRAR'S SIGNATURE** ▶
25. **DATE FILED** (Month, Day, Year)

CERTIFIER

26. **CERTIFIER** (Check only one):
26a. ☐ **PHYSICIAN** - To the best of my knowledge, death occurred at the date and place, and due to the cause(s) and manner stated.
26b. ☐ **MEDICAL EXAMINER** - On the basis of examination, and/or investigation, in my opinion, death occurred at the date, and place, and due to the cause(s) and manner stated.

PHYSICIAN OR MEDICAL EXAMINER EXECUTING CAUSE OF DEATH MUST COMPLETE AND SIGN WITHIN 48 HOURS.

27a. **SIGNATURE OF CERTIFIER** ▶
27b. **LICENSE NUMBER**
27c. **DATE SIGNED** (Month, Day, Year)
27d. **NAME AND ADDRESS**

MEDICAL CERTIFICATION

28. **PART I.** Enter the chain of events (diseases, injuries, or complications) that directly caused the death. DO NOT enter terminal events such as cardiac arrest, respiratory arrest, or ventricular fibrillation without showing the etiology. Enter only one cause on a line.

Approximate interval: Onset to death

IMMEDIATE CAUSE (Final disease or condition resulting in death) → a. ____________
Due to (or as a consequence of)
Sequentially list conditions, if any, leading to the cause listed on line a. Enter the **UNDERLYING CAUSE** (disease or injury that initiated the events resulting in death) **LAST**
b. ____________
Due to (or as a consequence of):
c. ____________
Due to (or as a consequence of):
d. ____________

PART II. Other significant conditions contributing to death but not resulting in the underlying cause given in PART I.
29a. **WAS AN AUTOPSY PERFORMED?** ☐ Yes ☐ No
29b. **WERE AUTOPSY FINDINGS AVAILABLE TO COMPLETE THE CAUSE OF DEATH?** ☐ Yes ☐ No

30. **MANNER OF DEATH** ☐ Natural ☐ Homicide ☐ Accident ☐ Pending Investigation ☐ Suicide ☐ Could not be determined
31. **DID TOBACCO USE CONTRIBUTE TO DEATH?** ☐ Yes ☐ Probably ☐ No ☐ Unknown
32. **IF FEMALE:** ☐ Not pregnant within past year ☐ Pregnant at time of death ☐ Not pregnant, but pregnant within 42 days of death ☐ Not pregnant, but pregnant 43 days to 1 year before death ☐ Unknown if pregnant within the past year
33. **IF TRANSPORTATION INJURY, SPECIFY:** ☐ Driver/Operator ☐ Passenger ☐ Pedestrian ☐ Other (Specify) ____________
34a. **DATE OF INJURY** (Month, Day, Year)
34b. **TIME OF INJURY**
34c. **INJURY AT WORK?** ☐ Yes ☐ No
34d. **PLACE OF INJURY** – at home, farm, street, factory, office, building, etc. (Specify)
34e. **DESCRIBE HOW INJURY OCCURRED**
34f. **LOCATION OF INJURY** (Street and Number, City or Town, State)

PH-1659 (Rev. 10/2011) RDA 1399

SAMPLE

Appendix 2 – Supplemental tables from Chapter 2 Prescription opioid use by injured workers: A descriptive study using linked statewide databases in Tennessee.

Table S2.1: Workers who reported one injury to TN Workers' Compensation 2013-2015 and received an opioid within 1 week, 1 month, and 6 months of injury by year and opioid-free status at time of injury (N=172,256). P value from Cochran-Armitage test for trend.

Year	Number of injured workers	Received opioids within 1 week	Received opioids within 1 month	Received opioids within 6 months
Opioid-free at the time of injury (n=154,636)				
	N	n (%)	n (%)	n (%)
2013	51589	11298 (21.9)	13824 (26.8)	15525 (30.1)
2014	51340	11118 (21.7)	13495 (26.3)	15161 (29.5)
2015	51707	10623 (20.5)	12952 (25.1)	14544 (28.1)
p-value for trend (2 sided)	<0.001	<0.001	<0.001	<0.001
Not opioid-free at the time of injury (n=17,620)				
Year	Number of injured workers	Received opioids within 1 week	Received opioids within 1 month	Received opioids within 6 months
	N	n (%)	n (%)	n (%)
2013	6174	2244 (36.4)	3891 (63.0)	4290 (69.5)
2014	5914	2124 (35.9)	3720 (62.9)	4110 (69.5)
2015	5532	1814 (32.8)	3291 (59.5)	3652 (66.0)
p-value for trend (2 sided)	<0.001	<0.001	<0.001	<0.001

Definitions: TN=Tennessee; Opioid free = no record for filling an opioid prescription in the 60 days prior to injury; Not opioid free = has a record for filling an opioid prescription in the 60 days prior to injury

Table S2.2: North American Industry Classification System (NAICS) code frequency in injured workers who reported one injury compared to those who reported 2 or more injuries to TN Workers' Compensation 2013-2015 (N=172,256)		
	Received opioid analgesics in 6 months	
Industry	No (n=114,974) n (%)	Yes (n=57,282) n (%)
Wholesale or Retail Trade	8835 (7.7)	5352 (9.3)
Health Care and Social Assistance	9053 (7.9)	3194 (5.6)
Manufacturing	5998 (5.2)	3167 (5.5)
Administrative and Support and Waste Manage	4355 (3.8)	2265 (4.0)
Accommodation and Food Services	3372 (2.9)	1724 (3.0)
Public Administration	3754 (3.3)	1314 (2.3)
Transportation and Warehousing	2397 (2.1)	1420 (2.5)
Construction	2069 (1.8)	1531 (2.7)
Professional, Scientific, and Technical Services	1987 (1.7)	1192 (2.1)
Finance and Insurance	2003 (1.8)	834 (1.5)
Information	1294 (1.1)	688 (1.2)
Real Estate, Rental, and Leasing	1118 (1.0)	740 (1.3)
Other Services	971 (0.8)	499 0.9)
Management of Companies and Enterprises	828 (0.7)	421 (0.7)
Educational Services	662 (0.6)	174 (0.3)
Arts, Entertainment, and Recreation	511 (0.4)	243 (0.4)
Utilities	378 (0.3)	246 (0.4)
Mining	193 (0.2)	129 (0.2)
Agriculture, Forestry, Fishing, and Hunting	129 (0.1)	74 (0.1)
Missing or not in NAICS code list	65067 (56.6)	32075 (56.0)
Definitions: TN=Tennessee; NAICS=North American Industry Classification		

Table S2.3: Most frequently injured parts of body injured for injured workers in TN Workers' Compensation Claims Database (2013-2015) who had only one injury during the study period by prescription opioid use within 6 months of injury (N=172,256)						
			Opioid prescription filled within 6 months of injury			
Type of injury	Part of body	Workers with one injury (N=172,256)	No (n=114,974) n (%)		Yes (n=57,282) n (%)	
Other injury (n=103,492)			n	%	n	%
	Finger(s)	16343	11758	16.0	4585	15.2
	Hand	10258	7419	10.1	2839	9.4
	Multiple body parts	9235	5968	8.1	3267	10.8
	Other part of body	67656	48239	65.8	19417	64.6
Sprain, strain, or tear (n=60,984)						
	Lower back	15355	9329	23.9	6026	27.4
	Shoulder(s)	8443	5220	13.4	3223	14.7
	Knee	6345	3890	10.0	2455	11.2
	Other part of body	30841	20557	52.7	10284	46.7
Fracture (n=7,780)						
	Finger(s)	1176	736	14.2	440	17.0
	Ankle	801	483	9.3	318	12.2
	Wrist	768	554	10.7	214	8.2
	Other part of body	5035	3412	65.8	1623	62.6
Definitions: TN=Tennessee						

Table S2.4: Estimated crude and adjusted associations (prevalence ratios [PRs] and 95% confidence intervals [CIs]) of demographic characteristics and type of injury with receiving an opioid within 6 months of injury in workers who reported one injury to TN Workers' Compensation 2013-2015 (N=172,256): Results from Poisson regression analyses

	Opioid prescription filled within 6 months of injury			
	No (n=114,974) n (%)	Yes (n=57,282) n (%)	Unadjusted PR (95% CI)	Adjusted† PR (95% CI)
Characteristic	n (%)	n (%)		
Age, years				
15 - 34	47892 (41.7)	18538 (32.4)	1.0 (ref)	1.0 (ref)
35 - 54	47652 (41.4)	27219 (47.5)	1.3 (1.28-1.33)	1.2 (1.18-1.22)
55 - 99	19430 (16.9)	11525 (20.1)	1.3 (1.30-1.37)	1.2 (1.17-1.23)
Sex				
Female	52070 (45.3)	24924 (43.5)	1.0 (ref)	1.0 (ref)
Male	62904 (54.7)	32358 (56.5)	1.05 (1.03-1.07)	1.1 (1.07-1.11)
Type of injury				
Other	73383 (63.8)	30109 (52.6)	1.0 (ref)	1.0 (ref)
Strain, sprain, or tear	38996 (33.9)	21988 (38.4)	1.2 (1.22-1.26)	1.2 (1.13-1.18)
Fracture	2595 (2.3)	5185 (9.0)	2.3 (2.22-2.36)	2.3 (2.20-2.33)
Part of body				
Other	67374 (58.6)	32180 (56.2)	1.0 (ref)	1.0 (ref)
Finger(s)	12773 (11.1)	5498 (9.6)	0.9 (0.90-0.96)	1.0 (0.97-1.03)
Lower back	10660 (9.3)	7005 ((12.2)	1.2 (1.19-1.26)	1.2 (1.16-1.23)
Multiple body parts	7847 (6.8)	4680 (8.2)	1.2 (1.12-1.19)	1.2 (1.14-1.22)
Hand	8705 ((7.6)	3466 (6.0)	0.9 (0.85-0.91)	0.95 (0.92-0.99)
Knee	7615 (6.6)	4453 (7.8)	1.1 (1.11-1.18)	1.1 (1.10-1.18)
Geographical area				
East	41538 (36.1)	20426 (35.7)	1.0 (ref)	1.0 (ref)
Middle	49784 (43.3)	23505 (41.0)	0.97 (0.95-0.99)	1.0 (0.97-1.01)
West	23652 (20.6)	13351 (23.3)	1.1 (1.07-1.12)	1.1 (1.09-1.14)
Prior opioid use	5568 (4.8)	12052 (21.0)	2.3 (2.29-2.39)	2.3 (2.24-2.33)

Definitions: TN=Tennessee; PR=prevalence ratio; CI=confidence interval
†Adjusted prevalence ratios control for all variables in table and age*prior opioid use interaction

Appendix 3 – Supplemental tables from Chapter 3 Patterns of prescription opioid use associated with nonfatal opioid overdose: A case-control study using linked statewide databases in Tennessee.

Table S3.1: Classification of comorbidities using Hospital Discharge Data Set

Comorbidity	ICD-9	ICD-10
Cancer	Diag(i) in: ('140','141','142','143','144','145','146','147','148','149','150','151','152','153', '154','155','156','157','158','159','160','161','162','163','164','165','170','171', '172','174','175','176','179','180','181','182','183','184','185','186','187','188', '189','190','191','192','193','194','195','200','201','202','203','204','205','206', '207','208','2386')	Diag(i) in: ('C00','C01','C02','C03','C04','C05','C06','C07','C08','C09','C10','C11', 'C12','C13','C14','C15','C16','C17','C18','C19','C20','C21','C22','C23', 'C24','C25','C26','C30','C31','C32','C33','C34','C37','C38','C39','C40', 'C41','C43','C45','C46','C47','C48','C49','C50','C51','C52','C53','C54', 'C55','C56','C57','C58','C60','C61','C62','C63','C64','C65','C66','C67', 'C68','C69','C70','C71','C72','C73','C74','C75','C76','C81','C82','C83', 'C84','C85','C88','C90','C91','C92','C93','C94','C95','C96','C97')
Substance use disorder (SUD)	substr(Diag(i),1,3) in ('291' '292' '303' '304' '305' '571') or substr(Diag(i),1,4) in ('3575' '5353') or substr(Ecode1,1,4) eq ('E860.0')	substr(Diag(i),1,3) in ('F10' 'F11' 'F12' 'F13' 'F14' 'F15' 'F16' 'F17' 'F18' 'F19')
Anxiety disorder	substr(Diag(i),1,5) in ('30000' '30001' '30002')	substr(Diag(i),1,3) in ('F41')
Depression	substr(Diag(i),1,4) in ('2962' '2963' '2980' '3090' '3091') or substr(Diag(i),1,3) eq '311'	substr(Diag(i),1,3) in ('F33' 'F32')
Bipolar/psychotic disorder	substr(Diag(i),1,3) in ('291' '292' '293' '294' '295' '296' '297' '298' '299' '301' '306')	substr(Diag(i),1,3) in ('F20' 'F21' 'F22' 'F23' 'F24' 'F25' 'F26' 'F27' 'F28' 'F29' 'F60' 'F61' 'F62' 'F63' 'F64' 'F65' 'F66' 'F67' 'F68' 'F69')

Table S3.2: Most frequent causes of hospitalization among injured workers who reported one injury to TN Workers' Compensation 2013 (N=84054), by age group								
Age 15-29 years			Age 30-59 years			Age 60-99 years		
Primary diagnosis	n	%	Primary diagnosis	n	%	Primary diagnosis	n	%
Abdominal pain	2700	2.8	Chest pain	9031	4.5	Chest pain	899	3.3
Chest pain	2167	2.2	Abdominal pain	4508	2.3	Screening for malignant neoplasms of colon	642	2.3
Urinary tract infection	2136	2.2	Headache	3715	1.9	Atherosclerotic heart disease	343	1.2
Headache	2059	2.1	Lumbago	2434	1.2	Abdominal pain	263	1.0
Pregnancy complication	1734	1.8	Urinary tract infection	2198	1.1	Urinary tract infection	233	0.9
Acute upper respiratory infection	1352	1.4	Low back pain	2085	1.1	Headache	210	0.8
Pharyngitis	1142	1.2	Acute bronchitis	2078	1.0	Lumbago	196	0.7
Acute bronchitis	1073	1.1	Acute upper respiratory infection	1531	0.8	Low back pain	160	0.6
Nausea with vomiting	1032	1.1	Lumbar sprain	1222	0.6	Hypertension	138	0.5
Low back strain	951	1.0	Nausea with vomiting	1193	0.6	Osteoarthritis	131	0.5
Lumbago	837	0.9	Pain in joint, lower leg	1109	0.6	Shoulder pain	133	0.5
Low back pain	774	0.8	Shoulder pain	1121	0.6	Pneumonia	128	0.5
Neck sprain	549	0.6	Screening for malignant neoplasms of colon	1070	0.5	Rotator cuff sprain	128	0.5
Ankle sprain	537	0.6	Neck sprain	1058	0.5	Pain in joint, lower leg	127	0.5
All others	78126	80.4	All others	164838	82.8	All others	23782	86.4
Definitions: TN=Tennessee Injured workers may appear in more than one category								

Appendix 4 – Supplemental tables from Chapter 4 A predictive model for injury as a gateway to long-term opioid use: A retrospective cohort study using linked statewide databases in Tennessee.

Table S4.1: Comparing definitions for long-term opioid use in injured workers who were opioid-free before injury and received opioids within 90 days of injury (N=46399)

	Received an opioid within 30 days of injury (n=38080)			Received an opioid within 90 days of injury (n=46399)		
Definition	n captured by this definition (%)	n captured only by this definition (%)	n captured by both definitions (%)	n captured by this definition	n captured only by this definition	n captured by both definitions
Definition 1: Receiving an opioid on ≥45 days in a 90 day period	1702 (4.5)	512 (1.3)	1190 (3.1)	1834 (4.0)	540 (1.2)	1294 (2.8)
Definition 2: Receiving an opioid on ≥60 days in a 120 day period	1416 (3.7)	226 (0.6)		1612 (3.5)	318 (0.7)	

Opioid-free at the time of injury=no record of opioid use in the 60 days prior to injury

Table S4.2: Baseline and clinical characteristics of injured workers who reported one injury to Tennessee Workers' Compensation, were opioid-free at the time of injury, and received opioids within 90 days of injury (N=55,656), by model and long-term use								
	Derivation Model				Validation model			
	Long-term opioid use				Long-term opioid use			
	No (n=29347)		Yes(n=1261)		No (n=15218)		Yes (n=573)	
Characteristic	n	%	n	%	n	%	n	%
Age (years)								
15 - 34	10380	35.4	283	22.4	5437	35.7	113	19.7
35-54	13433	45.8	688	54.6	6753	44.4	321	56.0
55-99	5534	18.9	290	23.0	3028	19.9	139	24.3
Type of injury								
Strain, sprain, or tear	11397	38.8	597	47.3	5588	36.7	251	43.8
Fracture	2559	8.7	196	15.5	1498	9.8	98	17.1
Other	15391	52.4	468	37.1	8132	53.4	224	39.1
Part of body injured								
Lower back	3480	11.9	243	19.3	1685	11.1	106	18.5
Finger(s)	3062	10.4	56	4.4	1498	9.8	26	4.5
Knee	2363	8.1	102	8.1	1201	7.9	45	7.9
Other	20442	69.7	860	68.2	10834	71.2	396	69.1
Residence type								
Urban	11294	38.5	387	30.7	5768	37.9	176	30.7
Rural	18053	61.5	874	69.3	9450	62.1	397	69.3
Opioid received within 7 days of injury	19789	67.4	868	68.8	10225	67.2	398	69.5
Days' supply of first prescription								
<5	17180	58.5	245	19.4	9085	59.7	135	23.54
5-9	8276	28.2	159	12.6	4162	27.35	86	14.93
10-19	2407	8.2	148	11.8	1126	7.4	71	12.42
≥20	393	1.4	105	8.3	228	1.5	45	7.85
Long-acting opioid received within 30 days of injury	149	0.5	101	8.0	75	0.5	39	6.8
Overlapping opioid and benzodiazepine prescription days within 30 days of injury	1015	3.5	151	12.0	586	3.9	56	9.8
Number of prescribers visited for opioids within 90 days of injury								
1	21010	71.6	261	20.7	10846	71.3	106	18.5
2	6240	21.3	407	32.3	3197	21.0	173	30.2
≥3	2097	7.1	593	47.0	1175	7.7	294	51.3
Number of pharmacies visited for opioids within 90 days of injury								
1	25102	85.5	545	43.2	13112	86.2	267	46.6
2	3555	12.1	434	34.4	1800	11.8	203	35.4
≥3	690	2.4	282	22.4	306	2.0	103	18.0
Maximum MME received within 30 days of injury								
<40	10565	36.0	436	34.6	5433	35.7	5144	33.8
40-99	10037	34.2	477	37.8	5265	34.6	5707	37.5
100-159	4549	15.5	207	16.4	2328	15.3	2557	16.8
≥160	4197	14.3	141	11.2	2191	14.4	1811	11.9

Definitions: Opioid-free at the time of injury=no record of opioid use in the 60 days prior to injury; Long-term use=receiving an opioid on most days in the 90 day period after injury; MME=morphine milligram equivalents
*All comparisons between non opioid free and opioid free injured workers were significantly different at p<0.05

Table S4.3: Estimated crude associations (odds ratios [ORs] and 95% confidence intervals [CIs]) of demographic, injury, and opioid use variables with long-term opioid use after injury in injured workers who reported one injury to Tennessee Workers' Compensation and were opioid-free at the time of injury: Results from unconditional logistic regression analyses.			
	Derivation Model (N=30,608)		
	Unadjusted OR	95% CI	
Characteristic		lower	upper
Part of body injured			
Other	ref		
Lower back	1.7**	1.43	1.92
Finger(s)	0.4**	0.33	0.57
Knee	1.0	0.83	1.27
Residence type			
Urban	ref		
Rural	1.3**	1.26	1.40
Opioid received within 7 days of injury	1.1	0.95	1.21
Days' supply of first prescription, dummy variables			
<5	ref		
5-9	3.2*	2.80	3.63
10-19	6.8*	5.86	7.96
≥20	36.6*	33.33	40.16
Long-acting opioid received within 30 days of injury	25.6*	21.80	29.98
Overlapping opioid and benzodiazepine prescription days within 30 days of injury	7.8*	7.19	8.44
Number of prescribers visited for opioids within 90 days of injury			
1	ref		
2	2.5*	2.31	2.66
≥3	9.1*	8.13	10.25
Number of pharmacies visited for opioids within 90 days of injury			
1	ref		
2	2.9*	2.70	3.12
≥3	11.6*	9.61	14.05
Maximum MME received within 90 days of injury			
<40	1.9*	1.73	2.03
40-99	2.2*	2.02	2.41
100-159	3.7*	3.29	4.22
≥160	1.5*	1.24	1.75

Definitions: Opioid-free at the time of injury=no record of opioid use in the 60 days prior to injury; Long-term use=receiving an opioid on most days in the 90 day period after injury; OR=odds ratio; CI=confidence interval
* p<0.05
** p<0.01

Appendix 5: Overview of opioid-related policy milestones in Tennessee

2018

- Governor Haslam announces $30 million to be applied towards prevention, treatment, and law enforcement aimed at opioid addiction. Specific components include limiting the state Medicaid's coverage of opioids, targeted outreach towards chronic opioid users who are women of childbearing age, $25 million towards treatment and recovery services including within the criminal justice system, improving the state's data systems to track the epidemic, and prosecuting the illicit sale and trafficking of opioids.

2016

- Prescription Safety Act of 2016 –The period allowed between dispensing a controlled substance and reporting it to the CSMD is decreased to "close of business day" for human patients, and certain law enforcement personnel are granted access to the CSMD.
- Public Chapter 820 of 2014, the "Fetal Assault Law", expires.

2015

- Public Chapter 26 – The Intractable Pain Act, which had provided a "Pain Patient's Bill of Rights" virtually guaranteeing access to opioids for patients who requested it, is deleted.
- Public Chapter 475 – Pain clinic certificates can only be held by a TN licensed doctor, advanced practice nurse, or physician's assistant who is a pain medicine specialist. Certificate holders must own the pain clinic for which they hold the certificate.
- Public Chapter 396 update – The Addiction Treatment Act of 2015 and "Good Samaritan naloxone law" which prevents criminal drug charges (e.g. violation of probation or parole) from being filed against a person who is experiencing a drug overdose or is in the company of a person who is experiencing a drug overdose and who seeks medical assistance, and limits buprenorphine prescribing.

2014

- Chronic Pain Guidelines define appropriate measures for treating chronic pain and set thresholds for opioid use that warrant referral to a pain specialist.
- Public Chapter 820 – The "Fetal Assault Law" allows for mothers to be charged with criminal assault for giving birth to babies with Neonatal Abstinence Syndrome.

2013

- Neonatal Abstinence Syndrome is made a reportable disease and cross-state surveillance begins.
- Public Chapter 396 – Tennessee Department of Health is required to annually identify the top 50 prescribers of controlled substances in the state, notify them of their inclusion of the list, request a justification for their prescribing patterns, and provide disciplinary action for failing to provide a justification. Schedule II and III drugs may not be dispensed in greater than 30 day supplies.

2012

- Prescription Safety Act of 2012 – Prescribers must check the Controlled Substances Monitoring Database before prescribing an opioid in a majority of cases of pain and routinely for patients with chronic opioid use

2006 (December)

- Reporting to the Controlled Substances Monitoring Database is required for pharmacists and other dispensers.

Works Cited

Al Achkar, M., Grannis, S., Revere, D., MacKie, P., Howard, M., & Gupta, S. (2018). The effects of state rules on opioid prescribing in Indiana. *BMC Health Serv Res, 18*(1), 29. doi:10.1186/s12913-018-2830-6

Alam, A., Gomes, T., & Zheng, H. (2012). Long-term analgesic use after low-risk surgery: a retrospective cohort study. *Arch Intern Med, 172*(5), 5.

Alam, A., & Juurlink, D. N. (2016). The prescription opioid epidemic: an overview for anesthesiologists. *Can J Anaesth, 63*(1), 61-68. doi:10.1007/s12630-015-0520-y

Allison, N. (2017). Metro police to begin administering opioid overdose reversing drug naloxone. *The Tennesseean*. Retrieved from https://www.tennessean.com/story/news/2017/08/11/metro-police-begin-administering-opioid-overdose-reversing-drug-naloxone/561395001/

Anderson, J. T., Haas, A. R., Percy, R., Woods, S. T., Ahn, U. M., & Ahn, N. U. (2016). Workers' Compensation, Return to Work, and Lumbar Fusion for Spondylolisthesis. *Orthopedics, 39*(1), e1-8. doi:10.3928/01477447-20151218-01

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

Ashworth, J., Green, D. J., Dunn, K. M., & Jordan, K. P. (2013). Opioid use among low back pain patients in primary care: Is opioid prescription associated with disability at 6-month follow-up? *Pain, 154*(7), 1038-1044. doi:10.1016/j.pain.2013.03.011

Atlas, S. J., Tosteson, T. D., Hanscom, B., Blood, E. A., Pransky, G. S., Abdu, W. A., . . . Weinstein, J. N. (2007). What Is Different About Worker's Compensation Patients?: Socioeconomic Predictors of Baseline Disability Status Among Patients With Lumbar Radiculopathy. *Spine (Phila Pa 1976), 32*(18), 2019-2026. doi:10.1097/BRS.0b013e318133d69b

Baumblatt, J. A., Wiedeman, C., Dunn, J. R., Schaffner, W., Paulozzi, L. J., & Jones, T. F. (2014). High-risk use by patients prescribed opioids for pain and its role in overdose deaths. *JAMA Intern Med, 174*(5), 796-801. doi:10.1001/jamainternmed.2013.12711

Berecki-Gisolf, J., Collie, A., & McClure, R. J. (2014). Prescription opioids for occupational injury: results from workers' compensation claims records. *Pain Med, 15*(9), 1549-1557. doi:10.1111/pme.12421

Berecki-Gisolf, J., Hassani-Mahmooei, B., Collie, A., & McClure, R. (2016). Prescription Opioid and Benzodiazepine Use After Road Traffic Injury. *Pain Med, 17*(2), 304-313. doi:10.1111/pme.12890

Bernacki, E. J., Yuspeh, L., Lavin, R., & Tao, X. G. (2012). Increases in the use and cost of opioids to treat acute and chronic pain in injured workers, 1999 to 2009. *J Occup Environ Med, 54*(2), 216-223. doi:10.1097/JOM.0b013e318240de33

Bohnert, A. S., Logan, J. E., Ganoczy, D., & Dowell, D. (2016). A Detailed Exploration Into the Association of Prescribed Opioid Dosage and Overdose Deaths Among Patients With Chronic Pain. *Med Care, 54*(5), 435-441. doi:10.1097/mlr.0000000000000505

Braden, J. B., Russo, J., Fan, M. Y., Edlund, M. J., Martin, B. C., DeVries, A., & Sullivan, M. D. (2010). Emergency department visits among recipients of chronic opioid therapy. *Arch Intern Med, 170*(16), 1425-1432. doi:10.1001/archinternmed.2010.273

Brady, K. T., McCauley, J. L., & Back, S. E. (2016). Prescription Opioid Misuse, Abuse, and Treatment in the United States: An Update. *Am J Psychiatry, 173*(1), 18-26. doi:10.1176/appi.ajp.2015.15020262

Brummett, C. M., Waljee, J. F., Goesling, J., Moser, S., Lin, P., Englesbe, M. J., . . . Nallamothu, B. K. (2017). New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. *JAMA Surg, 152*(6), e170504. doi:10.1001/jamasurg.2017.0504

Caudarella, A., Dong, H., Milloy, M. J., Kerr, T., Wood, E., & Hayashi, K. (2016). Non-fatal overdose as a risk factor for subsequent fatal overdose among people who inject drugs. *Drug Alcohol Depend, 162*, 51-55. doi:10.1016/j.drugalcdep.2016.02.024

Cauley, C. E., Anderson, G., Haynes, A. B., Menendez, M., Bateman, B. T., & Ladha, K. (2017). Predictors of In-hospital Postoperative Opioid Overdose After Major Elective Operations: A Nationally Representative Cohort Study. *Ann Surg, 265*(4), 702-708. doi:10.1097/sla.0000000000001945

Centers for Disease Control and Prevention. Opioid Data Analysis. Retrieved from https://www.cdc.gov/drugoverdose/data/analysis.html

Centers for Disease Control and Prevention. U.S. State Prescribing Rates, 2016. Retrieved from https://www.cdc.gov/drugoverdose/maps/rxstate2016.html

Centers for Disease Control and Prevention. (2011). *Vital signs: Prescription painkiller overdoses in the US*. Retrieved from http://www.cdc.gov/vitalsigns/opioid-prescribing/infographic.html.

Centers for Disease Control and Prevention. (2014). Opioid painkiller prescribing infographic. Retrieved from http://www.cdc.gov/vitalsigns/opioid-prescribing/infographic.html.

Centers for Disease Control and Prevention. (2015). Prescription Drug Overdose Data. Retrieved from http://www.cdc.gov/drugoverdose/data/overdose.html.

Centers for Disease Control and Prevention. (2016). Prescription Drug Overdose: Understanding the epidemic: Data Overview: Prescribing Data. Retrieved from http://www.cdc.gov/drugoverdose/data/prescribing.html

Centers for Disease Control and Prevention. (2017). *Annual surveillance report of drug-related risks and outcomes - United States, 2017*. Retrieved from https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf

Centers for Disease Control and Prevention Prescription Drug Overdose Team. (2013). *Prescription drug overdose data & statistics: Guide to ICD-9-CM and ICD-10 codes related to poisoning and pain*. Retrieved from https://www.cdc.gov/drugoverdose/pdf/pdo_guide_to_icd-9-cm_and_icd-10_codes-a.pdf

Chen, A., & Ashburn, M. A. (2015). Cardiac Effects of Opioid Therapy. *Pain Med, 16 Suppl 1*, S27-31. doi:10.1111/pme.12915

Cheng, M., Sauer, B., Johnson, E., Porucznik, C., & Hegmann, K. (2013). Comparison of opioid-related deaths by work-related injury. *Am J Ind Med, 56*(3), 308-316. doi:10.1002/ajim.22138

Chou, R., Turner, J. A., Devine, E. B., Hansen, R. N., Sullivan, S. D., Blazina, I., . . . Deyo, R. A. (2015). The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med, 162*(4), 276-286. doi:10.7326/m14-2559

Cifuentes, M., Webster, B., Genevay, S., & Pransky, G. (2010). The course of opioid prescribing for a new episode of disabling low back pain: opioid features and dose escalation. *Pain, 151*(1), 22-29. doi:10.1016/j.pain.2010.04.012

Committee on Education and Labor, U. H. o. R. (2008). Hidden tragedy: Underreporting of workplace injuries and illnesses. Retrieved from http://www.bls.gov/iif/laborcommreport061908.pdf.

Compton, W. M., Jones, C. M., & Baldwin, G. T. (2016). Relationship between Nonmedical Prescription-Opioid Use and Heroin Use. *N Engl J Med, 374*(2), 154-163. doi:10.1056/NEJMra1508490

Cottler, L. B., Ben Abdallah, A., Cummings, S. M., Barr, J., Banks, R., & Forchheimer, R. (2011). Injury, pain, and prescription opioid use among former National Football League (NFL) players. *Drug Alcohol Depend, 116*(1-3), 188-194. doi:10.1016/j.drugalcdep.2010.12.003

Coyle, D. T., Pratt, C. Y., Ocran-Appiah, J., Secora, A., Kornegay, C., & Staffa, J. (2017). Opioid analgesic dose and the risk of misuse, overdose, and death: A narrative review. *Pharmacoepidemiol Drug Saf*. doi:10.1002/pds.4366

Crowe, M. (2016). The cost of anti-overdose drug naloxone. *10News*. Retrieved from http://www.wbir.com/article/news/local/10listens-the-cost-of-anti-overdose-drug-naloxone/326323750

Dembe, A., Wickizer, T., Sieck, C., Partridge, J., & Balchick, R. (2012). Opioid use and dosing in the workers' compensation setting. A comparative review and new data from Ohio. *Am J Ind Med, 55*(4), 313-324. doi:10.1002/ajim.21021

Detox local. Needle exchanges in Tennessee.   Retrieved from https://www.detoxlocal.com/needle-exchanges/tennessee/

Deyo, R. A., Hallvik, S. E., Hildebran, C., Marino, M., Dexter, E., Irvine, J. M., . . . Millet, L. M. (2017). Association Between Initial Opioid Prescribing Patterns and Subsequent Long-Term Use Among Opioid-Naive Patients: A Statewide Retrospective Cohort Study. *J Gen Intern Med, 32*(1), 21-27. doi:10.1007/s11606-016-3810-3

Dilokthornsakul, P., Moore, G., Campbell, J. D., Lodge, R., Traugott, C., Zerzan, J., . . . Page, R. L., 2nd. (2016). Risk Factors of Prescription Opioid Overdose Among Colorado Medicaid Beneficiaries. *J Pain, 17*(4), 436-443. doi:10.1016/j.jpain.2015.12.006

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC Guidelines for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recomm Rep, 65*(1), 1-49. doi:10.15585/mmwr.rr6501e1

Dreyer, T. R., Michalski, T., & Williams, B. C. (2015). Patient Outcomes in a Medicaid Managed Care Lock-In Program. *J Manag Care Spec Pharm, 21*(11), 1006-1012. doi:10.18553/jmcp.2015.21.11.1006

Durand, Z., Krishnaswami, S., Nechuta, S., Hurwitz, E., & McPheeters, M. (2018). *Prescription opioid use by injured workers: A descriptive study using linked statewide databases*.

Edlund, M. J., Steffick, D., Hudson, T., Harris, K. M., & Sullivan, M. (2007). Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. *Pain, 129*(3), 355-362. doi:10.1016/j.pain.2007.02.014

Eriksen, J., Sjogren, P., Bruera, E., Ekholm, O., & Rasmussen, N. K. (2006). Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain, 125*(1-2), 172-179. doi:10.1016/j.pain.2006.06.009

Faul, M., Lurie, P., Kinsman, J. M., Dailey, M. W., Crabaugh, C., & Sasser, S. M. (2017). Multiple Naloxone Administrations Among Emergency Medical Service Providers is Increasing. *Prehosp Emerg Care, 21*(4), 411-419. doi:10.1080/10903127.2017.1315203

Frank, D., Mateu-Gelabert, P., Guarino, H., Bennett, A., Wendel, T., Jessell, L., & Teper, A. (2015). High risk and little knowledge: overdose experiences and knowledge among young adult nonmedical prescription opioid users. *Int J Drug Policy, 26*(1), 84-91. doi:10.1016/j.drugpo.2014.07.013

Franklin, G. M., Mai, J., Wickizer, T., Turner, J. A., Fulton-Kehoe, D., & Grant, L. (2005). Opioid dosing trends and mortality in Washington State workers' compensation, 1996-2002. *Am J Ind Med, 48*(2), 91-99. doi:10.1002/ajim.20191

Franklin, G. M., Rahman, E. A., Turner, J. A., Daniell, W. E., & Fulton-Kehoe, D. (2009). Opioid use for chronic low back pain: A prospective, population-based study among injured workers in Washington state, 2002-2005. *Clin J Pain, 25*(9), 743-751. doi:10.1097/AJP.0b013e3181b01710

Franklin, G. M., Stover, B. D., Turner, J. A., Fulton-Kehoe, D., & Wickizer, T. M. (2008). Early opioid prescription and subsequent disability among workers with back injuries: the Disability Risk Identification Study Cohort. *Spine (Phila Pa 1976), 33*(2), 199-204. doi:10.1097/BRS.0b013e318160455c

Frazier, W., Cochran, G., Lo-Ciganic, W. H., Gellad, W. F., Gordon, A. J., Chang, C. H., & Donohue, J. M. (2017). Medication-Assisted Treatment and Opioid Use Before and After Overdose in Pennsylvania Medicaid. *Jama, 318*(8), 750-752. doi:10.1001/jama.2017.7818

Fritz, J. M., King, J. B., & McAdams-Marx, C. (2017). Associations between Early Care Decisions and the Risk for Long-Term Opioid Use for Patients with Low Back Pain with a New Physician Consultation and Initiation of Opioid Therapy. *Clin J Pain*. doi:10.1097/ajp.0000000000000571

Fulton-Kehoe, D., Garg, R. K., Turner, J. A., Bauer, A. M., Sullivan, M. D., Wickizer, T. M., & Franklin, G. M. (2013). Opioid poisonings and opioid adverse effects in workers in Washington state. *Am J Ind Med, 56*(12), 1452-1462. doi:10.1002/ajim.22266

Gatchel, R. J., & Okifuji, A. (2006). Evidence-based scientific data documenting the treatment and cost-effectiveness of comprehensive pain programs for chronic nonmalignant pain. *J Pain, 7*(11), 779-793. doi:10.1016/j.jpain.2006.08.005

Glanz, J. M., Narwaney, K. J., Mueller, S. R., Gardner, E. M., Calcaterra, S. L., Xu, S., . . . Binswanger, I. A. (2018). Prediction Model for Two-Year Risk of Opioid Overdose Among Patients Prescribed Chronic Opioid Therapy. *J Gen Intern Med*. doi:10.1007/s11606-017-4288-3

Gross, D. P., Stephens, B., Bhambhani, Y., Haykowsky, M., Bostick, G. P., & Rashiq, S. (2009). Opioid prescriptions in canadian workers' compensation claimants: prescription trends and associations between early prescription and future recovery. *Spine (Phila Pa 1976), 34*(5), 525-531. doi:10.1097/BRS.0b013e3181971dea

Guy, G. P., Jr., Zhang, K., Bohm, M. K., Losby, J., Lewis, B., Young, R., . . . Dowell, D. (2017). Vital Signs: Changes in Opioid Prescribing in the United States, 2006-2015. *MMWR Morb Mortal Wkly Rep, 66*(26), 697-704. doi:10.15585/mmwr.mm6626a4

Hah, J. M., Sturgeon, J. A., Zocca, J., Sharifzadeh, Y., & Mackey, S. C. (2017). Factors associated with prescription opioid misuse in a cross-sectional cohort of patients with chronic non-cancer pain. *J Pain Res, 10*, 979-987. doi:10.2147/jpr.s131979

Harris, I., Mulford, J., Solomon, M., van Gelder, J. M., & Young, J. (2005). Association between compensation status and outcome after surgery: a meta-analysis. *Jama, 293*(13), 1644-1652. doi:10.1001/jama.293.13.1644

Heins, S. E., Feldman, D. R., Bodycombe, D., Wegener, S. T., & Castillo, R. C. (2016). Early opioid prescription and risk of long-term opioid use among US workers with back and shoulder injuries: a retrospective cohort study. *Inj Prev, 22*(3), 211-215. doi:10.1136/injuryprev-2015-041630

Inacio, M. C., Hansen, C., Pratt, N. L., Graves, S. E., & Roughead, E. E. (2016). Risk factors for persistent and new chronic opioid use in patients undergoing total hip arthroplasty: a retrospective cohort study. *BMJ Open, 6*(4), e010664. doi:10.1136/bmjopen-2015-010664

Jann, M., Kennedy, W. K., & Lopez, G. (2014). Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. *J Pharm Pract, 27*(1), 5-16. doi:10.1177/0897190013515001

Johnson, S. P., Chung, K. C., Zhong, L., Shauver, M. J., Engelsbe, M. J., Brummett, C., & Waljee, J. F. (2016a). Risk of Prolonged Opioid Use Among Opioid-Naive Patients Following Common Hand Surgery Procedures. *J Hand Surg Am, 41*(10), 947-957.e943. doi:10.1016/j.jhsa.2016.07.113

Johnson, S. P., Chung, K. C., Zhong, L., Shauver, M. J., Engelsbe, M. J., Brummett, C., & Waljee, J. F. (2016b). Risk of Prolonged Opioid Use Among Opioid-Naive Patients Following Common Hand Surgery Procedures. *J Hand Surg Am*. doi:10.1016/j.jhsa.2016.07.113

Johnston, S. S., Alexander, A. H., Masters, E. T., Mardekian, J., Semel, D., Malangone-Monaco, E., . . . Sadosky, A. (2016). Costs and Work Loss Burden of Diagnosed Opioid Abuse Among Employees on Workers Compensation or Short-term Disability. *J Occup Environ Med, 58*(11), 1087-1097. doi:10.1097/jom.0000000000000865

Jones, C. M., Paulozzi, L. J., & Mack, K. A. (2014). Sources of prescription opioid pain relievers by frequency of past-year nonmedical use United States, 2008-2011. *JAMA Intern Med, 174*(5), 802-803. doi:10.1001/jamainternmed.2013.12809

Katz, N. (2007). Opioids: after thousands of years, still getting to know you. *Clin J Pain, 23*(4), 303-306. doi:10.1097/AJP.0b013e31803cb905

Kesselheim, A. S., Huybrechts, K. F., Choudhry, N. K., Fulchino, L. A., Isaman, D. L., Kowal, M. K., & Brennan, T. A. (2015). Prescription drug insurance coverage and patient health outcomes: A systematic review. *American Journal of Public Health, 105*(2), e17-e30.

Kidner, C. L., Mayer, T. G., & Gatchel, R. J. (2009). Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. *J Bone Joint Surg Am, 91*(4), 919-927. doi:10.2106/jbjs.h.00286

Kolar, A. F., Brown, B. S., Haertzen, C. A., & Michaelson, B. S. (1994). Children of substance abusers: the life experiences of children of opiate addicts in methadone maintenance. *Am J Drug Alcohol Abuse, 20*(2), 159-171.

Kowalski-McGraw, M., Green-McKenzie, J., Pandalai, S. P., & Schulte, P. A. (2017a). Characterizing the Interrelationships of Prescription Opioid and Benzodiazepine Drugs With Worker Health and Workplace Hazards. *J Occup Environ Med, 59*(11), 1114-1126. doi:10.1097/jom.0000000000001154

Kowalski-McGraw, M., Green-McKenzie, J., Pandalai, S. P., & Schulte, P. A. (2017b). Characterizing the Interrelationships of Prescription Opioid and Benzodiazepine Drugs With Worker Health and Workplace Hazards. *J Occup Environ Med*. doi:10.1097/jom.0000000000001154

Kraut, A., Raymond, C. B., Ekuma, O., & Shafer, L. A. (2016). A comparison of opioid use between WCB recipients and other Manitobans for knee, shoulder, back and carpal tunnel release procedures. *Am J Ind Med, 59*(4), 257-263. doi:10.1002/ajim.22562

Krueger, A. (2017). Where have all the workers gone? An inquiry into the decline of the U.S. labor force participation rate. *Brookings Papers on Economic Activity.* Retrieved from https://www.brookings.edu/wp-content/uploads/2017/09/1_krueger.pdf

Lai, H. S., Szeto, G. P., & Chan, C. C. (2017). Injured workers' perception of loss and gain in the return to work process. *Risk Manag Healthc Policy, 10*, 7-16. doi:10.2147/rmhp.s119479

Larochelle, M. R., Liebschutz, J. M., Zhang, F., Ross-Degnan, D., & Wharam, J. F. (2016). Opioid Prescribing After Nonfatal Overdose and Association With Repeated Overdose: A Cohort Study. *Ann Intern Med, 164*(1), 1-9. doi:10.7326/m15-0038

Lavin, R. A., Tao, X. G., Yuspeh, L., & Bernacki, E. J. (2014). Impact of the combined use of benzodiazepines and opioids on workers' compensation claim cost. *J Occup Environ Med, 56*(9), 973-978. doi:10.1097/jom.0000000000000203

Lee, J. D., Nunes, E. V., Jr., Novo, P., Bachrach, K., Bailey, G. L., Bhatt, S., . . . Rotrosen, J. (2018). Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. *Lancet, 391*(10118), 309-318. doi:10.1016/s0140-6736(17)32812-x

Liveoak, K. (2017).

Manchikanti, L., Vallejo, R., Manchikanti, K. N., Benyamin, R. M., Datta, S., & Christo, P. J. (2011). Effectiveness of long-term opioid therapy for chronic non-cancer pain. *Pain Physician, 14*(2), E133-156.

Mao, J., Sung, B., Ji, R. R., & Lim, G. (2002). Chronic morphine induces downregulation of spinal glutamate transporters: implications in morphine tolerance and abnormal pain sensitivity. *J Neurosci, 22*(18), 8312-8323.

Miller, M., Barber, C. W., Leatherman, S., Fonda, J., Hermos, J. A., Cho, K., & Gagnon, D. R. (2015). Prescription opioid duration of action and the risk of unintentional overdose among patients receiving opioid therapy. *JAMA Intern Med, 175*(4), 608-615. doi:10.1001/jamainternmed.2014.8071

Morden, N. E., Munson, J. C., Colla, C. H., Skinner, J. S., Bynum, J. P., Zhou, W., & Meara, E. (2014). Prescription opioid use among disabled Medicare beneficiaries: intensity, trends, and regional variation. *Med Care, 52*(9), 852-859. doi:10.1097/mlr.0000000000000183

Morone, N. E., & Weiner, D. K. (2013). Pain as the fifth vital sign: exposing the vital need for pain education. *Clin Ther, 35*(11), 1728-1732. doi:10.1016/j.clinthera.2013.10.001

Mosher, H., Zhou, Y., Thurman, A. L., Sarrazin, M. V., & Ohl, M. E. (2017). Trends in Hospitalization for Opioid Overdose among Rural Compared to Urban Residents of the United States, 2007-2014. *J Hosp Med, 12*(11), 925-929. doi:10.12788/jhm.2793

Naloxone Community Collaborative. (2018). *Knox County naloxone deployment by first responders*. Retrieved from https://metrodrug.org/wp-content/uploads/2018/01/Naloxone-Report-18-FINAL.pdf

National Institute on Drug Abuse. (2017). Research on the use and misuse of fentanyl and other synthetic opioids. Retrieved from https://www.drugabuse.gov/about-nida/legislative-activities/testimony-to-congress/2017/research-use-misuse-fentanyl-other-synthetic-opioids

National Pharmaceutical Council. Pain: Current understanding of assessment, management, and treatments. Retrieved from http://americanpainsociety.org/uploads/education/section_2.pdf

Newton-John, T. R., & McDonald, A. J. (2012). Pain management in the context of workers compensation: a case study. *Transl Behav Med, 2*(1), 38-46. doi:10.1007/s13142-012-0112-0

Occupational Safety and Health Administration. OSHA Injury and Illness Recordkeeping and Reporting Requirements. Retrieved from https://www.osha.gov/recordkeeping/index.html

Orriols, L., Delorme, B., Gadegbeku, B., Tricotel, A., Contrand, B., Laumon, B., . . . Lagarde, E. (2010). Prescription medicines and the risk of road traffic crashes: a French registry-based study. *PLoS Med, 7*(11), e1000366. doi:10.1371/journal.pmed.1000366

Palamar, J. J., Shearston, J. A., Dawson, E. W., Mateu-Gelabert, P., & Ompad, D. C. (2016). Nonmedical opioid use and heroin use in a nationally representative sample of us high school seniors. *Drug Alcohol Depend, 158*, 132-138. doi:10.1016/j.drugalcdep.2015.11.005

Park, T. W., Lin, L. A., Hosanagar, A., Kogowski, A., Paige, K., & Bohnert, A. S. (2016). Understanding Risk Factors for Opioid Overdose in Clinical Populations to Inform Treatment and Policy. *J Addict Med, 10*(6), 369-381. doi:10.1097/adm.0000000000000245

Park, T. W., Saitz, R., Ganoczy, D., Ilgen, M. A., & Bohnert, A. S. (2015). Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *Bmj, 350*, h2698. doi:10.1136/bmj.h2698

Pensa, M. A., Galusha, D. H., & Cantley, L. F. (2017). Patterns of Opioid Prescribing and Predictors of Chronic Opioid Use in an Industrial Cohort, 2003 to 2013. *J Occup Environ Med*. doi:10.1097/jom.0000000000001231

Pergolizzi, J. V., Jr., LeQuang, J. A., Taylor, R., Jr., & Raffa, R. B. (2018). Going beyond prescription pain relievers to understand the opioid epidemic: the role of illicit fentanyl, new psychoactive substances, and street heroin. *Postgrad Med, 130*(1), 1-8. doi:10.1080/00325481.2018.1407618

Pidd, K., & Roche, A. M. (2014). How effective is drug testing as a workplace safety strategy? A systematic review of the evidence. *Accid Anal Prev, 71*, 154-165. doi:10.1016/j.aap.2014.05.012

Pinsker, J. (2015). The pointlessness of the workplace drug test. *The Atlantic*.

Pletcher, K. (2015). Opium wars *Encyclopedia Brittanica*.

Prescription Drug Overdose Program 2018 Report: Understanding and responding to the opioid epidemic inTN using Morbidity, Mortality, and Prescription Data. (January, 2018). Retrieved from

Prescription Requirements, (2013).

Prescription Safety Act of 2012, (2012).

Prevention, C. f. D. C. a. U.S. Prescribing Rate Maps. Retrieved from https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html

Public Broadcasting Service (Writer). (1998). Transforming opium poppies into heroin. In Frontline (Producer).

Quan, H., Sundararajan, V., Halfon, P., Fong, A., Burnand, B., Luthi, J. C., . . . Ghali, W. A. (2005). Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care, 43*(11), 1130-1139.

Rice, J. B., Kirson, N. Y., Shei, A., Cummings, A. K., Bodnar, K., Birnbaum, H. G., & Ben-Joseph, R. (2014). Estimating the costs of opioid abuse and dependence from an employer perspective: a retrospective analysis using administrative claims data. *Appl Health Econ Health Policy, 12*(4), 435-446. doi:10.1007/s40258-014-0102-0

Rice, J. B., White, A. G., Birnbaum, H. G., Schiller, M., Brown, D. A., & Roland, C. L. (2012). A model to identify patients at risk for prescription opioid abuse, dependence, and misuse. *Pain Med, 13*(9), 1162-1173. doi:10.1111/j.1526-4637.2012.01450.x

Rudd, R. A., Seth, P., David, F., & Scholl, L. (2016). Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. *MMWR Morb Mortal Wkly Rep, 65*(5051), 1445-1452. doi:10.15585/mmwr.mm655051e1

Schoenfeld, A. J., Nwosu, K., Jiang, W., Yau, A. L., Chaudhary, M. A., Scully, R. E., . . . Haider, A. H. (2017). Risk Factors for Prolonged Opioid Use Following Spine Surgery, and the Association with Surgical Intensity, Among Opioid-Naive Patients. *J Bone Joint Surg Am, 99*(15), 1247-1252. doi:10.2106/jbjs.16.01075

Shah, A., Hayes, C. J., & Martin, B. C. (2017). Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use - United States, 2006-2015. *MMWR Morb Mortal Wkly Rep, 66*(10), 265-269. doi:10.15585/mmwr.mm6610a1

Slavova, S., Bunn, T. L., & Talbert, J. (2014). Drug overdose surveillance using hospital discharge data. *Public Health Rep, 129*(5), 437-445. doi:10.1177/003335491412900507

Smyth, B. P., Barry, J., Keenan, E., & Ducray, K. (2010). Lapse and relapse following inpatient treatment of opiate dependence. *Ir Med J, 103*(6), 176-179.

Stover, B. D., Turner, J. A., Franklin, G., Gluck, J. V., Fulton-Kehoe, D., Sheppard, L., . . . Egan, K. (2006). Factors associated with early opioid prescription among workers with low back injuries. *J Pain, 7*(10), 718-725. doi:10.1016/j.jpain.2006.03.004

Substance Abuse and Mental Health Services Administration. (2016). *Prescription drug use and misuse in the United States: Results from the 2015 National Survey on Drug Use and Health*. Retrieved from https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR2-2015/NSDUH-FFR2-2015.htm

Substance Abuse and Mental Health Services Administration. (2017). *Opioid use in the older adult population*. Retrieved from https://www.samhsa.gov/capt/sites/default/files/resources/resources-opiod-use-older-adult-pop.pdf

Substance Abuse and Mental Health Services Administration. (2017). *State and substate estimates of nonmedical use of prescription pain relievers*. Retrieved from https://www.samhsa.gov/data/sites/default/files/report_3187/ShortReport-3187.html

Sun, E. C., Darnall, B. D., Baker, L. C., & Mackey, S. (2016). Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. *JAMA Intern Med, 176*(9), 1286-1293. doi:10.1001/jamainternmed.2016.3298

Workers' Compensation Act, (2010).

Tennessee Prescription Safety Act, (2012).

Good samaritan law, (2017).

Tedesco, D., Asch, S. M., Curtin, C., Hah, J., McDonald, K. M., Fantini, M. P., & Hernandez-Boussard, T. (2017). Opioid Abuse And Poisoning: Trends In Inpatient And Emergency Department Discharges. *Health Aff (Millwood), 36*(10), 1748-1753. doi:10.1377/hlthaff.2017.0260

Tennessee Bureau of Workers’ Compensation. A beginner's guide to Tennessee Workers' Compensation. Retrieved from

https://www.tn.gov/assets/entities/labor/attachments/BeginnersGuide_AFTERJuly1_14_English.pdf
Tennessee Department of Health. Data Dashboard. Retrieved from https://www.tn.gov/health/health-program-areas/pdo/pdo/data-dashboard.html
Tennessee Department of Health. Local and regional health departments. Retrieved from https://www.tn.gov/health/topic/localdepartments
Tennessee Department of Health. (2014). *Chronic pain guidelines: Clinical practice guidelines for outpatient management of chronic non-malignant pain*. Retrieved from https://www.tn.gov/assets/entities/health/attachments/ChronicPainGuidelines.pdf
Tennessee Department of Health. (2015). Legislative Update. Retrieved from https://www.tn.gov/health/article/CSMD-legislative
Tennessee Department of Health. (2017). *Controlled Substances Monitoring Database 2017 report to the 110th Tennessee General Assembly*. Retrieved from https://www.tn.gov/content/dam/tn/health/documents/2017_Concise_CSMD_Annual_Report.pdf
Tennessee Department of Labor. Drug free workplace programs. Retrieved from https://www.tn.gov/content/dam/tn/workforce/documents/injuries/0800-02-12.20120809.pdf
Tennessee Department of Mental Health. (2018). Tennessee opioid treatment clinics. Retrieved from https://www.tn.gov/content/dam/tn/mentalhealth/documents/TN%20Opioid%20Clinics%20Map%20with%20Hours%20of%20Op%202018.pdf
Tennessee Office of the Governor. (January 22, 2018). *Haslam announces aggressive, comprehensive plan to end Tennessee's opioid epidemic*. Retrieved from https://www.tn.gov/governor/news/2018/1/22/haslam-announces-aggressive--comprehensive-plan-to-end-tennessee-s-opioid-epidemicemic.html
Trang, T., Al-Hasani, R., Salvemini, D., Salter, M. W., Gutstein, H., & Cahill, C. M. (2015). Pain and Poppies: The Good, the Bad, and the Ugly of Opioid Analgesics. *J Neurosci, 35*(41), 13879-13888. doi:10.1523/jneurosci.2711-15.2015
Turk, D. C. (2002). Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. *Clin J Pain, 18*(6), 355-365.
U.S. Department of Health and Human Services. (2017). The U.S. Opioid Epidemic. Retrieved from https://www.hhs.gov/opioids/about-the-epidemic/
United States Census Bureau. (2016). QuickFacts: Tennessee, Population estimates, July 1, 2016.
United States. Cong. House. Committee on Energy and Commerce Subcommittee on Oversight and Investigation. (2014). *Hearing on prescription opioid and heroin abuse*. Washington: 113th Cong. 1st sess.
Veliz, P., Epstein-Ngo, Q. M., Meier, E., Ross-Durow, P. L., McCabe, S. E., & Boyd, C. J. (2014). Painfully obvious: a longitudinal examination of medical use and misuse of opioid medication among adolescent sports participants. *J Adolesc Health, 54*(3), 333-340. doi:10.1016/j.jadohealth.2013.09.002
Volinn, E., Fargo, J. D., & Fine, P. G. (2009). Opioid therapy for nonspecific low back pain and the outcome of chronic work loss. *Pain, 142*(3), 194-201. doi:10.1016/j.pain.2008.12.017

Webster, B. S., Cifuentes, M., Verma, S., & Pransky, G. (2009). Geographic variation in opioid prescribing for acute, work-related, low back pain and associated factors: a multilevel analysis. *Am J Ind Med, 52*(2), 162-171. doi:10.1002/ajim.20655

Webster, B. S., Verma, S. K., & Gatchel, R. J. (2007). Relationship between early opioid prescribing for acute occupational low back pain and disability duration, medical costs, subsequent surgery and late opioid use. *Spine (Phila Pa 1976), 32*(19), 2127-2132. doi:10.1097/BRS.0b013e318145a731

Welty, L. J., Harrison, A. J., Abram, K. M., Olson, N. D., Aaby, D. A., McCoy, K. P., . . . Teplin, L. A. (2016). Health Disparities in Drug- and Alcohol-Use Disorders: A 12-Year Longitudinal Study of Youths After Detention. *Am J Public Health, 106*(5), 872-880. doi:10.2105/ajph.2015.303032

White, A. G., Birnbaum, H. G., Schiller, M., Tang, J., & Katz, N. P. (2009). Analytic models to identify patients at risk for prescription opioid abuse. *Am J Manag Care, 15*(12), 897-906.

White, J. A., Tao, X., Artuso, R. D., Bilinski, C., Rademacher, J., & Bernacki, E. J. (2014). Effect of physician-dispensed medication on workers' compensation claim outcomes in the state of Illinois. *J Occup Environ Med, 56*(5), 459-464. doi:10.1097/jom.0000000000000145

White, J. A., Tao, X., Talreja, M., Tower, J., & Bernacki, E. (2012). The effect of opioid use on workers' compensation claim cost in the State of Michigan. *J Occup Environ Med, 54*(8), 948-953. doi:10.1097/JOM.0b013e318252249b

Witkiewitz, K., & Vowles, K. E. (2018). Alcohol and Opioid Use, Co-Use, and Chronic Pain in the Context of the Opioid Epidemic: A Critical Review. *Alcohol Clin Exp Res*. doi:10.1111/acer.13594

Wuellner, S. E., Adams, D. A., & Bonauto, D. K. (2016). Unreported workers' compensation claims to the BLS Survey of Occupational Injuries and Illnesses: Establishment factors. *Am J Ind Med, 59*(4), 274-289. doi:10.1002/ajim.22563

Zedler, B., Zie, L., Wang, L., Joyce, A., Vick, C., Kariburyo, F., . . . Murrelle, L. (2014). Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. *Pain Med, 15*, 1911-1929.