OPIOID PRESCRIBING AND HEALTH OUTCOMES IN OPIOID NAIVE PATIENTS IN INDIANA: ANALYSIS OF A STATEWIDE HEALTH INFORMATION EXCHANGE DATABASE

by

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To my family.

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LIST OF ABBREVIATIONS

CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CNCP	Chronic Noncancer Pain
DEA	Drug Enforcement Administration
DME	Diazepam Milligram Equivalent
ED	Emergency Department
EHR	Electronic Health Record
ER	Extended Release
HIE	Health Information Exchange
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
INPC	Indiana Network for Patient Care
IR	Immediate Release
LA	Long Acting
MAT	Medication-Assisted Treatment
MME	Morphine Milligram Equivalent
NDC	National Drug Code
OUD	Opioid Use Disorder
PDMP	Prescription Drug Monitoring Program
SA	Short Acting
SUD	Substance Use Disorder
US	United States
VA	Veterans Affairs
VHA	Veterans Health Administration

ABSTRACT

Background

Widespread use of prescription opioids has been a major public health concern since 1999. Many consequences are associated with the problem, such as opioid misuse, abuse, and drug overdose deaths. Opioids are not the only medications involved with drug overdose deaths. Due to stricter control of prescription opioids, those who misused opioids are associated with initiation of another illicit drug abuse. This results in increased drug overdose death involving heroin and semisynthetic/synthetic opioids. Another risk factor for increased overdose death is concurrent use of opioids with other central nervous system (CNS) depressants and some anticonvulsants. Concurrent use of opioids and benzodiazepine, z-drugs (zolpidem and zaleplon), gabapentin, and/or pregabalin is associated with increased risk of respiratory depression and drug overdose death. To combat problematic opioid use, many mitigation strategies were introduced. However, opioid-related problems remain.

Objective

To inform efforts that improve opioid prescribing for noncancer pain and health outcomes of patients receiving opioids in Indiana.

Methods

This is a retrospective cohort of patients whose data were contained within the Indiana Network for Patient Care (INPC). INPC was a statewide health information exchange database that captured and stored clinical data from Indiana's health systems including hospitals, health networks, and insurance providers. Data from the INPC used in this study included patient, pharmacy, and encounter data. The study period spanned from January 2012 to December 2017. The inclusion criteria included opioid naive adult patients who were at least 18 years old. Patients had to have at least one opioid prescription within the study period which was defined as index date. Opioid naive was defined as having no history of opioid prescription in the previous year. Patients must have at least six months of available data after index date. Patients with cancer, terminal illness, and those received hospice care were excluded.

Dependent variables included a composite outcome of opioid abuse, dependence, and overdose identified by ICD-9 or ICD-10 codes, all-cause mortality, number of all-cause

hospitalizations, and number of all-cause emergency department visits (ED). Independent variables included age, sex, race, Charlson Comorbidity Index (CCI), mental health conditions, long-term opioid use, opioid dose, opioid days supply, use of medication-assisted therapy, benzodiazepine dose, benzodiazepine days supply, and concurrent use of opioids and benzodiazepines and/or gabapentin/pregabalin within 30 days. Further, opioid dose and days supply, rate of composite outcome, and rate of mortality were further assessed before and after pivotal events related to opioid prescribing. The pivotal events included rescheduling of tramadol and hydrocodone in October 2014 and publication of CDC opioid prescribing guideline in January 2016.

Logistic regression with stepwise selection, Cox proportional hazards with stepwise selection, and Poisson regression with backward elimination were used to determine factors associated with the composite outcome, mortality, and healthcare utilization respectively. Interrupted time series analysis with segmented regression was used to assess changes of opioid prescribing and health outcomes before and after pivotal events related to opioid prescribing.

Results

A total of 341,722 patients were included in the cohort. The mean age was 52 (± 18.1). The majority was females and Caucasians. For comorbidities, 65.5% had CCI = 0 and 34.5% had CCI 1-10. Mental illness was found in 27% of the patients. The median time patients spent in the study was 1.8 years. Most of the patients (97.8%) used only short acting opioids and 78.8% used opioids alone without concurrent benzodiazepines, gabapentin, or pregabalin. A total of 1,328,287 opioid prescriptions were identified. Of those, the most commonly prescribed opioid was hydrocodone, followed by tramadol, oxycodone, codeine, and morphine. The median opioid dose was 30 morphine milligram equivalent (range 0.17-180) and the median days supply was 8 days (range 1-90). There were 593,833 prescriptions for benzodiazepines and 310.562 prescriptions for gabapentin/pregabalin.

Factors associated with higher risk of composite outcome of opioid abuse, dependence, and overdose included younger age, males, higher CCI, mental health conditions, long-term opioid use, higher opioid dose, longer opioid days supply, concurrent short and long acting opioids, and concurrent use of opioids and benzodiazepines and/or gabapentin/pregabalin. Factors associated with increased risk of mortality included older age, males, African Americans, higher CCI, mental health conditions, longer opioid days supply, concurrent short and long acting opioids, and

concurrent use of opioids and benzodiazepines and/or gabapentin/pregabalin. Using the same approach for composite outcome and mortality, higher benzodiazepine dose was associated with higher risk of composite outcome of opioid abuse, dependence, and overdose, but lower risk of death. Benzodiazepine days supply were not a significant predictor for both outcomes.

Factors associated with hospitalizations included older age, females, African Americans, higher CCI, mental health conditions, long-term opioid use, higher opioid dose, concurrent use of short and long acting opioids, and concurrent use of opioids and benzodiazepines and/or gabapentin/pregabalin. Opioid days supply was not a significant predictor for hospitalizations. For emergency department (ED) visits, the same significant factors were identified. However, opioids days supply was a significant predictor for ED visits. Older age, higher opioid dose, and longer opioid days supply were associated with lower risk of ED visits.

Using opioid-related factors and health outcomes to assess the impacts of pivotal events related to opioid prescribing, opioid dose declined after CDC guideline release, but not after rescheduling of tramadol and hydrocodone. Opioid days supply declined after rescheduling of tramadol and hydrocodone, but not after CDC guideline release. Composite outcome and mortality increased after tramadol and hydrocodone rescheduling and CDC opioid prescribing guideline release.

Conclusion

Several patient-related factors and opioid prescribing practices are associated with poor health outcomes. Leveraging HIE data may help identify patients at high risk of adverse outcomes. Additionally, policies or regulations could be effective in changing opioid practices especially short-term outcomes. These findings provide evidence to inform efforts to improve opioid prescribing and to develop clinical intervention tool to support clinical practice.

CHAPTER 1. INTRODUCTION

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in such terms".[1] Opioid analgesics are the most frequently prescribed medications for pain management due to their pain relief efficacy.[2] Prescription opioids have been used to treat moderate-to-severe pain in limited clinical conditions, such as surgery, injury, or cancer. In the 1990's, opioids were recommended to treat chronic painful conditions, i.e. chronic noncancer pain (CNCP), by some experts when treatment with non-opioid analgesics failed to adequately relieve pain.[3] In the late 1990s, there was less concern about the addictive properties of opioids due, in part, to the marketing of opioid products.[4,5] Further, the American Pain Society emphasized the importance of pain treatment, raised awareness of under-treatment of pain, and supported pain as the fifth vital sign campaign.[6] This subsequently led to a widespread use of prescription opioids for CNCP from 1999. Although opioids were frequently prescribed, many concerns were raised regarding their limited evidence of efficacy for CNCP and the associated adverse outcomes.[7,8]

1.1 Statement of problem

The widespread use of prescription opioids resulted in an increase in drug overdose deaths. From 1999 to 2017, almost 400,000 people died from an opioid-related overdose which accounted for 68% of those who died from any drug overdose.[9] Drug overdose death is a leading injury-related death, which is the third leading cause of death in the US.[10] To combat opioid-related problems, many important mitigation strategies were introduced including national or local guidelines and practice recommendations on opioid prescribing for clinicians. The most significant guideline was the Center for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain, United States 2016.[11] The purpose of this guideline was to improve safety and effectiveness of pain treatment with opioids and to minimize risks associated with long-term opioid use in patients with chronic pain, excluding active cancer treatment, palliative care, and end-of-life care.

1.2 Study rationale

Both patient and opioid prescribing characteristics contribute to patients' subsequent health outcomes. Identification of risk factors associated with adverse outcomes help providers identify patients who might be at risk for poor outcomes and could inform possible interventions. Different regions in the US have different opioid prescribing patterns, severity of problematic opioid use, and the risk factors associated with poor outcomes. Therefore, state specific information is needed to provide evidence for clinical practice and public health policy makers.

The aim of the study is to determine factors associated with adverse health outcomes specifically in Indiana, which is one of the states with increased use of prescription opioids in the past decade. In addition, this study aims to assess opioid prescribing and health outcomes in Indiana patients receiving opioids for noncancer pain and providing comparison of health outcomes before and after pivotal events related to opioid prescribing were enacted. The pivotal events related to opioid prescribing included placement of tramadol to a schedule IV controlled substance, rescheduling of hydrocodone from a schedule III to schedule II controlled substance, and publication of the CDC opioid prescribing guideline. Health outcomes compared in our study are (i) the composite outcome of opioid abuse, dependence, and overdose diagnoses; and (ii) all-cause mortality.

The overall objective of our research is to improve opioid prescribing and health outcomes in patients receiving opioids. The objective of this project is to improve opioid prescribing for noncancer pain and health outcomes of patients in Indiana. To achieve this objective, a statewide health information exchange data of opioid naive patients was used to identify factors associated with health outcomes and assess whether the hallmark events related to opioid prescribing, such as Drug Enforcement Administration (DEA) rescheduling of tramadol and hydrocodone and publication of the CDC opioid prescribing guideline affected prescribing trends and health outcomes. The rationale for this research was that clinicians, researchers, and policy makers may better understand specific factors associated with problematic opioid use, which is many health conditions and aberrant behaviors related to opioid use, and mortality and whether the hallmark events were associated with changes in opioid prescribing and reduction of negative outcomes. Towards the objectives, the following specific aims were pursued.

1.3 Specific aims

1. Identify factors associated with (i) the composite outcome of opioid abuse, dependence, and overdose diagnoses; and (ii) all-cause mortality using a statewide health information exchange.

   Hypothesis: Patients receiving higher doses, longer duration of opioids, and use opioids concomitantly with other psychoactive medications have higher risk of composite outcome and mortality.

   Sub aim 1: Identify characteristics of benzodiazepine prescriptions that are associated with (i) the composite outcome of opioid abuse, dependence, and overdose diagnoses; and (ii) all-cause mortality using health information exchange.

   Hypothesis: Patients receiving higher doses and longer duration of benzodiazepine use have higher risk of composite outcome and mortality.

2. Identify factors associated with healthcare utilization.

   Hypothesis: Patients receiving higher opioid doses, longer duration of opioids, and use opioids concomitantly with other psychoactive medications are more likely to utilize healthcare resources.

3. Compare opioid prescribing and associated adverse outcomes before and after pivotal events related to opioid prescribing.

   Hypothesis: High risk opioid prescribing (e.g. high dose and long duration prescribed), incidence of composite outcome, and mortality is lower after the pivotal events related to opioid prescribing.

CHAPTER 2. LITERATURE REVIEW

2.1 Pain and opioid use

Pain is one of the most common health problems reported in primary care settings.[12] It is most commonly classified as either acute or chronic pain. Acute pain is provoked by a specific disease or injury typically lasts less than 3-6 months.[13] In contrast, chronic pain is pain that persists past expected normal healing time.[14] Chronic pain, which occurs for most days or every day in the past six months, is one of the most common health problems to which adults seek medical care.[1,12] Chronic pain is often involved in multiple disease conditions and comorbidities that require management.[15] Chronic pain can be considered a symptom, a disease, or a condition that accompanies many other diseases.[16] Chronic pain affects health by limiting physical function and is also associated with many health consequences.

In the US, the 2016 National Health Interview Survey (NHIS) conducted by the Centers for Disease Control and Prevention (CDC) reported 20.4% of US adults had chronic pain and 8% had high-impact chronic pain (i.e., chronic pain that frequently limits life or work activities).[17] Pain can occur in anyone regardless of past medical history or comorbidity. Moreover, pain can complicate many other medical conditions such as dental problems, musculoskeletal conditions, gastrointestinal problems, neurological problems, mental health conditions, substance use disorders, cancer, and post-surgical care. If not properly managed, chronic pain can affect multiple organ systems and overall quality of life.[18] Chronic pain not only affects the individual's health, but also impacts the individual's family and society overall.

A study found chronic pain and high-impact chronic pain were more prevalent in adults with advanced-age, unemployment, living in or near poverty, living in rural areas, and having less than high school education.[17] For adults aged < 65 years, chronic pain and high-impact chronic pain were more prevalent in those with Medicaid and other public health care coverage compared to those having private insurance. For adults aged ≥ 65 years, those who have both Medicare and Medicaid had higher prevalence of pain compared to adults with all other types of health coverage. Chronic pain was more prevalent in non-Hispanic white adults compared to other racial groups and in veterans compared to non-veterans.[17] Another survey conducted in patients attending an outpatient drug and alcohol treatment program in the US revealed that 29% of the patients

experienced chronic severe pain and 26% had high intensity pain that interfered with their physical and psychosocial functioning.[19] Due to the high prevalence of chronic pain and a number of factors associated with pain, if not properly managed, chronic pain can result in neurological changes over time. This subsequently alters brain activity which can perpetuate pain or exacerbate pain experience.[16,18]

Opioid analgesics are the most frequently prescribed medications for pain management due to their pain relief efficacy.[2] The analgesic effect of opioids is produced through actions in the central nervous system (CNS). Opioid analgesics primarily act at the μ-opioid receptor, which is highly concentrated in the brain. Opioids can also be grouped into strong (e.g. oxycodone) and weak (e.g. tramadol) opioids according to their analgesic effect. Another way to group them is by their source i.e. natural (e.g. morphine), semi-synthetic (e.g. fentanyl), and synthetic opioids (e.g. methadone). There are multiple therapeutic uses of opioids including as an analgesic, preanesthetic agent, a cough suppressant, antidiarrheal, as well as opioid detoxification and maintenance. However, there are multiple harmful adverse effects, some of which can be fatal, including constipation, sedation, immunosuppression, hyperalgesia, withdrawal, tolerance, abuse, addiction, and respiratory depression.

2.2 Trends in opioid prescribing in the US

Since 1999, opioid prescribing in the US rose and reached a peak in 2010 according to the Drug Enforcement Administration's (DEA) records of opioid pain relievers sold to pharmacies, hospitals, and practitioners, sales of opioids quadrupled between 1999 and 2010.[20] Additionally, from 2009 to 2012, approximately 5 billion opioid analgesic prescriptions were dispensed from US retail pharmacies.[21] Annual opioid prescribing rates in the US increased from 72.4 to 81.2 prescriptions per 100 persons from 2006 to 2010.[22]

After this increase from 1999-2010, opioid prescribing rates were constant and later declined by approximately 13.1% in 2012.[22] In July 2012, the incidence of initial opioid prescriptions among opioid naive patients was 1.6% and later declined to 0.8% in December 2017.[23] In 2017, the prescribing rate had fallen to the lowest it had been in more than 10 years at 58.7 prescriptions per 100 persons (total of more than 191 million total opioid prescriptions).[24] Besides the decrease in opioid prescribing, the number of providers who initiated opioid therapy to opioid naive patients

also declined from 114,043 to 80,462. In summary, the overall trend in opioid prescribing in the US showed a dramatic increase since 1999, then later plateaued in 2010-2012, and began to decline since 2012.

Although opioid prescribing declined, the number of opioid prescriptions was higher in 2015, as compared to 1999 with the number of prescribed opioids three times higher. Moreover, high-risk prescribing (i.e. high dose and long duration) persisted in many regions of the country. A national study of Medicare part D beneficiaries in 2007-2012 found the proportions of recipients who received schedule II/III opioids more than 90 days in a year increased from 4.6% in 2007 to 7.4% in 2012.[25] Prescribed opioids with doses greater than 50 morphine milligram equivalent (MME)/day and for longer than a three-day supply were observed in opioid naive patients.[23] MME is dose conversion of opioids for comparison of different types of opioids. Another high-risk prescribing practice is the use of long-acting opioids for CNCP which is associated with increased risk of mortality.[26] Although overall opioid prescribing rates declined since 2012, high-risk prescribing has remained a problem which could result in adverse health outcomes.

In addition to high risk opioid prescribing, regional differences existed in prescribing rates with high prescribing rates remaining in certain areas of the country. Higher amounts of prescribed opioids were in counties with a larger proportion of non-Hispanic whites, higher prevalence of diabetes and arthritis, nonmetropolitan urban counties, and counties with higher rates of unemployment and Medicaid enrollment.[22] At the state level, Alabama, which has the highest number of opioid prescriptions in the country, had an opioid prescribing rate greater than the national rate and approximately three times greater than Hawaii, the lowest prescribing state. Indiana is among the US states with an opioid prescribing rate higher than the national rate. In 2017, the number of opioid prescriptions per 100 persons was 74.2 in Indiana while the national rate was 58.7 per 100 persons.[24] Although the national opioid prescribing rates decreased, many states still have prescribing rates that are higher than the national average which requires attention.

Opioid prescribing trends differ by prescribers' specialty. Primary care providers accounted for nearly half of the dispensed opioids in 2012.[27] Other than primary care providers, opioid prescribing rate were highest in pain medicine specialists, followed by surgery, and physical medicine/rehabilitation specialists. From 2012 to 2017, the largest increase in opioid prescribing rate was in physical medicine/rehabilitation specialists and the largest decline was in emergency medicine and dentistry. Another study in 2016-2017 reported the highest volume opioid

prescribers were internal medicine, followed by dentists, nurse practitioners, and family medicine.[28] The results suggest the need for focusing on specialties individually for safer opioid prescribing within each specialty.

2.3 Prescription opioid use in different populations

Many studies have evaluated opioid use patterns by assessing different populations, such as general population, older adults (age > 65), veterans, and patients with different diseases and conditions. A national telephone survey in 1998-2006 reported approximately 5% of US adults took an opioid.[29] The prevalence of those who used opioids regularly for at least five days per week for at least four weeks was 2% or 4.3 million individuals nationwide. Those who were older, less educated, females, and non-Hispanic whites were more likely to be regular users. Another study compared annual rates of opioid use and daily doses from 2007 to 2016 among commercially insured, Medicare (age ≥ 65), and disabled Medicare beneficiaries (age < 65).[30] Compared to the other two groups (commercial and Medicare > 65 years old), the disabled Medicare group had a higher annual opioid use prevalence, the highest rate of long term use, and the largest average daily doses across all years of study duration. The disabled Medicare group had increased annual use rates and average daily dose which did not increase in the other two groups.

Another population widely studied is veterans. A Veterans Health Administration (VHA) study reported the prevalence of opioid use for chronic noncancer pain (CNCP) increased from 1.3 million in 2009 to 1.4 million in 2011.[31] Each year, approximately 50% of VHA patients with CNCP received at least one opioid prescription. For those who received opioid prescriptions, the median daily dose was 21 MME and 4.5% had a mean daily MME higher than 120. The median days covered per year was 115 to 120 days in the years receiving opioid and 57% had at least 90 days per year opioids covered. Another study in veterans found that the number of opioids and MME prescribed within the VA had been rising since 2000 at its emergency departments (EDs), outpatient clinics, and hospitals.[32] Since 2011, the number of prescriptions written in outpatient clinics and EDs began to plateau and then declined slightly, but nonetheless, the doses prescribed continued to rise. To summarize, some groups of patients use opioids more commonly than the general population, these include Medicare, those with disabilities, and veterans.

2.4 Long-term opioid therapy

Long-term opioid use is also problematic. There is limited evidence on the effectiveness of long-term opioid therapy, especially for pain relief and functional status improvement.[33] Long-term opioid use often does not improve patients' functional status, but can cause many adverse effects including dizziness, nausea, vomiting, drowsiness, fatigue, pruritis, constipation, hyperalgesia, tolerance, and respiratory depression that further complicates pain control.[34-36] In addition, long-term use is associated with many aberrant behaviors and adverse health outcomes, such as opioid dependence, abuse, overdose, addiction, and mortality.[37-39] A study in patients with polyneuropathy receiving opioid prescription for at least 90 days did not find improvement in their functional status, but they had a higher risk of depression, opioid dependence, and opioid overdose compared to the control group.[39] Another study in patients with CNCP who remained in a pain management center for at least 3 years reported 29% of the patients had positive urine toxicity screens for illicit drugs and 22% had drug-seeking behavioral issues.[37] These behavioral issues included reports of lost or stolen opioid prescriptions, consumption in excess of prescribed dosage, visits without appointments, multiple drug intolerances and allergies, and frequent telephone calls to the clinic. Long-term opioid use in chronic pain patients is also associated with all-cause mortality.[38]

Definition of long-term use varies between studies, but the criteria used most frequently is continuous opioid use of at least 3-6 months.[40-42] CONSORT (Consortium to Study Opioid Risks and Trends) surveyed the overall trends in incident opioids prescribed for CNCP in more than 300,000 adults (age $\geq$ 18) enrolled in Group Health and Kaiser Permanente of Northern California health plans in 1997 to 2005.[43] The incidence and prevalence of long-term opioid use increased in both sites over the years. The incidence and prevalence increased by 6% and 5.5% respectively at Group Health and 8.5% and 8.1% respectively at Kaiser Permanente of Northern California. Long-term opioid use in this study was defined as receiving opioids for longer than 90-day episodes with at least 120-day total supply or at least 10 opioid prescriptions each year. An episode is defined as the days between the first and last opioid prescriptions. Another survey from the National Health and Nutritional Examination Survey (NHANES) reported an increased prevalence of prescription opioid use from 4.1% of US adults in 1999-2000 to 6.8% in 2013-2014.[44] The trend was largely contributed to the proportion of long-term users which increased from 45% to 79%.

Many factors are associated with a patient's transition to long-term use of prescription opioids. One important factor in transitioning patients to long-term opioid use is the initial opioid prescribing patterns.[45-47] Many opioid prescribing practices are associated with progression to long-term use including opioid use for acute post-surgical pain, use after accident and injury, and use in opioid naive patients. Patients who use opioids before and after surgery are more likely to transition to prolonged use compared to those with no history of opioid use.[48-53] Further, opioid naive patients receiving opioids for treatment of acute pain in the ED had increased risk of additional opioid use within one year after the initial ED visit.[54] Opioid naive patients who initiated long-acting opioids, had a high cumulative dose, and a higher number of prescription fills had higher risk of long-term use than those initiated with short acting opioids.[46] Patients who initially received a longer duration of opioids (> 5 days to 1 month) were more likely to transition from acute to long-term therapy.[42] In summary, the initial opioid prescription is a significant predictor of prolonged opioid use regardless of the opioid indication.[55]

Another important factor that contributes to long-term opioid use includes patients' medical conditions. As pain is involved in many diseases, there is significant evidence of opioid use patterns in patients with different medical conditions. The most common condition opioids are prescribed for is musculoskeletal pain. A study of 26,014 of primary care patients with low back pain, the most common musculoskeletal problem, found 61% received opioid treatment and 19% were long-term users.[56] Many factors are associated with longer duration of opioid use including psychological distress, obesity, smoking, increased health care utilization, and sedative hypnotic use. Persistent opioid use significantly increased the risk of dose escalation due to opioid tolerance.[57] However, increased dose of opioid therapy for chronic low back pain did not improve pain and function.

Another significant group of medical conditions associated with long-term prescription opioid use are mental health conditions. A study in 38.6 million Americans with mental health disorders reported 7.2 million (18.7%) used prescription opioids.[58] Adults with mental health conditions were more likely to use opioids compared to those without mental health conditions (OR 2.08; 95% CI: 1.83-2.35). A systematic review and meta-analysis reported high prevalence of mental health problems (32%) and pain (48%) in the general population who reported nonmedical prescription opioid use.[59] Nonmedical use is defined as the use of prescription drugs, whether obtained by prescription or otherwise, other than in the manner, for the reasons, or time

period prescribed or by a person for whom the drug was not prescribed.[60] Adults with mood disorders were more likely to start opioid therapy and to continue therapy long term for both acute and chronic pain.[61]

In addition to mental health conditions, history of substance use disorders (SUD) is another significant factor associated with long-term opioid use. Prescription opioid use for CNCP is more common in those with mental health and SUD compared to those without.[62] Patients with a history of SUD, suicide attempts, motor vehicle accidents, depression, anxiety, sleep disorders, tobacco cessation, and attention-deficit/hyperactivity disorder (ADHD) were more likely to fill opioid prescriptions, and subsequently progress to long-term use.[41] Another study using national MarketScan Commercial Claims databases from 2003-2013 reported those who had prior diagnoses of suicide attempt/self-injury, motor vehicle crash, opioid use disorders (OUD), SUD, depressive, anxiety, and sleep disorders were more likely to receive long-term opioid use compared to those who did not have these conditions.[41] Long-term use in this study was defined as having opioid refills of >90 day supply within a 6-month window. In summary, many factors contribute to long-term opioid treatment which significantly contributes to problematic opioid use behaviors and adverse health outcomes.

2.5 Drug overdose deaths

Overdose occurs in patients with chronic pain using higher prescribed doses of opioids (Table 2.1).[63,64] There has been a parallel increase in opioid pain reliever sales, overdose death rates, and substance abuse treatment admissions related to opioid pain relievers during 1999-2008.[20] Drug overdose deaths have been described in three waves.[65] **The first wave** of overdose deaths involved prescription opioids. The national trend in opioid-related overdose deaths compared to other substances rose between 1999 to 2009.[66] The increase was largely driven by prescription opioids followed by sedative hypnotics. Rates of drug overdose deaths increased for all age groups from 1999 to 2015, but the highest percent increase was within those 55-64 years of age in 1999 and in 45-54 years of age in 2015.[67] A report from Washington State in 2004 to 2007 found the majority of those who died of opioid-related overdoses were male, aged 45-54 years, and those enrolled in Medicaid.[68] Among those who died, methadone was the most commonly involved (64%) opioid, followed by oxycodone and hydrocodone. Of the decedents,

55% had at least one nonopioid medication listed in the death certificates, and in these cases, benzodiazepines and antidepressants were the two most commonly involved medications (21% and 32%).

Multiple factors are associated with risk of overdose death, including patient characteristics, social factors, environmental factors, past medical history, and patterns of opioid use. A study in Medicaid patients with CNCP found that factors associated with increased risk of opioid overdose death included dose greater than 50 MME/day and concurrent use of long and short acting opioids, sedative/hypnotics, and/or muscle relaxants.[69] Moreover, risk was significantly higher if opioids and other psychoactive substances especially sedative hypnotics were used together even when the opioid dose was not high.[69,70] Other factors included having four or more medication prescribers, using four or more pharmacies, and receiving opioids at dose > 100 MME/day.[71] Higher opioid dosage was associated with increased risk of overdose and death.[72] Other factors included middle-aged, non-Hispanic white, less educated, unmarried, living in rural areas, a history of potential opioid misuse and obtaining opioids from more than one doctor, financial problems, unemployment, physical disabilities, mental health conditions, cigarette smoking, alcohol, and illicit drug use.[73]

The second wave of drug overdose deaths was a rise in heroin-related overdose deaths since 2010. In 2015, heroin-related drug overdose death was 25% while it was only 8% in 2010.[67] Since more awareness and concerns were raised surrounding prescription opioid use and its consequences, prescription opioids became more difficult to access. Therefore, some people who had been misusing prescription opioids transitioned to heroin, which is cheaper and easier to obtain.[74,75] Many studies support that nonmedical use of prescription opioids is associated with heroin initiation.[74,76,77] Heroin use is considered a predictive factor of premature death in the US.[78] Factors associated with heroin initiation in those who used prescription opioids illicitly include white race, longer duration of prior opioid use, opioid dependence, and early age of opioid initiation.[79] A study using National Survey on Drug Use and Health (NSDUH) in 2010-2013 described the characteristics of US adults by grouping them into three groups including those who used heroin only, prescription opioids only, and both prescription opioids and heroin.[80] Factors associated with greater odds to be using only heroin include socioeconomic disadvantage, older age, disconnected from social institutions, criminal justice involvement, and easy access to heroin. Those in prescription opioid-only group were more likely to be economically stable, connected to

social institutions, less likely to have a criminal record, and had less access to heroin. Those who used both heroin and prescription opioids were younger white males with poor physical and mental health, had a history of other prescription misuse, and began misusing prescription at a young age.

In 2013, **the third wave** of overdose deaths was a sharp rise in deaths involving semisynthetic and synthetic opioids other than methadone, e.g. tramadol and fentanyl. Reports of increased fentanyl-related overdose deaths were published from multiple states.[81-83] Between 2013-2014, data from 27 US states reported the rate of death involving semisynthetic and synthetic opioids other than methadone increased by 26% and 80% respectively and continued to increase.[84,85] This was primarily due to the illicit manufacture of fentanyl. In March and October 2015, the DEA and CDC issued alerts indicating illicitly manufactured fentanyl as a national public health threat.[86] A study in Ohio reported that the highest death rate from fentanyl-related overdose decedents was in males, age 25-34 years, single or never married, and less than a high school diploma.[81] Another study found increased death rate for all sex, age, and ethnic groups.[85] Although there are some published articles attempting to understand fentanyl-related deaths, better surveillance of this issue at national level is still needed.

2.6 Physical, societal, and behavioral consequences of prescription opioid use

In addition to the parallel increase of prescription opioid use and drug overdose deaths, many adverse consequences are involved with opioid use including physical, societal, and behavioral impacts. First, some physical adverse effects of opioid use include tolerance and hyperalgesia that further complicate pain treatment (Table 2.1). Tolerance is a state in which the body no longer responds to a drug which subsequently leads to a higher dose required to achieve the same effect.[87] Hyperalgesia is a paradoxical state of nociceptive sensitization caused by exposure to opioid that leads the body to become more sensitive to pain.[88] One of the most serious opioid-related adverse effects is respiratory depression which can result in death.[89] Some short term adverse effects and worsening of sleep-disordered breathing can be reversed by opioid discontinuation, but some conditions that develop from repeated opioid exposure over a long period, such as addiction cannot simply be reversed with discontinuation. Second, there are societal and economic impacts related to chronic pain, opioid use, and consequences of opioids; these contribute to direct medical costs,

indirect medical costs, and nonmedical costs. Chronic pain contributed to an estimated of $560 billion each year in direct medical care costs, lost productivity, and disability programs.[90]

Third, behavioral consequences include many patterns of problematic opioid use. Problematic opioid use refers to many health conditions and aberrant behaviors related to opioid use, e.g. misuse, abuse, addiction, and OUD, see Table 2.1. Due to opioids' euphoric effects, they can be misused and diverted to individuals who were not prescribed the opioid. Misuse is defined as taking a medication in a manner or dose other than prescribed and diversion is defined as selling prescribed opioids or passing them on to others that later results in nonmedical use.[7,91] Common sources of nonmedical use of opioids include receiving opioids from friends or family members who received legitimate prescription opioids from healthcare providers.[92,93] All in all, prescription opioid use in chronic pain is a complex issue that have impacts on many dimensions.

2.7 Problematic opioid use

When use of prescription opioids increased dramatically in 1999, the rates of problematic opioid use also increased.[94] A systematic review and data analysis of 38 studies reported the prevalence of abuse to be 21-29% and rate of addiction to be 8-12% in patients with CNCP.[95] In 2007-2008, one telephone survey of US adults in the Geisinger Health System who were prescribed opioids reported the prevalence of OUD to be approximately 35%.[96] Patients with a history of nonfatal opioid overdose continued to receive opioid therapy after the overdose resulting in repeated overdose.[97] While studies reported the prevalence of aberrant medication-taking behaviors and OUDs to be significant, evidence on effectiveness of opioids for CNCP is limited.[98]

Multiple studies have been published on the risk factors associated with problematic opioid use.[99-102] A study in an addiction treatment clinic found that 33% of patients reported persistent pain and 47% reported intermittent pain.[103] Those who reported persistent pain were more likely to use alcohol or abuse other drugs and had worse Addiction Severity Index (ASI) scores for alcohol at 12 months, more likely to be hospitalized for any medical reason, and had higher total service costs compared to the other group who experienced less pain. One of the risk factors for opioid abuse and dependence was non-medical use of prescription opioids.[72,104] Patients reported using opioids not prescribed for them were more likely to report poor health, misused other prescription medications, and had used heroin.[104] A study reported that younger age, depression,

smoking, illicit drug use, and chronic pain were associated with prescription drug abuse.[105] Other factors associated with opioid overdoses include repeated opioid overdose episodes, frequent medical service use and high service cost, and received higher quantities of prescription opioids. Other associated comorbidities included mental health conditions, history of SUD, and concurrent use of psychotropic medications.[106,107] Opioid-related factors, such as prescription opioid use for CNCP, duration of treatment, and daily dose were also predictors of incident OUDs.[108] These factors are important to help clinicians identify drug aberrant taking behaviors and guide clinical decisions for treating patients with CNCP to prevent negative consequences.

Table 2.1. Commonly used terms to describe problematic opioid use

Terms	Definition
Abuse[109]	Harmful or hazardous use of psychoactive substances, including alcohol and illicit drugs.
Addiction[110]	A primary, chronic disease of brain reward, motivation, memory and related circuitry. Dysfunction in these circuits leads to characteristic biological, psychological, social and spiritual manifestations. This is reflected in an individual pathologically pursuing reward and/or relief by substance use and other behaviors. Inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.
Dependence[109]	A cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.
Misuse[91]	Taking a medication in a manner or dose other than prescribed, taking someone else's prescription even if for a legitimate medical complaint such as pain, or taking a medication to feel euphoria.

Table 2.1 continued

Terms	Definition
Opioid use disorder (OUD)[111]	A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following in the 12-month period. 1. Opioids are often taken in larger amounts or over a longer period than was intended. 2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use. 3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects. 4. Craving, or a strong desire or urge to use opioids. 5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home. 6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids. 7. Important social, occupational, or recreational activities are given up or reduced because of opioid use. 8. Recurrent opioid use in situations in which it is physically hazardous. 9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance. 10. Exhibits tolerance. 11. Exhibits withdrawal.
Overdose[112]	Injury to the body (poisoning) that happens when a drug is taken in excessive amounts. An overdose can be fatal or nonfatal.

2.8 Concomitant use of opioids and other medications

Concurrent use of opioids and some other psychoactive medications can subsequently increase the risk of adverse outcomes. Among psychoactive medications, there is considerable evidence of negative consequences from concurrent use of opioids and benzodiazepines. Benzodiazepine use in patients receiving opioid therapy is common.[113,114] Concomitant use of this

combination results in increased risk of respiratory depression and overdose death.[113-119] From 2004 to 2011, rates of ED visits involving nonmedical use of opioids and benzodiazepines increased from 11.0 to 34.2 per 100,000 population and drug overdose deaths increased from 0.6 to 1.7 per 100,000 population.[116] Increased risk of death was associated with concomitant use, current and former benzodiazepine users, and higher daily benzodiazepine dose.[114] Benzodiazepine use was a predictor of unsuccessful treatment with opioids.[115] Other adverse effects resulting from concomitant use included wounds, injuries, violence-related injuries, opioid/nonopioid overdose accidents, self-inflicted injuries, and death.[118]

There is growing evidence of adverse effects related to use of opioids with *z-drugs* (i.e. zolpidem, zaleplon, zopiclone), gabapentin, and pregabalin. Similar to benzodiazepines, when used with opioids the risk of respiratory depression increases as well as overdose death.[120-122] A study reported that z-drugs and pregabalin prescriptions were associated with overdose death in patients using methadone or buprenorphine for opioid maintenance therapy.[123] A study in Medicare adults (age ≥ 65) reported the prevalence of at least one controlled substance use to be 58%.[113] Of those, 44% received an opioid, 19% received a benzodiazepine, and 7% were prescribed non-benzodiazepine hypnotics. Further, factors related to the receipt of controlled substance including younger age, white race, recent surgery, injuries, referral from inpatient settings, and living in a rural location.

Because gabapentin and pregabalin are commonly used for pain, concurrent use of these medications and opioids is common. A study reported pregabalin as a drug of abuse in patients with opioid addiction.[124] Another study found that opioid abusers sought gabapentin to amplify the potency of opioids.[125] Use of moderate (900 – 1,799 mg/day) and high (≥ 1,800 mg/day) gabapentin dose was associated with almost 60% increase in the odds of opioid-related deaths compared to those without opioids and gabapentin concurrent use.[121] Additionally, high pregabalin dose (> 300 mg/day) was associated with significantly increased odds of opioid-related deaths compared to those without concurrent use of opioids and pregabalin.[120] To summarize, concurrent use of opioids and psychoactive medications result in increased risk of many adverse health outcomes, including risk of respiratory depression and overdose death.

2.9 Economic burden and healthcare utilization related to prescription opioids

As problems of opioid use has been a public health issue since 1999, not only did the problems result in adverse health outcomes, but there was also impacts on societal costs and increased healthcare utilization. A study from an administrative claims database in 1998 to 2002 in the US found that mean annual direct health care costs for opioid abusers were more than eight times higher than nonabusers ($15,884 versus $1,830).[126] The increase in health care costs was largely due to higher drug utilization. Abusers incur higher costs from hospital inpatient, physician-outpatient, and mean drug utilization compared to nonabusers.[127] A study estimated the total US societal costs of prescription opioid abuse in 2007 was $55.7 billion.[128] Of those, 46%, 45%, and 9% were workplace, health care, and criminal justice costs respectively. Workplace costs were largely from lost earnings, premature death, and reduced compensation/lost employment. Health care costs comprised of excess medical and prescription costs. Criminal justice costs were mostly from correctional facility and police costs.

Chronic opioid therapy and problematic opioid use are also associated with increased healthcare utilization, e.g. emergency department (ED) visits, hospitalization, medical encounters, addiction treatment, and utilization of other medical services.[103,129-135] In patients who used opioids persistently (at least 90 continuous days within 6 months), significant factors associated with ED visits and alcohol or drug-related encounters included use of long acting opioids, use of any schedule II opioids, and MME dose of greater than 120 mg/day.[134] A study in veterans who reported persistent pain were more likely to be hospitalized than those without pain.[103] The CDC reported an 111% increase in ED visits involving nonmedical use of opioids from 2004-2008.[131] The opioids most commonly associated with visits were oxycodone, hydrocodone, and methadone. During the same period, ED visits involving nonmedical use of benzodiazepines increased by 89%. The increase in ED visits represented an impact of morbidity associated with prescription drug overdoses in the US. In conclusion, opioid users utilized more healthcare resources than nonusers.[136] Opioid use for CNCP and problematic use is not only associated with patients' poor health outcomes, but also associated with increased societal costs and healthcare utilization.

2.10 Mitigation strategies to combat problematic opioid use

Since prescription opioids have become a public health concern in North America, especially in the US, many strategies have been introduced to mitigate opioid misuse. Some strategies target prescribing practices including limiting opioid use to the lowest effective dose for the shortest effective duration, regular monitoring and assessment of benefits as well as risks, physician-patient communication, and patient education.[137,138] Urine screening is also recommended as a tool to monitor treatment of CNCP with opioids.[37,139-142] Another strategy is the use of screening tools or prediction models to detect patients at high risk of OUDs.[143-146] Many studies on factors associated with OUDs have been published to help prescribers identify patients at risk of problematic opioid use.[55,99,106,147-151] Some common factors associated with OUDs include severity of pain, opioid dose, duration of opioid use, patient's history of drug and alcohol abuse, and mental health issues.[64,99,107,108,152-156] In addition to these factors, concurrent use of opioids and other psychoactive drugs (i.e. benzodiazepine, z-drug hypnotics, and gabapentin) is associated with an increased risk of drug overdose mortality.[123] Moreover, use of medication-assisted treatment (MAT) with methadone, buprenorphine, naloxone, and naltrexone are recommended to combat problematic opioid use. However, access to these treatments may be limited and under-ulilized.[157,158]

An important mitigation strategy is the use of Prescription Drug Monitoring Programs (PDMPs). PDMPs are statewide electronic databases that help providers track patients' use of controlled substance prescriptions. The PDMP in Indiana is called INSPECT which summarizes the controlled substances a patient has been prescribed, the practitioner who prescribed them, the dispensing pharmacy where the patient obtained them, dosing, MMEs, and opioid risk score.[159] PDMPs help providers identify patients at risk of opioid misuse, OUD, and/or overdose due to overlapping prescriptions, high dose, or co-prescribing of opioids with other controlled substances, e.g. benzodiazepines.[112] Monitoring controlled substance usage using PDMPs is meant to be one strategy to detect doctor and pharmacy shopping behavior and potential overdoses.[160] PDMPs are associated with reduced opioid use and doctor shopping in the US compared to the states not using PDMPs.[161,162] However, use of PDMPs are not consistent across the US because of differential mandates in the use and there are limitations in information sharing across states.

The most significant guideline release was the Center for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain, United States 2016.[11] This guideline

consists of three domains that include 12 recommendations for primary care clinicians (Table 2.2). The purpose of this guideline was to improve safety and effectiveness of pain treatment with opioids and to minimize risks associated with long-term opioid use in patients with chronic pain excluding active cancer treatment, palliative care, and end-of-life care.

The CDC guideline is intended to be a practice guide for clinicians to improve opioid prescribing. Many providers find the guideline necessary for decision making and suggest that this guideline can improve opioid prescribing practices.[163,164] However, there have been debates about its impact on patients. Many issues and concerns were raised including that it might not affect opioid prescribing practices. In addition, treatment access problems were not considered because many patients do not have access to other treatments for their pain, so they have to rely on medications treatment including opioids. This subsequently result in some patients being negatively affected by stricter prescribing. Further, challenges in balancing between adequate pain control and safe opioid use remains a problem.[165-170]

Table 2.2. Recommendations of CDC Guideline for Prescribing Opioids for Chronic Pain, United States 2016 [11]

Recommendations	Details
Domain A: Determining when to initiate or continue therapy	
1	Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred
2	Establish treatment goals and weigh benefits and risks
3	Discuss realistic benefits and risks with patients before and periodically during treatment – both are responsible for managing treatment
Domain B: Opioid selection, dosage, duration, follow-up, and discontinuation	
4	Use immediate release opioids instead of extended-release or long-acting when starting therapy
5	Prescribe the lowest effective dose (High Dose = MME/day > 90)
6	Preferred treatment duration of 3 days or less for acute pain (> 7 days rarely needed)
7	Evaluate benefits and harms after 1-4 weeks of starting therapy and consider tapering down to lower dose or discontinue
Domain C: Assessing risks and addressing harms of opioid use	
8	Evaluate risk factors for opioid-related harms

Table 2.2 continued

Recommendations	Details
9	Review patients' history of controlled substance prescriptions using PDMP data
10	Use urine drug testing before and during therapy
11	Avoid prescribing opioid and benzodiazepine together
12	Arrange treatment for patients with opioid use disorders, i.e. MAT

A study by the CDC used a US opioid prescription database from 2012-2017 and compared opioid prescribing before and after the guideline release.[163] Many opioid prescribing measurements were decreasing before the guideline release and significantly declined at the time after its release. However, opioid prescribing measurements in this study included prescribing rate, average dose in morphine milligram equivalent (MME) per day, average days supply, percentage of patients prescribed overlapping opioids and benzodiazepines, and percentage of opioid naive patients prescribed long acting opioids. One limitation of this study was using non-specific patient group because this study used data of all opioids prescribed nationwide. Another limitation is the absence of health outcome comparison before and after guideline release.

In addition to the CDC guideline, there had been many national and local guidelines as well as regulations that were enforced to guide opioid prescribing and mitigate opioid misuse. At the national level in 2014, the US Drug Enforcement Administration (DEA) announced rescheduling of controlled substances including placement of tramadol into Schedule IV and reschedule of hydrocodone combination products from Schedule III to Schedule II.[171,172] In July 2017, Indiana passed Senate Bill 266 on prescribing and dispensing opioids which limited the initial opioid prescription for an adult to not exceed a 7 day supply.[173,174] Changes of national and state regulations could also affect opioid prescribing patterns and health outcomes in Indiana.

CHAPTER 3. METHODS

3.1 Study duration, study design, and data source

Data obtained for this study spanned 6 years from January 1, 2012 to December 31, 2017. The study was designed as a retrospective cohort using medical, pharmacy, and encounter data contained within the Indiana Network for Patient Care (INPC). INPC is managed by Regenstrief Institute (Indianapolis, IN). INPC is a statewide health information exchange (HIE) database that captures and stores clinical data from a majority of Indiana's health systems, hospitals, clinics, providers, payers, health departments, laboratories, and public health data.[175,176] Most clinical data in the INPC are from electronic health record (EHR) entries. In addition, health systems participating in the network contribute other data, such as patient encounters, admission and discharge summaries, laboratory results, radiology reports, pathology reports, inpatient medication data, outpatient medication lists, and pharmacy prescription data.[177] Pharmacy prescription data is contributed from Surescripts®, a health information network that connects over 95% of US pharmacies.[178] INPC is housed within the Regenstrief Institute Data Core, whose analysts have full access to the data repository and handle protected health information (PHI). The INPC data used in this study were deidentified and extracted by data analysts included patient, pharmacy, and clinical encounter data. This study was exempt from Indiana University Institutional Review Board approval. Data were obtained as SAS (Cary, NC) data sets. Specific details regarding data management are provided in the next chapter. Appendix E outlined what was in the data files.

3.2 Inclusion and exclusion criteria

The opioid index date was defined as the first date that an opioid was prescribed. Patients were included if they were at least 18 years old, opioid naive, and had an opioid index date within the study period. Patients were considered opioid naive if they had no prior opioid prescription history in the past 12 months. Patients must also have at least 6 months of available data after the index date. Exclusion criteria included patients diagnosed with cancer, terminal illness, and malignant neoplasm after index date, as well as those receiving hospice care. These patients were excluded because opioid use in these patients differ substantially from others.

3.3 Dependent variables

Dependent variables included a composite outcome measuring problematic opioid use, as well as all-cause mortality, and healthcare utilization. The composite outcome comprised of at least one diagnosis of either opioid abuse, opioid dependence, or opioid overdose determined by International Classification of Diseases (ICD) codes including ICD9-CM or ICD10-CM codes (Appendix A) within the study period. The composite outcome of opioid abuse, dependence, and overdose was used as an outcome to include more patients with the outcome related to problematic opioid use than using each individual outcome alone because these outcomes are likely related to opioid use disorders (OUDs). Further, many patients had at least one outcome of opioid abuse, dependence, and overdose or either of these combined. Time from index date to first diagnoses of opioid abuse, dependence, and overdose were recorded separately for each individual outcome. Time from index date to the composite outcome was determined by number of days from index to the first diagnosis of any of abuse, dependence, or overdose. Healthcare utilization consisted of number of all-cause ED visits and all-cause hospitalizations as determined by EHR data within the INPC. Death was determined by data analysts using recorded death data in the INPC linked by social security number in Indiana State death registry. Number of days from index date to death was also recorded for those who died.

3.4 Independent variables

Independent variables related to patient characteristics included patients' age at index date, sex, and race. Additional variables included time spent in the study (number of days from opioid index date to last encounter in the study), modified Charlson Comorbidity Index (CCI)[179-184] which represents the patients' comorbidity score at baseline (Appendix B), presence of mental health conditions, long-term opioid user, and whether or not patients received medication-assisted therapy (MAT), i.e. buprenorphine, buprenorphine/naloxone, and naltrexone. Long-term opioid use was defined by having a total day supply of an opioid for at least 90 days within six months. Opioid-related independent variables include index date (exact calendar date of index), subsequent opioid prescription dates, specific opioids, National Drug Code (NDC), number of opioid prescriptions, opioid strength, opioid dose in morphine milligram equivalent (MME), dispensed amount, and days supply. Opioid strength in milligrams was converted to unit MME using opioid

conversion factors by multiplying the product strength with the conversion factor. Each opioid dose in MME compares to one milligram of oral morphine. (Appendix C.1).[185] Converting opioid dose in milligram to MME allowed for standardized comparisons of doses across different types of opioids. The unit MME was further calculated to MME per day using the following formula.[185]

$$\text{MME/day} = \frac{\text{Unit strength (mg) x Dispensed amount x MME conversion factor}}{\text{Number of days supply}}$$

Use of short (SA) and long acting (LA)/extended release (ER) opioids were considered concurrent when the prescribed dates were within 30 days of each other. See Appendix C.2 for a list of short and long-acting opioids classified by the CDC.[185] Opioid and concurrent medication use was determined when the medications were prescribed within 30 days of the opioid index date. Non-opioid medications in this study consisted of benzodiazepines (including z-drugs; zolpidem), gabapentin, and pregabalin. Pharmacy prescription records for medications included medication name, NDC code, strength, dispense amount, and days supply. From the pharmacy data, concurrent use of opioid and non-opioid medications was explored. The non-opioid combinations of interest consisted of combinations of opioids with benzodiazepines, gabapentin/pregabalin, and both benzodiazepine-gabapentin/pregabalin.

Standardization of benzodiazepine dose was conducted using benzodiazepine equivalent doses which allowed dose comparisons across different types of benzodiazepines (Appendix D).[186] Benzodiazepine dose was converted into unit diazepam milligram equivalent (DME). Each benzodiazepine dose in DME compares to one milligram of oral diazepam. Then DME per unit was further calculated to DME per day using the same formula as opioid calculation. See Appendix E for full details of variables in each data set and their definitions.

3.5 Statistical analyses

Statistical analyses were performed on the final patient cohort and data sets after data management. SAS 9.4 (Cary, NC) was used for all data manipulation and most statistical analyses. For descriptive analyses of normally-distributed continuous variables, mean and standard variation were reported, otherwise median and range were reported. Normality was determined by QQ plots

in SAS and differences between mean and median. Continuous variables that were not normally distributed were grouped into categorical variables. For categorical variables, frequency and percent were used to report summary data. For summary data comparison of variables, parametric t-test or nonparametric Wilcoxon Rank Sum was used for continuous variables. Chi-square or Fisher's Exact Test was used for comparison between categorical variables. For all analyses, $p < 0.05$ was considered statistically significant.

3.5.1 Specific aim 1: Factors associated with composite outcome of opioid abuse, dependence, and overdose diagnoses, and mortality

Patients were considered to have the composite outcome if they had the first diagnosis of either opioid abuse, dependence, or overdose within the study period. Patients who did not have any of these diagnoses by their last encounter in the data were considered to not have the outcome. The independent variables in the full model included index age, sex, race, CCI, mental health conditions, long-term opioid use, time spent in the study, opioid dose (MME/day), opioid days supply, and concurrent uses of SA/LA opioids, opioid-benzodiazepine, opioid-gabapentin/pregabalin, and opioid-benzodiazepine-gabapentin/pregabalin. Logistic regression with stepwise selection was used for final model selection to determine significant factors associated with composite outcome of opioid abuse, dependence, and overdose diagnoses. Odds ratios (OR) and 95% confidence intervals (CI) were used to report composite outcome.

For mortality, death and time from opioid index date to death were recorded. Those who were still alive at the last encounter within the study period were censored and time from index date to the last encounter was used meaning that the outcome of interest was not observed within the study period. The independent variables in the full model included index age, sex, race, CCI, mental health conditions, long-term opioid user, receipt of MAT, opioid dose (MED), opioid day supply, and concurrent use of SA-LA opioids, opioid-benzodiazepine, opioid-gabapentin/pregabalin, and opioid-benzodiazepine-gabapentin/pregabalin. Cox proportional hazards with stepwise selection was used for final model selection to identify associated factors with all-cause mortality. Hazard ratios (HR) and 95% CIs were used to report these outcomes. Both logistic regression and Cox proportional hazards were controlled for effect modifiers and confounders, such as age, sex, race, time patients spent in the study, long-term opioid use, CCI, and mental health conditions.

3.5.2 Sub aim 1: Association between benzodiazepine use and composite outcome of opioid abuse, dependence, and overdose and mortality

Logistic regression and Cox proportional hazards were repeated with both composite outcome and mortality to determine the association of these outcomes and benzodiazepine use. All independent variables used in specific aim 1 were included in the full model for analyses of sub aim 1. However, variables of opioid dose (in MME/day) and opioid days supply were replaced with benzodiazepine dose converted to diazepam milligram equivalent (DME) per day and benzodiazepine days supply in the full model. SAS 9.4 (Cary, NC) was used for all analyses.

3.5.3 Specific aim 2: Factors associated with healthcare utilization

Number of all-cause ED visits and hospitalizations were recorded for each patient and were counted throughout the study duration. For patients who did not have any ED visits or hospitalizations during the study period, the number of visits was zero. The independent variables in the full model included index age, sex, race, CCI, mental health conditions, long-term opioid use, time spent in the study, opioid dose (MED), opioid day supply, and concurrent uses of SA-LA opioids, opioid-benzodiazepine, opioid-gabapentin/pregabalin, and opioid-benzodiazepine-gabapentin/pregabalin. Poisson regression with backward elimination was used for final model selection to determine significant factors associated with the outcomes. Continuous variables were converted to categorical variables for Poisson regression because Poisson regression was used to analyze discrete variables, but not continuous variables. Backward elimination was used instead of stepwise selection because of the absence of stepwise model selection function in SAS Poisson regression. Likelihood-based Akaike Information Criterion (AIC) was used to determine a better model.[187] AIC is an estimation of prediction error and lower AIC suggests a better model with a better fit to the data. Risk ratios (RR) and 95% CIs were used to estimate effect sizes. The models were analyzed separately for each outcome of ED visits and hospitalizations. SAS 9.4 was used for all analyses.

Sensitivity analyses of specific aim 1 and 2 were conducted to determine the robustness of outcomes. The variables of CCI and mental health conditions were omitted in sensitivity analyses due to missing diagnosis codes. Logistic regression, Cox proportional hazards, and Poisson regression were analyzed for composite outcome, mortality, and healthcare utilization respectively.

3.5.4 Specific aim 3: Opioid prescribing and associated adverse outcomes before and after pivotal events related to opioid prescribing

The outcomes of interest included median opioid dose (MED), median opioid day supply, incidence rate of composite outcome, and death rate. Changes of these outcomes were determined over time within the study period, 2012-2017. Each outcome was measured at every month in the study period which resulted in a total of 72 time points. The first and last time points comprised of data from January 2012 and December 2017 respectively. Pivotal events related to opioid prescribing assessed in the analyses comprised of three policies including rescheduling of tramadol to a schedule IV controlled substance which occurred in August 2014, rescheduling of hydrocodone from a schedule III to II controlled substance which occurred in October 2014, and CDC opioid prescribing guideline release. Scheduling changes of tramadol and hydrocodone were assessed together as a single time point because these changes occurred two months apart. Therefore, the time points for the pivotal events related to opioid prescribing included tramadol and hydrocodone rescheduling in October 2014 and publication of CDC opioid prescribing guideline in January 2016.[11,171,172] The 72 time points were divided into three phases, consisting of 34, 14, and 24 time points representing time before any policies were implemented, time after tramadol and hydrocodone schedule change, and time after CDC guideline release respectively. Another policy that might affect opioid prescribing was Indiana's Senate Bill 266 which limited initial prescription opioid day supply to 7 days.[173] This bill was effective in July 2017; therefore, this policy change was not included in the analysis because there were not adequate time points to determine impact after this bill became effective.

The outcomes were measured at each time point and plotted to see changes over time. For continuous outcomes of opioid dose (MME/day) and opioid day supply, the mean of each outcome was measured at each time point. For categorical variables, death and composite, the incidence rate was calculated by the number of events divided by person-days of the people in the cohort at each time point and compared overtime. Interrupted time series analysis of segmented regression and quadratic time trend was used to evaluate the impact of pivotal events on opioid prescribing and adverse outcomes in Indiana. The impact of policies implemented and guideline published was tested by changes in time and trend (slope). R 1.2.1335 (R Core Team (2014), Vienna, Austria) was used for interrupted time series analysis to determine the impact of guideline release on opioid prescribing and generating graphs representing changes of outcomes over time.

CHAPTER 4. DATA MANAGEMENT

Data were grouped into five main data sets including patient, opioid, benzodiazepine, gabapentin/pregabalin, and encounter. The opioid, benzodiazepine, and gabapentin/pregabalin data sets were referred to as the pharmacy data set. Each patient was assigned a unique identification number (study ID). Each observation in the patient data set had a single patient observation while all other data sets had multiple observations for each patient per single study ID. Every study ID in the data set had at least one observation in the opioid data set because of the inclusion of at least one opioid prescription. However, not every study ID in the patient data set had an observation in the benzodiazepine, gabapentin/pregabalin, or visit data sets if the patients did not have a prescribed benzodiazepine or gabapentin/pregabalin in the pharmacy record or had no non-pharmacy visit encounters.

Descriptive statistics and data distribution of every variable in each data set were examined using SAS 9.4 (Cary, NC). Proc univariate was used to examine the distribution of numeric variables and proc freq was used to examine categorical variables. Further, removal of observations from the data sets was done to exclude outliers or verifiable inaccurate data. Data management was performed using SAS to prepare data for statistical analyses. Each of the five data sets was explored and manipulated separately for further analyses. To ensure accuracy of opioid, benzodiazepine, and gabapentin/pregabalin data, documents from US Food and Drug Administration (FDA) and CDC were used for verification of the data by linking the same NDC of the medications in our data set to the NDC listed in the CDC document.[185,188] Some variables not provided in the original data sets were pulled from the CDC document, such as dosage form. Some variables were added to verify the calculation in our data set. For example, our data set was explored if medication name and medication strength were recorded accurately for each NDC and if MME was accurately converted. Details of data verification in each data set are described in the following sections. A full list of variables and definitions in each data set can be found in the data dictionary (Appendix E).

4.1 Patient data set

This data set had a single observation per study ID (Appendix E). The number of patients in this data set before data manipulation was 483,683 observations and included 25 variables. The variables in this data set were patients' characteristics, e.g. sex, race, age, and some variables related to the outcomes, e.g. total number of hospitalizations. Then, 98,183 observations were removed after examination of data distribution (See Figure 4.1). First, number of days from index date to last encounter was less than 0 indicating that the encounter came before the index date. The day of last encounter should be at least zero or a positive integer. The second reason was for patients who died, the number of days from index date to last encounter was greater than number of days from index to death. This was possible because some financial data were later processed and appeared as the last encounter after death date. However, for calculation purposes, day of last encounter that exceeded death date was changed to the day death was recorded. Third, number of days from index date to last encounter was greater than 2192 days. The duration of this study was 2012-2017 or 2,192 days. Thus, the number of days from index to last encounter that exceeded 2,192 days were replaced to a maximum of 2,192 days. Fourth, the maximum age was limited to 99 years to reduce the likelihood of erroneous data. Finally, patients who had diagnosis codes of malignant neoplasms after index date and those receiving only medications for medication-assisted therapy (MAT) were excluded from the analyses. Therefore, the remaining number of observations in patient data set was 341,721. Figure 4.1 provides the breakdown of these exclusions.

Some variables related to the outcomes were also recorded in the patient data set, e.g. diagnoses of opioid abuse, dependence, overdose, and death. Number of days from index date to the first diagnosis of each outcome was also recorded. Binary variables including dependence, abuse, overdose, and death were created according to the existing variables related to the outcomes (Appendix E). Binary variable of the composite outcome was defined as "Yes" if patients had at least one diagnoseis of either of opioid abuse, dependence, or overdose. Using the same definition, binary variable of death was defined as "Yes" of patients had the number of days from index date to death recorded in the data. If number of days from index date to the outcome was missing, the binary outcome was defined as "No". For example, new variable abuse = "Yes" when number of days from index to first abuse diagnosis was not missing, otherwise abuse = "No". Observations in patient data set were further excluded after examination of opioid data set. Each study ID in patient data set had at least one observation in opioid data set and these two data sets were managed

separately. Therefore, the study ID's that appeared in both patient and opioid data sets after exclusion remained.

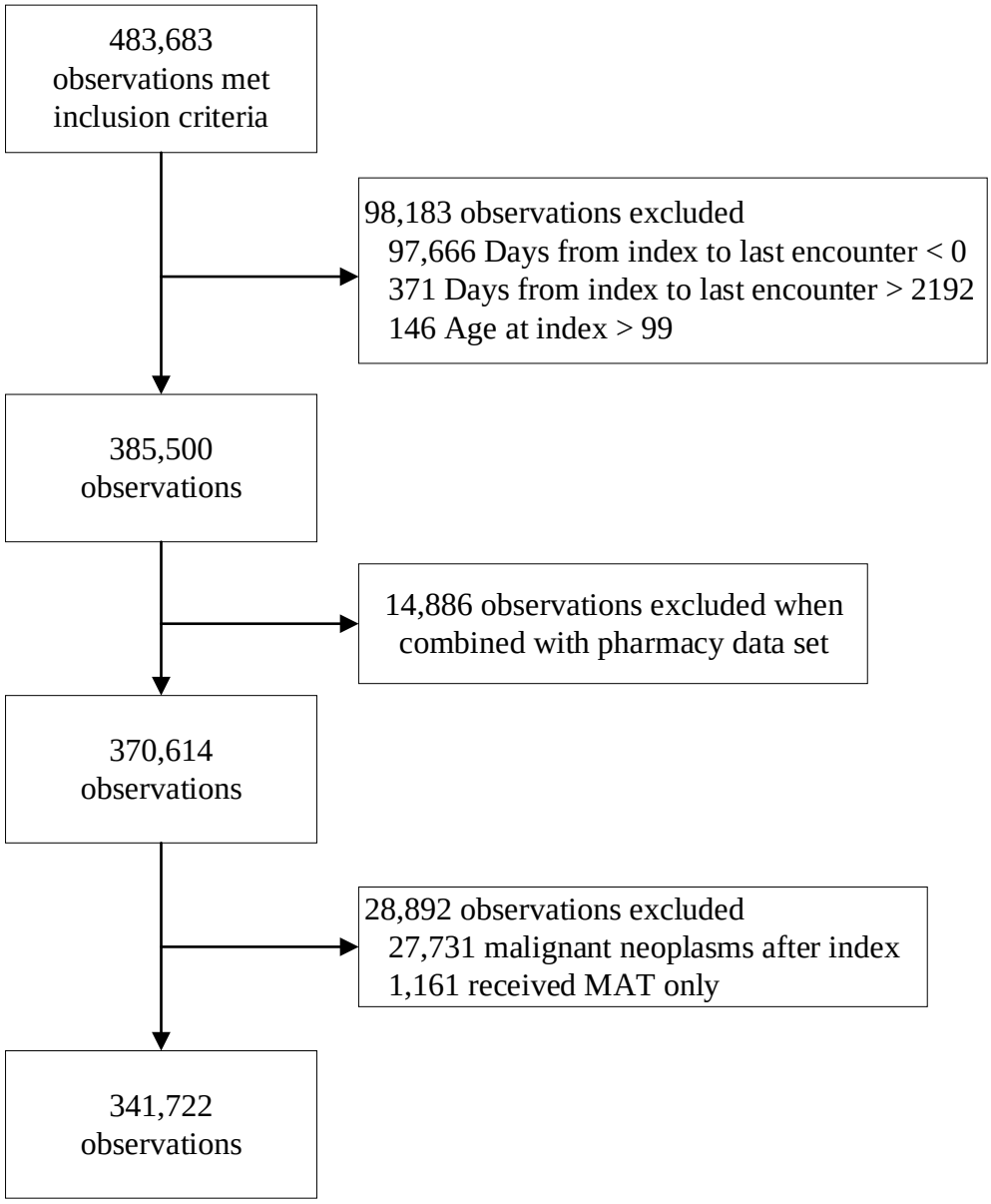

Figure 4.1. Cohort creation

4.2 Opioid data set

This data set had multiple records for opioid prescriptions per study ID. It contained 1,812,243 observations and 10 variables. There was at least one opioid observation for each patient. Data from the CDC compilation of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral morphine milligram equivalent conversion factors, 2018 version documentation were obtained.[185] Data regarding opioids from this document were used to verify the accuracy of opioids identified in this data set. Opioid data from CDC's document were linked to the opioid data set by NDC9 codes for data reconciliation. Some variables that were not contained in our original opioid data set were pulled from the CDC document including dosage form, duration of action (short/long acting), and MME conversion factor. So, other data were pulled from the CDC document to put in the data set to verify data accuracy in our data set including opioid trade name, generic name, strength, and MME calculation. For example, unit strength of opioid in MME contained in our data set was cross checked with the calculation using opioid strength and MME conversion factor from the CDC document. Some inaccurate calculations were corrected according to the CDC document. Further exploration of fentanyl patches was done regarding CDC's recommendation on the clinical use of fentanyl patches that one fentanyl patch was intended for three days of use. Thus, the conversion factor of fentanyl patch was 7.2 instead of 2.4 and the days supply for one fentanyl patch was three days.

After verifying the data set with CDC's document, there were some NDC codes in our data set that did not appear in the CDC document. These NDC codes were explored manually to define the specific opioid. After manually exploring NDC codes, some medications were excluded because they were not opioids, i.e. loperamide. Further, some opioids not used to control pain were excluded, for instance, opium tincture for diarrhea. Additionally, opioids for the common cold and in cough medications were excluded because these preparations were used widely in many other patients that might not be our target population. In particular, cough preparations containing opioids are used widely in long-term care facilities which might include terminally ill patients which are excluded. Moreover, other dosage forms that were not oral or transdermal were excluded, such as injectable medications because these were infrequent in the pharmacy database. After removal of these medications, descriptive statistics of each variable were explored to see data distribution. Some outliers were excluded, for example day supply greater than 365 days. Then observations with dispense amount of zero were changed to missing for calculation purposes.

In the opioid data set, methadone and buprenorphine were further evaluated to differentiate between opioids for pain and medication-assisted therapy (MAT) in the context of OUD treatment. All methadone prescriptions in this dataset were considered to be used for pain and not MAT because methadone for MAT was prescribed in methadone clinics of whose data was not in our database. Our pharmacy database was from Surescripts® which included only outpatient prescriptions. For buprenorphine, dosage was used to determine its clinical indication because different dosages are used for different indications. Extended release transdermal patch (Butrans®) buprenorphine and some products of buccal films (Belbuca®) were categorized as for pain control while other dosage forms, such as oral tablets and sublingual films (Suboxone®) were categorized as MAT. Medications indicated for MAT were excluded from the opioids used for analyses, but were used as an independent variable.

Because our data sets were from a HIE, one observation might have been from more than one data source. This resulted in observations that seemed to be duplicates for a single pharmacy visit observed by the same study ID having the same opioid medication with the same dose on the same day. Further data exploration of duplicate records was done for the remaining 1,746,914 observations to find patterns of duplicates as described in Appendix F. After removal of duplicate records, the opioid data set was linked to patient data set using inner join in SAS proc sql to determine the study ID's that remained in both data sets. Inner join was used because the patient and opioid data sets were manipulated separately. Some patients were excluded from the patient data set while some were excluded from the opioid data set. Only the patients that remained in both data sets were used for further analysis. Finally, there were 1,488,087 observations in opioid data set for 370,613 patients (Figure 4.2).

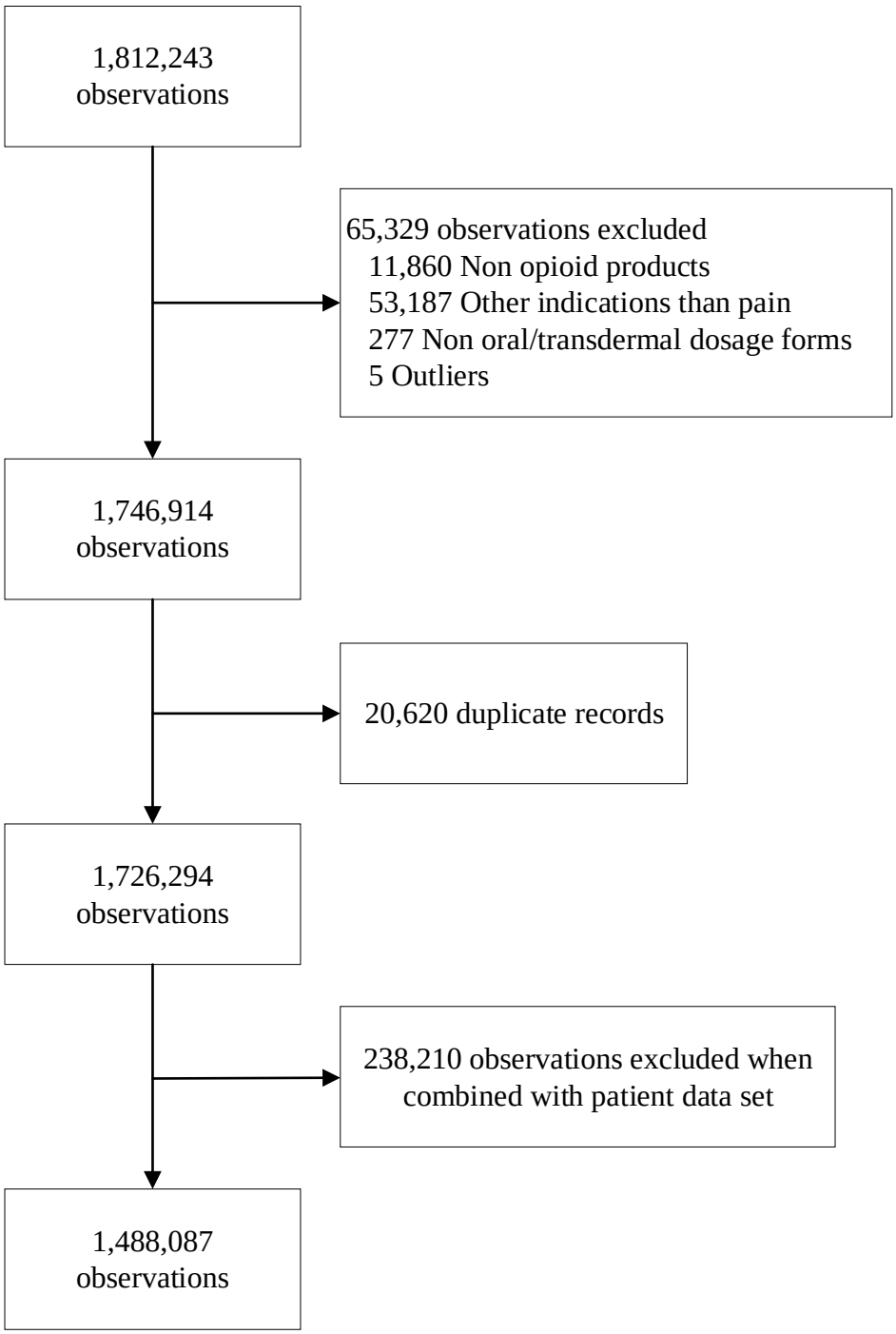

Figure 4.2. Cohort creation of opioid data set

4.3 Benzodiazepine data set

A total of 776,675 observations and 8 variables were contained in the benzodiazepine data set. Similar to what was done for opioids, benzodiazepine data from the same CDC compilation (2018 version) of benzodiazepines, muscle relaxants, stimulants, zolpidem, and opioid analgesics with oral MME conversion factors was imported to cross check with our data set.[185] The data sets were linked using NDC codes. Benzodiazepine data that were pulled from the CDC document included medication brand name, generic name, dosage form, product strength, and unit of measurement. These data were used to verify the accuracy of data in our benzodiazepine data set. Dosage form was added as a variable because this information was not available in our data set. In addition to benzodiazepines, zolpidem and zaleplon ("z-drugs") are hypnotics that should be considered when used concurrently with opioids because the combination could increase risk of overdose deaths due to enhanced respiratory depression. However, the data set only had benzodiazepines and zolpidem. Zolpidem data from CDC documents were also imported to verify data accuracy of zolpidem.

After linking CDC's benzodiazepine and zolpidem data to our data set for reconciliation, there were some NDC codes in the data set that do not appear in the CDC document. These NDC codes were explored manually to define the medications. After exploration, some NDC codes were neither benzodiazepine nor z-drugs, e.g. lisinopril. Therefore, these codes were excluded. Data were added for the NDC codes that appeared in our data set but not in the CDC document if the products were benzodiazepines or z-drugs. Dosage forms of benzodiazepines were then explored. The only non-oral dosage form was rectal lubricant gel/jelly diazepam. This dosage form was excluded because it is likely that this product was not used in regular outpatient settings, e.g. palliative care.

A total of 3,182 observations were removed form benzodiazepine data set and 773,493 observations remained. After verification of data accuracy, the benzodiazepine data set was linked to the opioid data set using left join in SAS proc sql to link all observations in the opioid data set with corresponding observations in the benzodiazepine data set. The reason left join was used was because the opioid data set has been linked with patient data set to determine the final cohort. When linked to opioid data set, 112,075 observations were removed from benzodiazepine data set and 661,418 remained. Multiple observations were excluded in this step because these observations might have been from the patients that were excluded in patient and opioid data sets.

These 661,418 observations were further used to determine patients who had concurrent use of opioids and benzodiazepines (Figure 4.3).

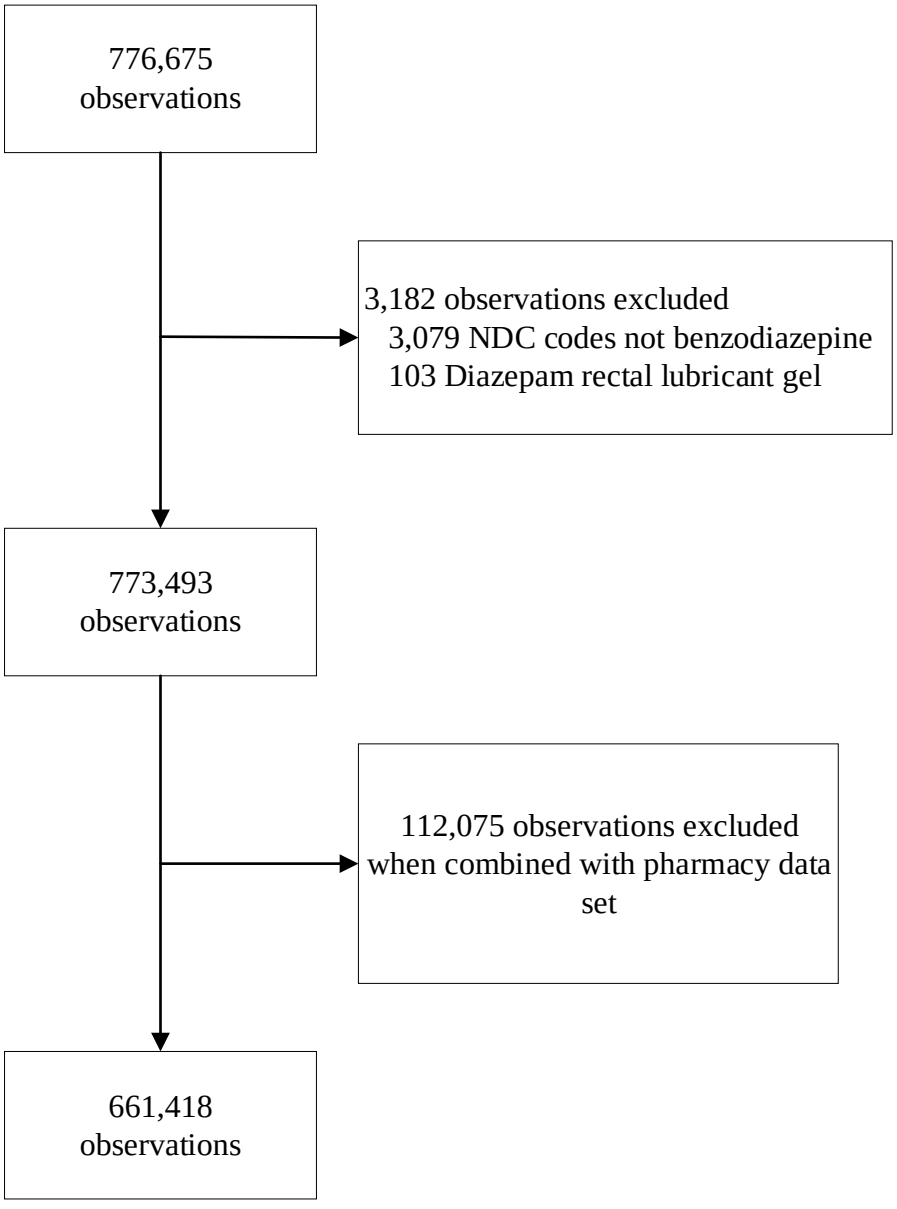

Figure 4.3. Cohort creation of benzodiazepine data set

4.4 Gabapentin/pregabalin data set

A total of 568,427 observations and 8 variables were contained in the gabapentin/pregabalin data set. The dosage form and strength were available in the data set. All dosage forms for these medications were oral forms. Descriptive statistics were explored for each variable. One outlier was excluded which was a dispense amount of 90,000. After the outlier was removed, 568,426 remained. Further, the gabapentin data set was linked to the opioid data set using left join in SAS proc sql to link all observations in the opioid data set with corresponding observations in the gabapentin/pregabalin data set. The reason left join was used was because the opioid data set has been linked with patient data set to determine the final cohort. Finally, 86,504 observations were removed when linked with opioid data set because these observations were from patients excluded in patient and opioid data sets. Finally, 481,922 observations remained in the gabapentin data set and these observations were further used to determine patients who had concurrent use of opioids and gabapentin/pregabalin (Figure 4.4).

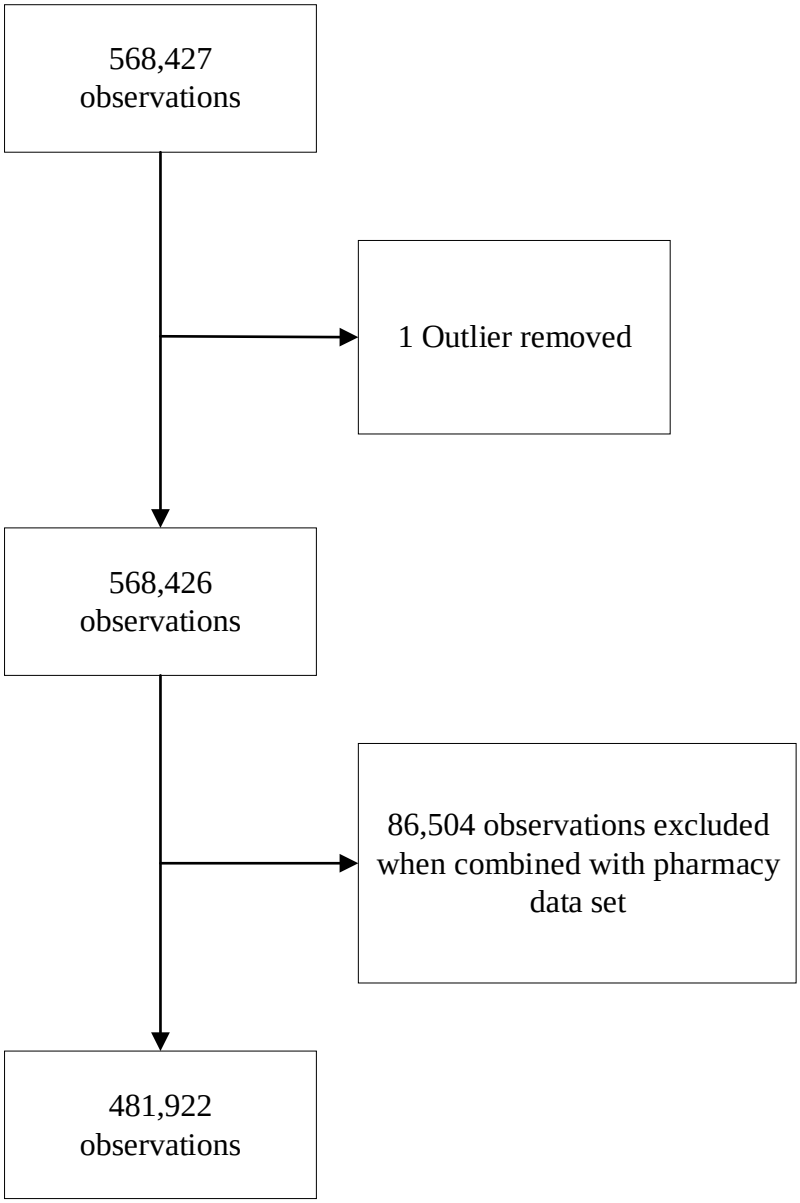

Figure 4.4. Cohort creation of gabapentin/pregabalin data set

4.5 Visit data set

A total of 26,128,614 observations and 6 variables were contained in the visit data set. This data set included clinical encounters mainly comprising outpatient, inpatient (hospitalization), and ED visits. On each visit date, the corresponding ICD9 or ICD10 codes represented the diagnoses of each particular visit, which were also recorded. However, not all visits had an ICD code associated with it. ICD9 was used until October 1, 2015, when ICD10 was then utilized afterwards. Therefore, this visit data set contained both ICD9 and ICD10 codes because the study period was 2012-2017.

For initial data management, visit dates before the index date and those that exceeded the study duration (2,192 days or 6 years) were removed (Figure 4.5). Subsequently, ICD codes were defined. To define which disease group was associated with each code, the codes were grouped into ICD9 and ICD10. In general, ICD9 and ICD10 codes had different formats. The first character of ICD9 was either numeric or alpha (only E or V), while the first character of ICD10 was always alpha followed by numeric second character. Therefore, there were some overlapped E or V codes between ICD9 and ICD10. The codes were grouped into all numeric, alpha and numeric, E codes, and V codes. Each ICD9 or ICD10 group was determined separately to determine the appropriate ICD group according to its format. For the E and V groups that could appear in both ICD9 and ICD10, if the format could not be used to distinguish them, the date of that visit was used. If codes were with the visit before October 1, 2015, they were grouped to ICD9. Those from October 1, 2015 were grouped to ICD10. After the ICD codes were defined, visit data set was linked to the patient data set to include only the visits for patients in the final cohort.

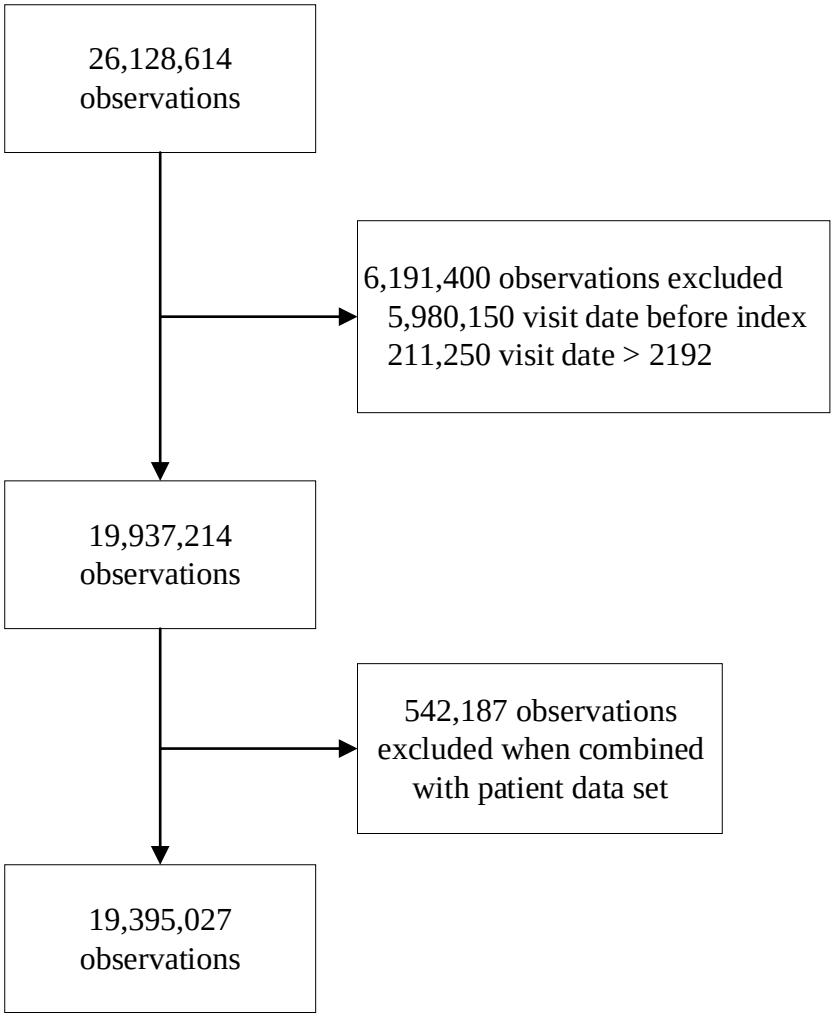

Figure 4.5. Cohort creation of visit data set

CHAPTER 5. RESULTS

5.1 Descriptive statistics for patient cohort

A total of 1,328,287 opioid prescriptions were identified for 341,722 opioid naive patients in the INPC during the six-year study duration. From these patients, 20,732,312 clinical encounters were recorded in the INPC. The mean age of patients in the cohort at the index was 52.3 (SD ± 18.1) years (Table 5.1). Of the 341,722 patients, 199,761 (58.5%) were female and 141,961 (41.5%) were male. The majority of patients were Caucasian (83.2%), followed by African American (11.2%), Hispanic/Latino (0.6%), Asian (0.3%), Native Hawaiian and other Pacific Islanders (0.3%), American Indian and Alaska Native (0.09%), and others (4.2%). The median time patients spent in the study was 666 days (range 1-2,192) or 1.82 years. Each patient was assessed for comorbidities using Charlson Comorbidity Index (CCI).[183] From 20,732,312 clinical encounters, 14,064,232 (67.8%) had ICD9/10 codes associated with the encounters. Therefore, CCI was only assessed for 271,840 patients. Most of the patients had CCI of 0 (65.5%) and 34.4% had CCI of 1-10. From the total cohort, 271,863 patients had non-missing diagnosis codes that could be assessed for mental health conditions. Of those, 73,515 (27.0%) had mental health conditions.

Table 5.1. Patients' baseline characteristics (n=341,722)

Variables	Non-missing observations	n (%)
Age (years), mean (SD)	341,722	52.31 (18.11)
Sex	341,722	
Male		141,961 (41.54)
Female		199,761 (58.46)
Race	272,418	
Caucasian		226,728 (83.23)
African American		30,578 (11.22)
Hispanic/Latino		1,543 (0.57)
Asian		907 (0.33)

Table 5.1 continued

Variables	Non-missing observations	n (%)
Race (continued)	272,418	
Native Hawaiian and other Pacific Islanders		887 (0.32)
American Indian and Alaska Native		245 (0.09)
Others		11,530 (4.23)
Charlson Comorbidity Index (CCI)	271,840	
0		178,025 (65.49)
1-10		93,815 (34.51)
Mental health conditions	271,863	
Yes		73,515 (27.04)
No		198,348 (72.96)
Time spent in study duration (days), median (range)	341,722	666 (1-2192)

Note: CCI is a calculated score of comorbidities consisted of 17 groups of medical conditions[183] (Appendix B)

5.2 Characteristics of opioid use patterns

Of 341,722 patients, 280,525 (82.1%) received fewer than 5 opioid prescriptions per year, 27,157 (8.0%) received 5-10, and 34,040 (10.0%) received more than 10 prescriptions per year (Table 5.2). Of these patients, 2,270 (0.7%) received at least one prescription for medication-assisted therapy (MAT). Of the total cohort, 334,243 (97.8%) patients received only short acting opioids, 6,301 (1.8%) received prescriptions for both short (SA) and long acting (LA)/extended release (ER) opioids within 30 days, 830 (0.2%) received both SA and LA opioids anytime during the study period but not within 30 days, and 348 (0.1%) received only LA opioid. For concurrent use of opioids and other medications, date of prescriptions within 30 days was used to determine concurrent use. Most patients (269,395, 78.8%) had prescriptions for opioids only, 40,789 (11.9%) received prescriptions for opioids and benzodiazepines within 30 days of each other, 20,372 (5.9%) received concurrent opioids and gabapentin/pregabalin, 8,733 (2.6%) received concurrent opioids, benzodiazepines, and gabapentin/pregabalin within 30 days, and 2,432 (0.7%) received

either concurrent opioids and benzodiazepines or concurrent opioids and gabapentin/pregabalin within 30 days, but not all three prescriptions within 30 days.

Table 5.2. Patterns of opioid prescriptions (n=341,722)

Variables	Non-missing observations	n (%)
Number of opioid prescriptions (per year)	341,722	
<5		280,525 (82.09)
5-10		27,157 (7.95)
>10		34,040 (9.96)
Long term user	341,722	
Yes		23,721 (6.94)
No		318,001 (93.06)
Patients receiving MAT	341,722	
Yes		2,270 (0.66)
No		339,452 (99.34)
Concurrent short/long acting opioids	341,722	
Short acting only		334,243 (97.81)
Short + Long acting within 30 days		6,301 (1.84)
Short + Long acting not within 30 days		830 (0.24)
Long acting only		348 (0.10)
Concurrent medications with opioids	341,722	
None (opioid only)		269,395 (78.83)
Benzodiazepine		40,789 (11.94)
Gabapentin/Pregabalin		20,372 (5.96)
Benzodiazepine + Gabapentin/pregabalin within 30 days		8,734 (2.56)
Benzodiazepine + Gabapentin/pregabalin not within 30 days		2,432 (0.71)

Note: Patients received prescriptions for each medication not within 30 days means anytime in the study period, but not within 30 days. Long term use indicates patients who had a cumulative opioid days supply of at least 90 days within 6 months after the index opioid prescription. MAT=Medication-Assisted Therapy

5.3 Characteristics of opioid prescriptions

Of all 1,328,287 opioid prescriptions, the median dose standardized to morphine milligram equivalent (MME) per day was 30 (range 0.17-180) and the median day supply was 8 days (range 1-90). Characteristics of opioid prescriptions are presented in Table 5.3. The most frequently prescribed opioid was hydrocodone (787,081 prescriptions, 59.9%), followed by 251,274 tramadol prescriptions (19.1%), 179,622 oxycodone (13.7%), 45,980 codeine (3.5%), 17,038 morphine (1.3%), and 32,503 other prescriptions (2.5%). From all opioid prescriptions, 1,264,436 (96.3%) and 49,179 (3.7%) were SA and LA opioids respectively. Of 1,328,287 prescriptions identified in the INPC, 14,672 were MAT. Of those, 10,607 (72.3%) were either buprenorphine, naloxone, or combined and 4,065 (27.7%) were naltrexone.

Table 5.3. Characteristics of opioid prescriptions (n=1,328,287)

Variables	Non-missing observations	n (%)
Opioid dose per prescription (MME/day), median (range)	1,134,104	30 (0.17-180)
Number of day supply per prescription, median (range)	1,313,474	8 (1-90)
Types of opioid products	1,313,615	
Hydrocodone		787,081 (59.92)
Tramadol		251,274 (19.13)
Oxycodone		179,662 (13.68)
Codeine		45,980 (3.50)
Morphine		17,038 (1.30)
Fentanyl		14,974 (1.14)
Hydromorphone		5,795 (0.44)
Tapentadol		2,775 (0.21)
Oxymorphone		2,661 (0.20)
Buprenorphine patch, ER		2,639 (0.20)
Methadone		2,239 (0.17)
Meperidine		1,441 (0.11)
Levorphanol		56 (0.00)

Table 5.3 continued

Variables	Non-missing observations	n (%)
Short/Long acting opioids	1,313,615	
Short acting		1,264,436 (96.26)
Long acting/ER		49,179 (3.74)
Medications for MAT	14,672	
Buprenorphine/Naloxone Film		7,521 (51.26)
Buprenorphine/Naloxone Tablet		2,406 (16.40)
Naltrexone Tablet		2,315 (15.78)
Naltrexone/Bupropion Tablet, ER		1,632 (11.12)
Buprenorphine Hydrochloride Tablet		613 (4.18)
Methylnaltrexone Injection		118 (0.80)
Naloxone Injection		67 (0.46)

Note: MME=Morphine Milligram Equivalent[185] ER=Extended Release MAT=Medication-Assisted Therapy

5.4 Characteristics of benzodiazepines and gabapentin/pregabalin

From the patient cohort, 593,833 and 310,562 prescriptions were identified for benzodiazepines and gabapentin/pregabalin respectively. The most frequently prescribed benzodiazepine was alprazolam (31.4%), followed by zolpidem (23.3%), clonazepam (18.3%), lorazepam (12.6%), diazepam (8.6%), and others (see Table 5.4). Benzodiazepine dose was standardized to one diazepam milligram equivalent (DME).[186] From 593,833 benzodiazepine prescriptions, 527,949 observations were able to be calculated for DME per day due to the missing dispense amount. Of those, 355,560 (67.4%) prescriptions were prescribed at a dose lower than 10 DME/day, 132,149 (25.0%) prescriptions had dose 10-20 DME/day, and 40,240 (7.6%) prescriptions were prescribed at dose greater than 20 DME/day. For 310,562 gabapentin/pregabalin prescriptions, 264,691 (85.2%) were gabapentin and 45,871 (14.8%) were pregabalin.

Table 5.4. Characteristics of benzodiazepine (n=593,833) and gabapentin/pregabalin (n=310,562)

Variables	Non-missing observations	n (%)
Types of benzodiazepine	593,833	
Alprazolam		186,525 (31.41)
Zolpidem		138,208 (23.27)
Clonazepam		108,836 (18.33)
Lorazepam		74,569 (12.56)
Diazepam		51,342 (8.65)
Temazepam		21,171 (3.57)
Triazolam		4,345 (0.73)
Chlordiazepoxide		3,872 (0.65)
Clorazepate		2,931 (0.49)
Oxazepam		969 (0.16)
Clobazam		507 (0.09)
Flurazepam		296 (0.05)
Estazolam		256 (0.04)
Quazepam		6 (0.00)
Benzodiazepine dose per prescription (DME/day)		
<10	527,949	355,560 (67.35)
10-20		132,149 (25.03)
>20		40,240 (7.62)
Gabapentin/Pregabalin		
Gabapentin	310,562	264,691 (85.23)
Pregabalin		45,871 (14.77)

Note: DME=Diazepam Milligram Equivalent[186]

5.5 Specific aim1: Factors associated with composite outcome of opioid abuse, dependence, and overdose

By the end of the study, the incidence of composite outcome of opioid abuse, dependence, and overdose was 1.90 per 1,000 person-years for the full patient cohort. This incidence represented 1,408 patients who had composite outcome of opioid abuse, dependence, and overdose. A total of 11 independent variables were included in the full model which comprised of age, sex, race, CCI, mental health conditions, long-term opioid use, time in the study, opioid dose (MME/day), opioid day supply, concurrent SA and LA opioid, and concurrent opioid, benzodiazepine, and gabapentin/pregabalin. Stepwise selection resulted in six variables that were significantly associated with the composite outcome (Table 5.5). Older age was associated with lower risk of composite outcome (OR 0.956 [95%CI: 0.952-0.960], p<0.0001). Males had higher risk of the outcome than females (OR 1.50 [95%CI: 1.34-1.67], p<0.0001). Patients having CCI between 1-10 (OR 1.52 [95%CI: 1.34-1.72], p<0.0001) were at higher risk of composite outcome compared to those with CCI = 0. In addition, those with mental health conditions were much more likely to have composite outcome compared to those without (OR 7.04 [95%CI: 6.05-8.23], p<0.0001). Patients who were long-term opioid users had higher risk of composite outcome compared to those who only used opioids short term (OR 2.74 [95%CI: 2.29-3.29], p<0.0001). Those who spent longer time in the study cohort were more likely to have composite outcome (OR=1.001 [95%CI: 1.001-1.001], p<0.0001). Opioid dose in MME/day (OR 1.004 [95%CI: 1.001-1.006], p=0.0050) and number of opioid days supply (OR=1.026 [95%CI: 1.019-1.033], p<0.0001) were significantly associated with higher risk of composite outcome. Patients who had prescriptions for SA and LA opioids within 30 days (OR 2.21 [95%CI: 1.84-2.66], p<0.0001) and not within 30 days (OR 2.10 [95%CI: 1.24-3.36], p=0.0034) had significantly higher risk of composite outcome compared to those who received SA opioid alone. Those receiving LA only also had higher risk of composite outcome (OR=2.01 [95%CI: 0.60-5.05) but this result was not statistically significant.

Table 5.5. Factors associated with composite outcome of opioid abuse, dependence, and overdose for patients in the full cohort

Variables	OR (95% CI)	P value
Age (years)	0.956 (0.952-0.960)	<0.0001
Sex		
Male	1.50 (1.34-1.67)	<0.0001
Female	Ref	Ref
Charlson comorbidity Index (CCI)		
1-10	1.52 (1.34-1.72)	<0.0001
0	Ref	Ref
Mental health conditions		
Yes	7.04 (6.05-8.23)	<0.0001
No	Ref	Ref
Long term user		
Yes	2.74 (2.29-3.29)	<0.0001
No	Ref	Ref
Number of days in the study duration	1.001 (1.001-1.001)	<0.0001
Number of days supply	1.026 (1.019-1.033)	<0.0001
Opioid dose (MME/day)	1.004 (1.001-1.006)	0.0050
Concurrent short/long acting opioids		
Short + Long acting within 30 days	2.21 (1.84-2.66)	<0.0001
Short + Long acting not within 30 days	2.10 (1.24-3.36)	0.0034
Long acting only	2.01 (0.60-5.05)	0.1898
Short acting only	Ref	Ref
Concurrent medications with opioid		
Benzodiazepine	1.50 (1.28-1.75)	<0.0001
Gabapentin/Pregabalin	1.63 (1.35-1.97)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin within 30 days	1.79 (1.47-2.18)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin not within 30 days	1.86 (1.36-2.50)	<0.0001
None (opioid only)	Ref	Ref

Note: Ref=Reference group MME=Morphine Milligram Equivalent

5.6 Specific aim 1: Factors associated with all-cause mortality

By the end of the study, the incidence of death was 3.52 per 1,000 person-years. From those 2,616 patients who died, the median time from index date to death was 662 days (range 1-2,174) or 1.8 years. A total of 11 independent variables were included in the full model including age, sex, race, CCI, mental health conditions, long-term opioid user, opioid dose (MME/day), opioid day supply, receipt of MAT, concurrent SA and LA opioid, and concurrent opioid, benzodiazepine, and gabapentin/pregabalin. Stepwise selection resulted in eight variables that were significantly associated with mortality (Table 5.6). Older age was associated with significantly higher risk of mortality (HR 1.077 [95%CI: 1.073-1.181], p<0.0001). Males had higher risk of mortality compared to females (HR 1.47 [95%CI: 1.35-1.61]). Compared to African Americans, Caucasians had significantly lower risk of mortality (HR 0.80 [95%CI: 0.70-0.91]). Patients who had higher CCI were more likely to die compared to those with CCI = 0. Those with CCI 1-10 had a HR of 3.48 (95%CI: 3.04-3.98, p<0.0001). Patients with mental health conditions were more likely to die compared to those without mental health conditions (HR 1.39 [95%CI: 1.26-1.52], p<0.0001). Those who had higher opioid day supply were more likely to die (HR 1.009 [95%CI: 1.005-1.014], p<0.0001). Patients using concurrent SA/LA opioids had higher risk of mortality comparted to those receiving only SA opioids (HR 1.40[95%CI: 1.14-1.70], p=0.0010). Patients who had prescriptions for opioids, benzodiazepines, and gabapentin/pregabalin within 30 days of each other had higher risk of mortality compared to those receiving opioids alone (HR 1.15 [95%CI: 0.95-1.39], p=0.1429).

Table 5.6. Factors associated with all-cause mortality for patients in the full cohort

Variables	HR (95% CI)	P value
Age (years)	1.077 (1.073-1.181)	<0.0001
Sex		
Male	1.47 (1.35-1.61)	<0.0001
Female	Ref	Ref
Race		
Caucasian	0.80 (0.70-0.91)	0.0009

Table 5.6 continued

Variables	HR (95% CI)	P value
Race (continued)		
Hispanic/Latino	1.40 (0.69-2.83)	0.3509
Asian	0.61 (0.23-1.64)	0.3290
Others	0.93 (0.73-1.18)	0.5513
African American	Ref	Ref
Charlson comorbidity Index (CCI)		
1-10	3.48 (3.04-3.98)	<0.0001
0	Ref	Ref
Mental health conditions		
Yes	1.39 (1.26-1.52)	<0.0001
No	Ref	Ref
Number of days supply	1.009 (1.005-1.014)	<0.0001
Concurrent short/long acting opioids		
Short + Long acting within 30 days	1.40 (1.14-1.70)	0.0010
Short + Long acting not within 30 days	1.35 (0.87-2.11)	0.1821
Long acting only	1.62 (0.60-4.32)	0.3393
Short acting only	Ref	Ref
Concurrent medications with opioids		
Benzodiazepine	0.97 (0.85-1.10)	0.6315
Gabapentin/Pregabalin	0.94 (0.82-1.08)	0.3836
Benzodiazepine + Gabapentin/Pregabalin within 30 days	1.15 (0.95-1.39)	0.1429
Benzodiazepine + Gabapentin/Pregabalin not within 30 days	0.56 (0.37-0.87)	0.0097
None (opioid only)	Ref	Ref

5.7 Sub aim 1: Factors associated with composite outcome of opioid abuse, dependence, and overdose and all-cause mortality for subgroup of benzodiazepine users

From the total 341,722 patients in the cohort, 77,372 (22.6%) used a benzodiazepine at any time during the study period. Benzodiazepine users who received a dose greater than 20 DME/day

had significantly higher risk of composite outcome compared to those receiving less than 10 DME/day (OR 4.53 [95%CI: 1.14-2.01], p=0.0032), see Table 5.7.

Table 5.7. Factors associated with composite outcome of opioid abuse, dependence, and overdose for subgroup of patients taking opioids and benzodiazepines, n=77,372 (22.64%)

Variables	OR (95% CI)	P value
Age (years)	0.96 (0.95-0.97)	<0.0001
Sex		
Male	1.27 (1.06-1.51)	0.0097
Female	Ref	Ref
Charlson comorbidity Index (CCI)		
1-10	1.76 (1.45-2.15)	<0.0001
0	Ref	Ref
Mental health conditions		
Yes	5.91 (4.56-7.78)	<0.0001
No	Ref	Ref
Long term user		
Yes	5.72 (4.77-6.87)	<0.0001
No	Ref	Ref
Number of days in the study cohort	1.001 (1.001-1.001)	0.0002
Benzodiazepine dose (DME/day)		
> 20	1.53 (1.14-2.01)	0.0032
10-20	0.99 (0.77-1.26)	0.9364
< 10	Ref	Ref

Note: DME=Diazepam milligram equivalent[186]

For mortality, patients using benzodiazepine at doses between 10-20 DME/day had significantly lower risk of mortality compared to those using doses less than 10 DME/day. Benzodiazepine dose greater than 20 DME/day was not significantly associated with mortality (HR 0.08 [95%CI: 0.59-1.11]), see Table 5.8.

Table 5.8. Factors associated with all-cause mortality for subgroup of patients taking opioids and benzodiazepines, n=77,372 (22.64%)

Variables	HR (95% CI)	P value
Age (years)	1.07 (1.06-1.08)	<0.0001
Sex		
Male	1.61 (1.36-1.91)	<0.0001
Female	Ref	Ref
Charlson comorbidity Index (CCI)		
1-10	4.28 (3.23-5.67)	<0.0001
0	Ref	Ref
Mental health conditions		
Yes	1.24 (1.03-1.48)	0.0239
No	Ref	Ref
Long term user		
Yes	1.22 (1.02-1.47)	0.0325
No	Ref	Ref
Benzodiazepine dose (DME/day)		
>20	0.81 (0.59-1.11)	0.1800
10-20	0.66 (0.51-0.85)	0.0013
<10	Ref	Ref

Note: DME=Diazepam milligram equivalent[186]

5.8 Specific aim 2: Factors associated with all-cause hospitalizations

At the end of the study, 137,124 (40.1%) patients had at least one hospitalization. For those with at least one hospitalization, the median number of hospitalizations was 2 (range 1-335). Eleven independent variables were included in the full model including age, sex, race, CCI, mental health conditions, long-term opioid user, time in the study, opioid dose (MME/day), opioid day supply, concurrent SA and LA opioids, and concurrent opioids, benzodiazepines, and gabapentin/pregabalin. Backward elimination resulted in 10 significant variables (Table 5.9). Opioid day supply was the only variable not included in the final model due to statistical insignificance. Age greater than 50 was significantly associated with hospitalizations when compared with those younger (RR 1.34 [95%CI: 1.32-1.35], p<0.0001). Males were less likely to

be hospitalized compared to females (RR 0.89 [95%CI: 0.88- 0.90], p<0.0001). Compared to African Americans, Caucasians were less likely to have hospitalizations (RR 0.80 [95%CI: 0.79-0.81], p<0.0001). Patients who had CCI 1-10 (RR 2.32 [95%CI: 2.30-2.34], p<0.0001) were more likely to be hospitalized compared to those with CCI = 0. Those with mental health conditions were more likely to have hospitalizations (RR 1.43 [95%CI: 1.42-1.45], p<0.0001). Further, patients in the study cohort longer than 2 years were more likely to have hospitalizations than those who stayed 1-2 years (RR 1.21 [95%CI: 1.20-1.22], p<0.0001). Patients who received opioid dose greater than 50 MME/day had higher risk of hospitalizations compared to those having opioid dose less than or equal to 50 MME/day (RR 1.12 [95%CI: 1.23-1.28], p<0.0001). Patients who had SA and LA opioids prescribed within 30 days of each other compared with SA alone were more likely to be hospitalized (RR 1.36 [95%CI: 1.34-1.38], p<0.0001). Those prescribed opioids, benzodiazepines, and gabapentin/pregabalin within 30 days of each other compared to receiving opioid only were more likely to have hospitalizations (RR 1.35 [95%CI: 1.33-1.37, p<0.0001).

Table 5.9. Factors associated with all-cause hospitalizations

Variables	RR (95% CI)	P value
Age group		
50+	1.34 (1.32-1.35)	<0.0001
< 50	Ref	Ref
Sex		
Male	0.89 (0.88- 0.90)	<0.0001
Female	Ref	Ref
Race		
Caucasian	0.80 (0.79-0.81)	<0.0001
Hispanic/Latino	0.71 (0.67-0.74)	<0.0001
Asian	0.73 (0.69-0.78)	<0.0001
Others	0.78 (0.77-0.79)	<0.0001
African American	Ref	Ref

Table 5.9 continued

Variables	RR (95% CI)	P value
Charlson comorbidity Index (CCI)		
1-10	2.32 (2.30-2.34)	<0.0001
0	Ref	Ref
Mental health conditions		
Yes	1.43 (1.42-1.45)	<0.0001
No	Ref	Ref
Long term user		
Yes	1.18 (1.17-1.19)	<0.0001
No	Ref	Ref
Duration in the study period (years)		
> 2	1.21 (1.20-1.22)	<0.0001
≤ 2	Ref	Ref
Opioid dose (MME/day)		
> 50	1.12 (1.11-1.13)	<0.0001
≤ 50	Ref	Ref
Concurrent short/long acting opioids		
Short + Long acting within 30 days	1.36 (1.34-1.38)	<0.0001
Short + Long acting not within 30 days	1.32 (1.26-1.37)	<0.0001
Long acting only	1.06 (0.97-1.17)	0.1974
Short acting only	Ref	Ref
Concurrent medications with opioid		
Benzodiazepine	1.14 (1.13-1.15)	<0.0001
Gabapentin/Pregabalin	1.25 (1.23-1.26)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin within 30 days	1.35 (1.33-1.37)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin not within 30 days	1.33 (1.30-1.37)	<0.0001
None (opioid only)	Ref	Ref

Note: MME=Morphine Milligram Equivalent[185]

5.9 Specific aim 2: Factors associated with all-cause ED visits

At the end of the study, 213,844 (62.6%) patients had at least one ED visit. For those with at least one ED visit, the median number of ED visits was 3 (range 1-381). Eleven independent variables were included in the full model including age, sex, race, CCI, mental health conditions, long-term opioid user, time in the study, opioid dose (MME/day), opioid day supply, concurrent SA and LA opioid, and concurrent opioid, benzodiazepine, and gabapentin/pregabalin. All 11 variables remained significant variables in the model after a backward elimination procedure (Table 5.10). Patients who were older than 50 years were less likely to have ED visits compared to those younger (RR 0.59 [95%CI: 0.58-0.59], p<0.0001). Males had higher risk of ED visits compared to females (RR 1.02 [95%CI: 1.01-1.03], p<0.0001). Compared to African Americans, Caucasians were less likely to have ED visits (RR 0.60 [95%CI: 0.59-0.61], p<0.0001). Patients who had CCI 1-10 (RR 1.51 [95%CI: 1.50-1.52], p<0.0001) were more likely to have ED visits compared to those with CCI = 0. Further, those with mental health conditions were more likely to visit the ED (RR 1.58 [95%CI: 1.57-1.58, p<0.0001). Patients who remained in the study cohort longer than two years had higher risk of ED visits compared to those in the study cohort for less than 2 years (RR 1.31 [95%CI: 1.30-1.32, p<0.0001). Those receiving higher opioid day supply (RR 0.74 [95%CI: 0.72-0.75]. p<0.0001) and higher dose (RR 0.85 [95%CI: 0.84-0.85], p<0.0001) were less likely to have ED visits. Patients who had SA and LA opioids prescribed within 30 days of each other compared to SA alone were more likely to have ED visits (RR 1.15 [95%CI: 1.14-1.17], p<0.0001). Finally, patients having concurrent prescriptions for opioids, benzodiazepines, and gabapentin/pregabalin within 30 days of each other compared to those receiving opioid only had higher risk of ED visits (RR 1.03 [95%CI: 1.02-1.05], p<0.0001).

Table 5.10. Factors associated with all-cause ED visits

Variables	RR (95% CI)	P value
Age group		
50+	0.59 (0.58-0.59)	<0.0001
< 50	Ref	Ref

Table 5.10 continued

Variables	RR (95% CI)	P value
Sex		
Male	1.02 (1.01-1.03)	<0.0001
Female	Ref	Ref
Race		
Caucasian	0.60 (0.59-0.61)	<0.0001
Hispanic/Latino	0.77 (0.75-0.78)	<0.0001
Asian	0.33 (0.31-0.34)	<0.0001
Others	0.55 (0.54-1.56)	<0.0001
African American	Ref	Ref
Charlson comorbidity Index (CCI)		
1-10	1.51 (1.50-1.52)	<0.0001
0	Ref	Ref
Mental health conditions		
Yes	1.58 (1.57-1.58)	<0.0001
No	Ref	Ref
Long term user		
Yes	1.32 (1.31-1.33)	<0.0001
No	Ref	Ref
Duration in the study cohort (years)		
> 2	1.31 (1.30-1.32)	<0.0001
≤ 2	Ref	Ref
Opioid dose (MME/day)		
> 50	0.85 (0.84-0.85)	<0.0001
≤ 50	Ref	Ref
Opioid day supply (days)		
> 5	0.74 (0.72-0.75)	<0.0001
1-5	Ref	Ref
Concurrent short/long acting opioids		
Short + Long acting within 30 days	1.15 (1.14-1.17)	<0.0001
Short + Long acting not within 30 days	1.19 (1.15-1.23)	<0.0001

Table 5.10 continued

Variables	RR (95% CI)	P value
Concurrent short/long acting opioids (continued)		
Long acting only	1.20 (1.12-1.28)	<0.0001
Short acting only	Ref	Ref
Concurrent medications with opioid		
Benzodiazepine	1.29 (1.28-1.30)	<0.0001
Gabapentin/Pregabalin	1.29 (1.28-1.30)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin within 30 days	1.03 (1.02-1.05)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin not within 30 days	1.62 (1.59-1.65)	<0.0001
None (opioid only)	Ref	Ref

Note: MME=Morphine Milligram Equivalent[185]

5.10 Specific aim 3: Changes of opioid prescribing and the associated outcomes before and after pivotal events related to opioid prescribing

5.10.1 Opioid dose

Overall changes of opioid dose prescribed before and after pivotal events related to opioid prescribing were presented in Figure 5.1. After the DEA scheduling changes of tramadol and hydrocodone in October 2014, the mean dose of opioid prescription (MME/day) slightly decreased (-0.114, 95%CI [-0.576, 0.347], p=0.6294) but was not statistically significant (Table 5.11) as indicated by level change, which represents the immediate impact of the event. However, there was a slight increase in trend (0.074, 95%CI [0.027, 0.121], p=0.0030). Trend change represented sustained change over time after the event. In 2016, after the CDC opioid prescribing guideline was released in January, there was a nonsignificant reduction in opioid dose both for level (-0.007, 95%CI [-0.485, 0.470], p=0.9758) and trend (-0.045, 95%CI [-0.093, 0.002], p=0.0635).

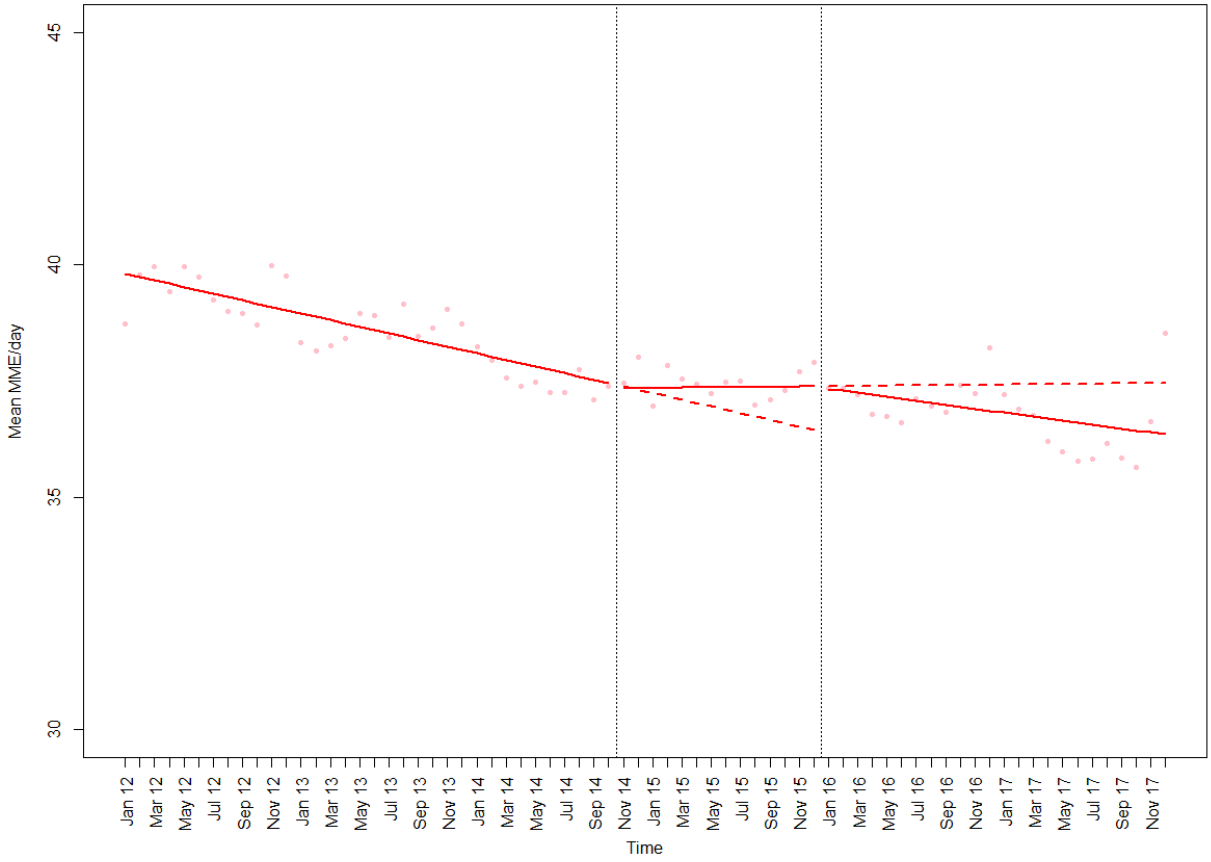

Figure 5.1. Changes of opioid dose prescribed (red scattered dots) before and after pivotal events (black dotted lines) related to opioid prescribing denoted by mean opioid dose (y axis) measured at each month (x axis)

Table 5.11. Effects of pivotal events related to opioid prescribing on opioid dose denoted by level and trend change

Coefficients	Value	Std. Error	t-value	95% CI	p-value
(Intercept)	39.878	0.09505703	419.5175	39.692, 40.064	0.0000
Time	-0.071	0.00482821	-14.7730	-0.081, -0.062	0.0000
Level1	-0.114	0.23543500	-0.4848	-0.576, 0.347	0.6294
Trend1	0.074	0.02405953	3.0807	0.027, 0.121	0.0030
Level2	-0.007	0.24383456	-0.0305	-0.485, 0.470	0.9758
Trend2	-0.045	0.02404868	-1.8873	-0.093, 0.002	0.0635

5.10.2 Opioid day supply

Overall changes of opioid day supply before and after pivotal events related to opioid prescribing were presented in Figure 5.2. After the DEA scheduling changes of tramadol and hydrocodone, there was a nonsignificant decrease in the mean opioid day supply level (-0.333, 95%CI [-1.259, 0.594], p=0.4839), and a significant decrease in trend (-0.263, 95%CI [-0.471, -0.054], p=0.0161), Table 5.12. Then after the CDC opioid prescribing guideline release, there were slight increases in both level (0.585, 95%CI [-0.316, 1.487], p=0.2078) and trend (0.038, 95%CI [-0.197, 0.274], p=0.7514), but these were not statistically significant.

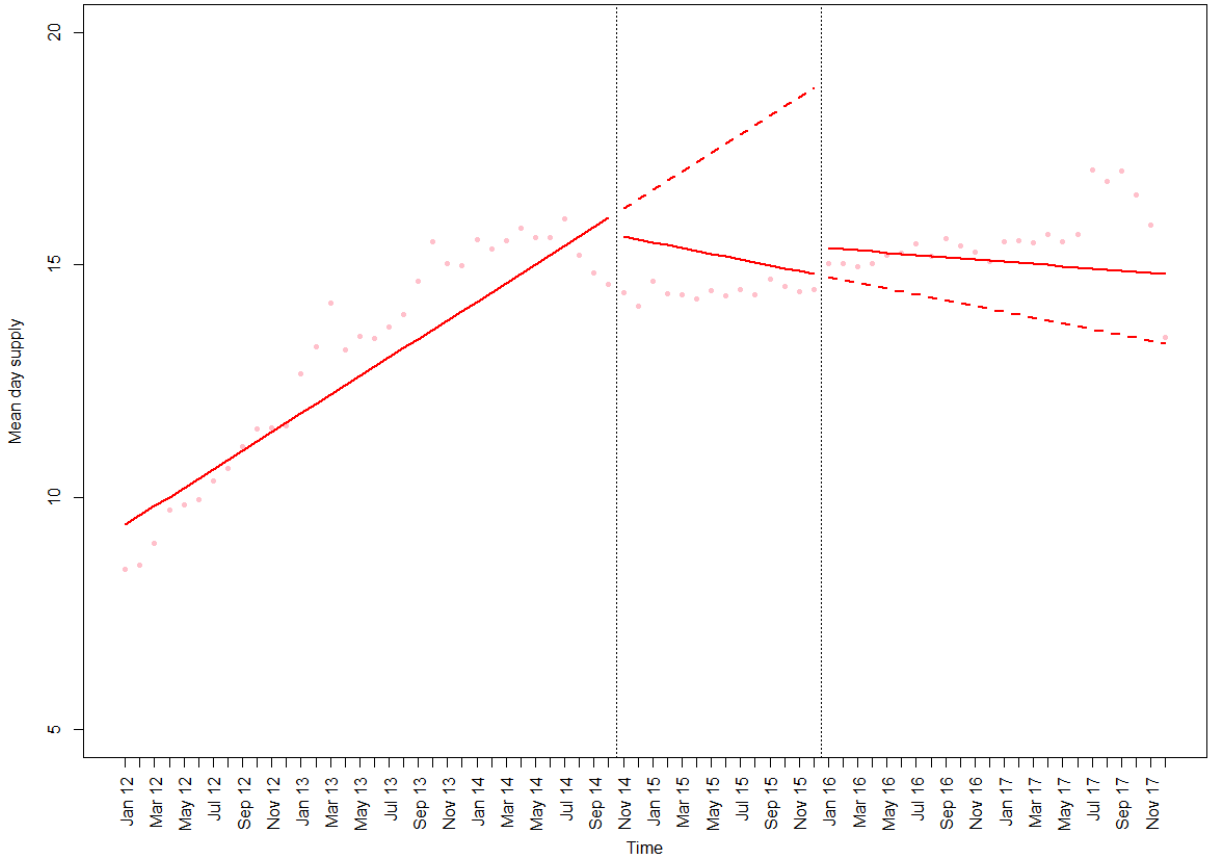

Figure 5.2. Changes of opioid days supply prescribed (red scattered dots) before and after pivotal events (black dotted lines) related to opioid prescribing denoted by mean opioid days supply (y axis) measured at each month (x axis)

Table 5.12. Effects of pivotal events related to opioid prescribing on opioid days supply denoted by level and trend change

Coefficients	Value	Std. Error	t-value	95% CI	p-value
(Intercept)	9.199	0.7932176	11.597013	0.764, 10.754	0.0000
Time	0.200	0.0361317	5.542619	0.129, 0.271	0.0000
Level1	-0.333	0.4726354	-0.704038	-1.259, 0.594	0.4839
Trend1	-0.263	0.1063645	-2.471177	-0.471, -0.054	0.0161
Level2	0.585	0.4601993	1.272226	-0.316, 1.487	0.2078
Trend2	0.038	0.1203769	0.318118	-0.197, 0.274	0.7514

5.10.3 Composite outcome of opioid abuse, dependence, and overdose

Overall changes of composite outcome of opioid abuse, dependence, and overdose before and after pivotal events related to opioid prescribing were presented in Figure 5.3. After the DEA scheduling changes of tramadol and hydrocodone, both level (0.086, 95%CI [-0.228, 0.400], p=0.5938) and trend (0.030, 95%CI [-0.009, 0.069], p=0.1383) increased but were not statistically significant (Table 5.13). However, after the CDC opioid prescribing guideline release, the level increased (0.204, 95%CI [-0.152, 0.561], p=0.2656), but the trend decreased immediately after the release (-0.102, 95%CI [-0.182, -0.021], p=0.0161). Then the trend later increased in a quadratic trend (0.005, 95%CI [0.002, 0.007], p=0.0003).

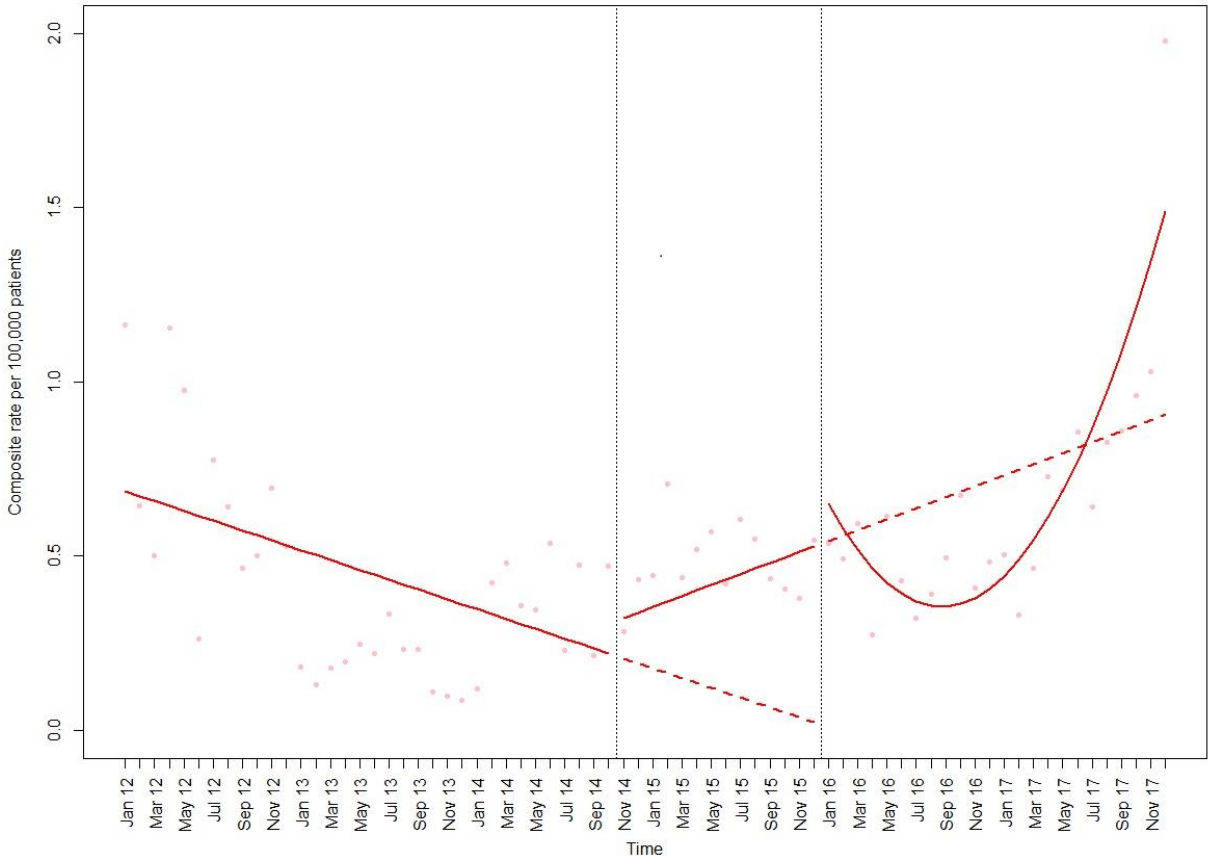

Figure 5.3. Changes of composite outcome rate (red scattered dots) before and after pivotal events (black dotted lines) related to opioid prescribing denoted by rate of composite outcome of opioid abuse, dependence, and overdose (y axis) measured at each month (x axis)

Table 5.13. Effects of pivotal events related to opioid prescribing on rate of composite outcome of opioid abuse, dependence, and overdose denoted by level and trend change

Coefficients	Value	Std. Error	t-value	95% CI	p-value
(Intercept)	0.700	0.12707122	5.512355	0.451, 0.950	0.0000
Time	-0.014	0.00606579	-2.327253	-0.026, -0.002	0.0231
Level1	0.086	0.16044643	0.535910	-0.228, 0.400	0.5938
Trend1	0.030	0.01991838	1.500447	-0.009, 0.069	0.1383
Level2	0.204	0.18183919	1.123006	-0.152, 0.561	0.2656
Trend2	-0.102	0.04111658	-2.470585	-0.182, -0.021	0.0161
Trend2 squared	0.005	0.00129173	3.787300	0.002, 0.007	0.0003

5.10.4 Mortality

Overall changes of mortality before and after pivotal events related to opioid prescribing were presented in Figure 5.3. After the DEA scheduling changes of tramadol and hydrocodone, the level slightly decreased (-0.099, 95%CI [-0.703, 0.505], p=0.7492), but the trend significantly increased (0.122, 95%CI [0.019, 0.226], p=0.0236). Then after the CDC opioid prescribing guideline release, there was an increase in level (0.371, 95%CI [-0.273, 1.015], p=0.2628) and a decrease in trend (-0.511, 95%CI [-0.774, -0.247], p=0.0003); these changes were not statistically significant. However, there was a quadratic increase in trend afterwards (0.022, 95%CI [0.013, 0.030], p<0.0001).

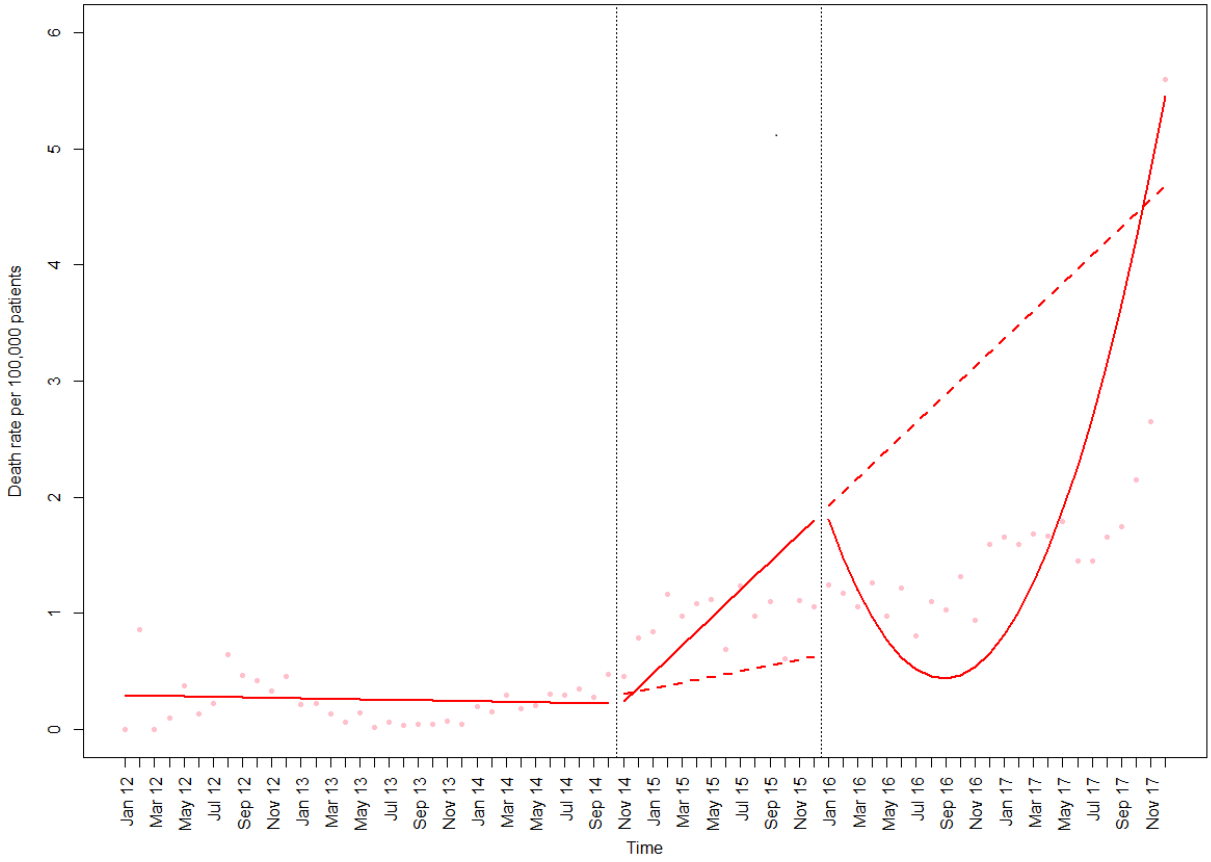

Figure 5.4. Changes of mortality rate (red scattered dots) before and after pivotal events (black dotted lines) related to opioid prescribing denoted by rate of mortality (y axis) measured at each month (x axis)

Table 5.14. Effects of pivotal events related to opioid prescribing on rate of mortality denoted by level and trend change

Coefficients	Value	Std. Error	t-value	95% CI	p-value
(Intercept)	0.293	0.3129644	0.936505	-0.320, 0.906	0.3525
Time	-0.002	0.0148992	-0.148300	-0.031, 0.027	0.8826
Level1	-0.099	0.3083156	-0.321104	-0.703, 0.505	0.7492
Trend1	0.122	0.0527961	2.318561	0.019, 0.226	0.0236
Level2	0.371	0.3285112	1.129545	-0.273, 1.015	0.2628
Trend2	-0.511	0.1343584	-3.801300	-0.774, -0.247	0.0003
Trend2 squared	0.022	0.0043397	5.063245	0.013, 0.030	0.0000

5.11 Sensitivity analyses

Several sensitivity analyses were conducted to test the robustness of our findings, particularly as they relate to missing variables (including diagnostic codes). In sensitivity analyses, CCI and mental health conditions variables were omitted from the models to include more patients in the analyses in specific aims 1 and 2 (i.e., patients with missing diagnostic codes were not excluded, increasing the number of patients in the models from 203,249 to 271,920). For specific aim 1, factors associated with composite outcome, the number of significant variables in the final model remained the same as the main analysis (Appendix G, Table G.1). Direction of association was the same for all variables. The odds ratio for patients with mental health conditions increased from the main analysis in the same direction of relationship (OR 8.99 [95%CI: 7.70-10.54], $p<0.0001$). For mortality, opioid dose in MME/day was an additional variable that became significant in the final model of sensitivity analysis, but was not significant in the main analysis. However, although statistically significant, the hazards ratio does not seem to have an effect (HR 0.997 [95%CI: 0.995-1.000], $p=0.0337$) on mortality (Appendix G, Table G.2). All other variables in the final model remained the same as the main analysis both for significance and direction of association.

The same analyses were performed for specific aim 2, factors associated with healthcare utilization. For hospitalizations, the number of significant variables remained the same as in the main analysis with the same direction of association (Appendix G, Table G.3). For ED visits, the number of significant variables in the final model remained the same as the main analysis (Appendix G, Table G.4). Direction of association was the same for all variables. Other sensitivity analyses included using missingness of CCI and mental health conditions as independent variables in the models and using CCI as a continuous variable. The results of these analyses did not differ from the main analyses.

CHAPTER 6. DISCUSSION AND CONCLUSION

Widespread use of prescription opioids has been a major public health concern since 1999. Many consequences are associated with the problem, such as opioid misuse, abuse, and drug overdose deaths. Opioids are not the only medications involved with drug overdose deaths. Due to stricter control of prescription opioids, misuse of prescription opioids is also associated with abuse of other illicit drugs. This is associated with an increase in drug overdose death involving heroin and semisynthetic/synthetic opioids. Another risk factor for increased overdose deaths is concurrent use of opioids with other central nervous system (CNS) depressants and some anticonvulsants. Concurrent use of opioids and benzodiazepine, z-drugs, gabapentin, and/or pregabalin is associated with increased risk of respiratory depression and drug overdose death. To combat problematic opioid use, many mitigation strategies were introduced including practice recommendations, utilization of prescription drug monitoring program (PDMP), national and/or local guidelines, and legislation related to opioid prescribing. However, opioid-related problems remain and overdose deaths remain relatively high.

In our study, we evaluated new opioid prescriptions in patients in Indiana. The majority of patients in our study are Caucasians, followed by African Americans, and other races. There are more females than males. These distributions are reflective of what is observed in the INPC and aligns with Indiana's population. In 2019 census, 85% of Indiana's population was Caucasians followed by African Americans (10%).[189] There were more females than males (51% vs 49%). The mean age of patients in this study is 52.3 years and there are more patients who are at least 50 years old than those younger. The median age of Indiana's population is 37.9 years which is younger than the mean age of patients in this study. Almost all patients (97.8%) in our study used only short acting opioids and less than 1% used only long acting/extended release opioids. For concurrent use, 78.8% of patients received opioids only and less than 3% received both opioids and benzodiazepines prescriptions at some time in the study. The most commonly prescribed opioid was hydrocodone, followed by tramadol, and oxycodone. This distribution of frequently prescribed opioids remains the same before and after rescheduling of tramadol and hydrocodone.

6.1 Specific aim 1: Factors associated with composite outcome (opioid abuse, dependence, and overdose) and mortality

This specific aim assessed the association between multiple factors and (i) composite outcome of opioid abuse, dependence, and overdose (ii) mortality. The hypothesis was that patients receiving high dose, long duration of opioids, and concurrent use with other CNS medications were at higher risk of the composite outcome and mortality. This hypothesis was based on some previous studies that found high risk opioid prescribing as a risk factor for opioid-related adverse outcomes. Our analyses found that significant variables included younger age, male gender, CCI of one or more, mental health conditions, using opioid long term, higher opioid day supply, higher opioid dose in MME/day, concurrent use of short and long acting opioids, and concurrent use of opioids, benzodiazepines, and/or gabapentin/pregabalin. Mental health was a strong predictor of the composite outcome. However, the variable mental health conditions did not include specific groups of mental illnesses. Number of days in the study duration was also added to the logistic regression model to adjust for different duration each patient remained in the study. For Cox proportional hazards, time in the study was not added to the model because survival analysis already adjusted for time in the study by using time to event.

The findings are in agreement with previous studies that chronic opioid users, mental health conditions, longer days supply, larger average daily dose were associated with increased risk of diagnoses of opioid abuse, dependence, and overdose death.[64,95,99,107] Many studies indicate high opioid daily dose as a significant factor for problematic opioid use and opioid-related overdose death.[190] However, one study suggested that duration of opioid therapy was more important than daily dose for risk of OUD.[108] Further, risk of opioid overdose was significantly higher in patients who were also exposed to other sedative hypnotics compared to those only taking opioids.[114,123] Our study added evidence to this finding that concurrent use of opioids and benzodiazepines is a risk factors for all outcomes analyzed.

Patients in the cohort who used benzodiazepines were assessed as a subgroup analysis. Significant variables associated with adverse outcomes included age, male gender, CCI, mental health conditions, long-term opioid use, time in study duration (for logistic regression), and benzodiazepine dose. Many studies reported adverse outcomes of concurrent use of opioids and benzodiazepines, but evidence of patterns of benzodiazepine use, especially benzodiazepine doses, in patients receiving opioid therapy is limited.[114,191] Unlike opioids, benzodiazepine dose

conversion to compare between different types of benzodiazepines is uncommon. However, a study of benzodiazepine use pattern calculated benzodiazepine doses as diazepam equivalents using the previously published conversion table.[186] In this table, all other benzodiazepine doses reported were equivalent to 10 mg of diazepam. The strategy of benzodiazepine dose conversion was applied to this study. In our calculation, we further standardized all other benzodiazepine doses to 1 mg of diazepam using conversion factors. Therefore, benzodiazepine dose in our study was calculated to diazepam milligram equivalent (DME) per day.

From our findings, higher benzodiazepine dose was significantly associated with composite outcome of opioid abuse, dependence, and overdose. Benzodiazepine dose greater than 20 DME/day was significantly associated with composite outcome, but dose between 10-20 DME/day did not have a significant association compared to dose less than 10 DME/day. This result supports the previously published evidence of a dose-response relationship between benzodiazepines and risk of overdose death.[114] However, the association between benzodiazepine dose and all-cause mortality was contrary to our hypothesis. Cox proportional hazards found benzodiazepine dose greater than 10 DME/day inversely associated with risk of death compared to dose less than 10 DME/day. One reason could be the underestimated number of deaths. The number of deaths that are captured in the INPC only include deaths that occur within the institutions that contribute data to the INPC. Therefore, there could be some deaths that occur outside the institutions that are not captured in the INPC. Another reason could be because the prescribed doses of benzodiazepines in DME/day are the doses used in normal clinical practice. For example, the daily dose of zolpidem, one of the most commonly used z-drugs, is 10 mg/day. The converted dose is 20 DME/day. Thus, moderate dose is not associated with higher risk of death. Further, another reason that may affect the association between benzodiazepine use and mortality could be other confounders that were not controlled for, such as indications for benzodiazepines and some medical conditions including pain and anxiety, which could be directly associated with increased risk of death.

6.2 Specific aim 2: Factors associated with healthcare utilization

This specific aim assessed the association between multiple factors and healthcare utilization. The hypothesis was that patients receiving high dose, long duration of opioids, and

concurrent use with other medications were more likely to be hospitalized and to have more ED visits. For hospitalizations, those who were older, had higher CCI, had mental health conditions, used opioids long term, received opioids daily dose greater than 50 MME/day, used concurrent short and long acting opioids, and used opioids concurrently with benzodiazepines and/or gabapentin/pregabalin were associated with more hospitalizations. Opioid days supply was not a significant predictor for this outcome. For ED visits, patients with higher CCI, mental health conditions, long-term opioid use, concurrent use of short and long acting opioids, and concurrent use with benzodiazepines and/or gabapentin/pregabalin were associated with more ED visits. Contrary to our hypothesis, people who were older, received higher opioid daily dose and received longer opioid days supply were associated with less ED visits. We found a dose response relationship for hospitalizations, but not for ED visits. One of the reasons that older patients were less likely to have ED visits compared to those younger could be because older people have well-established primary care resources. Therefore, they are less likely to be dependent on ED visits compared to younger people. Further, patients who received high opioid doses and longer days supply may be patients who developed tolerance to opioids and are under pain specialists' medical care. Therefore, although they received high opioid doses for a long duration, risk of ED visits does not increase.

Other studies have found high dose opioid prescribing, concurrent use of opioids and benzodiazepines, and those with history of substance use disorders were associated with more opioid-related hospitalizations and ED visits.[116,134,192,193] Most of the findings in this study coincided with these studies, especially high opioid dose, longer days supply, and concurrent use of opioids and other medications; however, this study found opioid dose and days supply not consistently associated with hospitalizations and ED visits. The inconsistency in results of opioid dose and days supply was also observed in one study that reported a non-consistent association between opioid days supply and daily dose.[134] This study found that opioid days supply was not a predictor of ED visits and alcohol/drug-related encounters. Further, opioid daily dose greater than 120 MME/day was not associated with ED visits, but significantly increased risk of alcohol/drug-related encounters.[134] To summarize, there are mixed findings of dose-response relationship between opioid dose and ED visits.

6.3 Specific aim 3: Opioid prescribing and health outcomes before and after pivotal events related to opioid prescribing

This specific aim assessed changes over time of opioid prescribing and health outcomes in Indiana before and after pivotal events related to opioid prescribing and whether each event had impact on opioid prescribing and health outcomes. The events assessed in this study included rescheduling of tramadol and hydrocodone and the release of the CDC opioid prescribing guideline in January 2016. Rescheduling of tramadol and hydrocodone did not seem to have a significant immediate (level change) or sustained (trend change) impact on opioid dose prescribed. After the CDC guideline release, there was also no immediate impact on opioid dose, but there seems to be a sustained decline in dose following the guideline release. Conversely, rescheduling of tramadol and hydrocodone had both immediate and sustained decline on opioid day supply per prescription. But CDC guideline did not have significant effects on opioid days supply. Effects of all pivotal events were similar for the composite outcome of opioid abuse, dependence, and overdose, and mortality rates. After rescheduling of tramadol and hydrocodone, the rates of both outcomes did not immediately decline and there seemed to be a sustained increase. After CDC guideline release, significant sustained increase was observed for both outcomes. This could be due to increased attention in opioid-related problems that may lead to more diagnoses of opioid abuse and overdose. Further, there is an increase in drug overdose deaths involving heroin and semisynthetic opioids nationwide.

Before rescheduling of tramadol and hydrocodone, a declining trend was observed for opioid dose and composite outcome. This could be due to increased attention in opioid prescribing and increased risk of adverse outcomes. For the same reason, it is difficult to determine pre and post periods of each pivotal event. Some prescribing practices might have changed gradually before the time each event became effective. Thus, immediate change after each event was minimally observed. Although there was no immediate decline in opioid prescribing and the health outcomes, there were some decline in trends of opioid dose and days supply after the pivotal events. Another reason there was no significant drop in the outcomes measured immediately after CDC guideline release may be because of a lag in guideline adoption. As with other guidelines, time of guideline adoption varies and there is no clear defined lag. The CDC opioid prescribing guideline is controversial and might not be universally embraced, especially the recommendations on opioid dose tapering. This could negatively affect patients with chronic pain who were using a stable

opioid dose with well-controlled pain. Moreover, there could be a seasonal effect that may affect pain severity that was not adjusted for in the interrupted time series analysis (ITS). Longer data collection duration could provide better explanation of the trend change because this allows time for guideline adoption. Further, composite and mortality are not short-term outcomes that might not be immediately affected by regulations or guidelines. Short-term outcomes could be better for ITS because the outcomes are expected to change relatively quickly after an intervention or policy is implemented.

One legislative change that could have affected opioid prescribing in Indiana is Senate Bill 226 which limits the initial opioid prescription for an adult who was prescribed an opioid for the first time by the prescriber to not exceed 7 days supply. This Senate Bill became effective in July 2017; therefore, there was not enough data to assess the level and trend change in the post period because our last data point was December 2017. ITS evaluates changes in rates of an outcome at population level. Therefore, confounding by individual-level variables does not introduce serious bias. For the time points each outcome was measured, we included a total of 72 equally spaced time points. Each time point represented one month of data. Although there is no definite criteria on the number of appropriate time points, monthly and yearly time points are commonly used in ITS and 72 time points are adequate. However, more time points included in the analysis would increase power.

6.4 Strengths and limitations

The strengths of this study include the use of a statewide HIE from different regions of the state that represents the population of Indiana. INPC is a large and rich database that provides data from multiple health care settings and from different providers. Data contained in INPC has many components, such as patient-related, prescription, and clinical components. Using INPC allows leveraging a broad range of data from prescription data, clinical data, and health outcomes. In addition, we were able to include opioid naive patients who were initiated on opioid therapy without opioid history in the prior year before the index prescription. Therefore, the association between opioid initiation and health outcomes could be assessed. The use of retrospective database saves time and financial resources needed compares to prospective data collection. Our study contains longitudinal data of six years which is appropriate for demonstrating a pattern over time

and also assessing the associations between variables. We also included many confounders in the models and conducted sensitivity analyses to test the robustness of results.

Our study may be associated with several limitations. The analyses of this study are based on multiple variables contained in the database. Although many variables were used in multivariate analyses to control for effects of confounders, there might be other data available in the INPC that were not pulled into our data sets for analysis, for example geographic location, types of providers, smoking status, indications for opioids, insurance status, and income status. The available variables in our data sets were used in multivariate analyses, but there were not enough confounders to perform propensity score matching. In addition, there could be possible unmeasured confounders that could have an effect on the outcomes, for example seasonality effect of opioid use and exact time of guideline phase-in period.

The number of deaths can be underestimated in this database. This is because deaths captured in our data sets are from the INPC which are deaths observed in included institutions. Deaths that occur outside of the institutions might not be included in the INPC. Further, our data did not have specific cause of death. Another limitation is using ICD codes for diagnoses of the outcomes, i.e. opioid abuse, dependence, and overdose. By depending on the ICD codes, some diagnoses that did not have ICD codes associated with these diagnoses could not be captured. Our study did not use opioid use disorder (OUD) as the outcome related to opioid use because OUD is defined as a problematic pattern of opioid use leading to clinically significant impairment or distress that requires diagnosis using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) assessment criteria.[111] Many problematic patterns of opioid use are contained in the OUD, such as opioid abuse, dependence, and overdose. Although poor outcomes related to opioid use in this study did not include using DSM-5 criteria to identify patients with OUDs, but a composite outcome of opioid abuse, dependence, and overdose identified by ICD codes was used. The composite outcome of opioid abuse, dependence, and overdose are related to OUD and the factors that predict OUD and the composite outcome are the same, such as history of substance abuse, mental health conditions, and persistent pain.[106]

The pharmacy data used in this study is from Surescripts® which is prescription data. Some of the variables we use include date of prescription, medication name, dose, dispense amount, and day supply. Analyses using these variables were based on some assumptions. First, concurrent use of short and long acting opioids and concurrent use of opioids and benzodiazepines and/or

gabapentin/pregabalin was determined if the date of prescriptions were within 30 days. This does not necessarily reflect the actual dates patients take the medications. Second, opioids are commonly prescribed as needed; therefore, the days supply contained in this study may not accurately reflect duration of therapy. Third, some specific information was not able to be obtained, such as indications for opioid prescribing and the exact days patients take the medications.

One of the most important issues of secondary database analysis is quality of data especially retrospective data collection. The main purpose of data collected is not for research purposes, but is collected in the context of daily clinical practice. Thus, there is no defined criteria or protocol how data are collected. This results in variability of data collected, for example some institutions record ICD codes with different formats. Because data were collected retrospectively, some data are not verifiable, for example wrong coding in the diagnosis codes and missing data. Wrong coding of data or missing data were not possible to retrieve retrospectively. Additionally, data in INPC are dynamic. There were some intermittent disruptions in the data submitted to the INPC. Some institutions or participants in the network do not consistently provide data resulting in incomplete data for some period of time. This results in missing data and loss of data continuity. Unfortunately, data loss from absence of data sharing were not possible to obtain. Further, some patients move in and out of state and INPC is not able to capture any data occurs outside of the state.

Another limitation is that data are from multiple sources. This may result in instances of duplicate data for the same pharmacy/clinical encounter. It is difficult to determine if the duplicates are in fact duplicates of data from different sources or separate observations. However, data manipulation was done to remove duplicates where they are likely the duplicates of the same prescriptions. We assumed that the duplicate records are the same prescription from different sources if the patient has the same medication, dose, day supply, and dispense amount on the same day (Appendix F). Moreover, data from different sources are difficult to determine whether they are related. The pharmacy data of our study are from Surescripts® where there is no clinical data contained when encounter data are from hospital's electronic medical records. It is difficult to determine which prescription record is from which visit of the clinical encounters. Because Surescripts® is based on prescription data and not dispensing data, it is not possible to find out if

each prescription is actually dispensed and if patients take the medications. Likewise, the rationale or intention of prescribers was not possible to assess.

Finally, a proportion of patients in our study had missing data, particularly diagnostic codes. Missing diagnosis codes are considered missing completely at random; therefore, multiple imputation is not possible. Missing diagnosis codes results in missing CCI and medical conditions which resulted in a smaller number of patients (i.e., those with non-missing diagnostic codes) in our models. We addressed this issue by performing sensitivity analyses. In the sensitivity analyses, CCI and mental health conditions variables were omitted from the analyses to include a greater number of observations analyzed in the models, using missingness of CCI and mental health conditions as independent variables, and using CCI as a continuous variable. The results of our study are robust because almost all factors associated with the outcomes in the main analysis remained significant factors in sensitivity analyses with the same direction of relationship. Although opioid dose in Cox proportional hazards on mortality and opioid days supply in Poisson on hospitalizations became significant in sensitivity analyses when they were not significant in the main analyses because the OR and RR were close to 1 and 95% CI covered 1. Further, multiple sensitivity analyses of CCI and mental health conditions did not result in different results of the main analyses. To summarize, missing diagnosis codes can affect the analyses because patients' comorbidities and co-occurring medical conditions are important confounders that should be controlled for, but sensitivity analyses were performed to test the robustness of our findings.

6.5 Conclusion

Several opioid prescribing characteristics are associated with poor outcomes in patients initiated on opioid therapy. Many high-risk prescribing practices are associated with adverse health outcomes. In agreement with other studies, we found higher CCI, mental health conditions, higher opioid dose, longer opioid day supply, use of opioids concurrently with benzodiazepines, gabapentin, and/or pregabalin as significant factors of opioid abuse, dependence, overdose, mortality, and healthcare utilization. We also found that rescheduling of tramadol and hydrocodone seemed to reduce opioid dose and days supply, but reduction in opioid abuse, dependence, overdose, and mortality was not observed after CDC guideline release. Leveraging an HIE gives credence to the ability to use clinical data to predict opioid harms. Our findings add

to the existing evidence that high-risk opioid prescribing increased risk of poor health outcomes. High-risk opioid prescribing could decline due to opioid-related legislation and/or policies. The results of this study may guide further assessment of other legislation that could affect opioid prescribing. Therefore, future interventions which target high risk opioid prescribing can be promising and could ultimately lead to safer opioid prescribing practices and reduce associated poor health outcomes.

The future directions include focusing on specific groups of patients and develop specific recommendations, such as patients with mental health conditions and compare risks between different conditions because the presence of mental health conditions is a strong predictor of poor outcomes. The results of this study may inform efforts to improve opioid prescribing, such as strategies to prevent concurrent use of opioids and benzodiazepines and/or gabapentin/pregabalin. Additionally, other prospective studies may be developed to confirm the results and ultimately develop clinical intervention tools to support clinical practice. Finally, continuation of work for guideline and recommendations should be further conducted to ensure that guidelines actually make an impact on opioid prescribing and improve patients' health outcomes.

APPENDIX A. ICD-9 AND ICD-10 CODES USED FOR DIAGNOSES OF OPIOID ABUSE, DEPENDENCE, AND OVERDOSE

Table A.1. List of ICD-9 and ICD-10 codes used for identifying opioid abuse, dependence, and overdose diagnoses

ICD-9	ICD-10	Description
305.50 305.51 305.52 305.53	F11.10 F11.11 F11.12	Opioid abuse
304.00 304.01 304.02 304.03 304.70 304.71 304.72 304.73	F11.20 F11.21 F19.20 F19.21	Opioid dependence
965.00 965.01 965.02 965.09 E850.1 E850.2	T40.0X1-0X4 T40.1X1-1X4 T40.2X1-2X4 T40.3X1-3X4 T40.4X1-4X4 T40.601-604 T40.691-694	Opioid overdose

APPENDIX B. GROUP OF MEDICAL CONDITIONS USED TO CALCULATE CHARLSON COMORBIDITY INDEX (CCI)

Table B.1. Medical conditions used to calculate Charlson comorbidity index (CCI)

CCI Group	**Medical condition**
1	Myocardial Infarction
2	Congestive Heart Failure
3	Peripheral Vascular Disease
4	Cerebrovascular Disease
5	Dementia
6	Chronic Pulmonary Disease
7	Connective Tissue Disease-Rheumatic Disease
8	Peptic Ulcer Disease
9	Mild Liver Disease
10	Diabetes without complications
11	Diabetes with complications
12	Paraplegia and Hemiplegia
13	Renal Disease
14	Cancer
15	Moderate or Severe Liver Disease
16	Metastatic Carcinoma
17	AIDS/HIV

APPENDIX C. CDC'S MORPHINE MILLIGRAM EQUIVALENT CONVERSION FACTOR AND CLASSIFICATION OF OPIOID PRODUCTS

Table C.1. Morphine Milligram Equivalent (MME) conversion factor of opioids[185]

Opioids	**MME conversion factor**
Buprenorphine	N/A
Codeine	0.15
Fentanyl	7.2
Hydrocodone	1
Hydromorphone	4
Levorphanol	11
Meperidine	0.1
Methadone	3
Methylnaltrexone	N/A
Morphine	1
Naloxone	N/A
Naltrexone	N/A
Oxycodone	1.5
Oxymorphone	3
Tapentadol	0.4
Tramadol	0.1

Table C.2. Classification of short and long acting opioid products[185]

Opioids	**Short/long acting**
Buprenorphine tablet	LA
Buprenorphine patch, ER	LA
Buprenorphine/naloxone film	LA
Codeine tablet	SA
Fentanyl patch	LA
Hydrocodone tablet	SA
Hydrocodone ER tablet/capsule	LA
Hydromorphone tablet	SA
Hydromorphone ER tablet	LA
Levorphanol tablet	LA
Meperidine tablet	SA
Methadone tablet	LA
Methylnaltrexone injection	SA
Morphine tablet	SA
Morphine ER tablet/capsule	LA
Naloxone injection	SA
Naltrexone tablet	LA
Oxycodone tablet	SA
Oxymorphone tablet	SA
Oxymorphone ER tablet	LA
Tapentadol tablet	SA
Tapentadol ER tablet	LA
Tramadol tablet	SA
Tramadol ER tablet	LA

Note: SA=Short acting, LA=Long acting, All extended-release (ER) products are LA

APPENDIX D. BENZODIAZEPINES EQUIVALENT DOSES AND CONVERSION FACTORS

Table D.1. Benzodiazepines equivalent doses and conversion factors standardized to one milligram of diazepam[186]

Benzodiazepines	**Approximate equivalent oral doses (mg)**	**Conversion factor to DME**
Alprazolam	0.5	0.05
Chlordiazepoxide	25	2.5
Clobazam	20	2
Clonazepam	0.5	0.05
Clorazepate	15	1.5
Diazepam	10	1
Estazolam	2	0.2
Flunitrazepam	1	0.1
Flurazepam	20	2
Lorazepam	1	0.1
Midazolam	15	1.5
Oxazepam	20	2
Prazepam	20	2
Quazepam	20	2
Temazepam	20	2
Triazolam	0.5	0.05
Eszopiclone	3	0.3
Zaleplon	20	2
Zolpidem	20	2

Note: DME=Diazepam Milligram Equivalent

APPENDIX E. DATA DICTIONARY

Table E.1. Data dictionary in patient data set

#	Variable	Type	Definition
1	STUDYID	Num	Study ID
2	SEX	Char	Sex
3	RACE	Char	Race
4	YEAR_BIRTH	Num	Year of birth
5	YEAR_DEATH	Num	Year of death (all-cause)
6	INDEX_YEAR	Num	Year of index
7	INDEX_AGE	Num	Age at index
8	DAYS_LAST_INDEX	Num	Days from index to last visit (data must be available at least six months after index, last visit corresponds to the last visit in the visit data set)
9	DAYS_DEATH_INDEX	Num	Days from index to death
10	MED_HX	Num	# Days of available (any med) data before index
11	N_INP	Num	# Inpatient visits since index regardless of Dx available
12	N_INP_ALL	Num	# All Inpatient visits ever regardless of Dx available
13	N_INP_OPIOID	Num	# Inpatient visits since index for opioid-specific Dx (identified by ICD codes)
14	N_ER	Num	# ER visits since index regardless of Dx available
15	N_ER_ALL	Num	# All ER visits ever regardless of Dx available
16	N_ER_OPIOID	Num	# ER since index for opioid-specific Dx (identified by ICD codes)
17	N_ABUSE	Num	# of dates with opioid abuse Dx
18	FIRST_ABUSE_INDEX	Num	Days from index to first abuse
19	N_DEPEND	Num	# of dates with opioid dependence Dx
20	FIRST_DEPEND_INDEX	Num	Days from index to first opioid dependence
21	N_OVERDOSE	Num	# of dates with opioid overdose Dx
22	FIRST_OVERDOSE_INDEX	Num	Days from index to first opioid overdose
23	N_HEROI	Num	# of dates with heroin Dx
24	FIRST_HEROI_INDEX	Num	Days from index to first heroin

Table E.2. Data dictionary for opioid data set

#	Variable	Type	Definition
1	STUDYID	Num	Study ID
2	DAYS_PHARM_INDEX	Num	Days from index to drug (opioid)
3	GIVE_CODE	Char	NDC Code (11 digit)
4	NUMBER_OF_DAYS_SUPPLY	Num	Number of day supply
5	DISPENSE_AMOUNT	Num	Amount dispensed
6	GIVE_STRENGTH	Num	Strength of medication
7	NDC9	Char	NDC Code (9 digit)
8	Unit_strength_in_Oral_MME_adjust	Num	Unit strength in oral MME adjusted for 1 unit dose
9	Drug_Category	Char	Drug name
10	Opioid_Deterrent	Num	Opioid deterrent (1=yes)

Table E.3. Benzodiazepine data set

#	Variable	Type	Definition
1	STUDYID	Num	Study ID
2	DAYS_PHARM_INDEX	Num	Days from index to BZD drug (benzodiazepine)
3	GIVE_CODE	Char	NDC Code (11 digit)
4	GIVE_STRENGTH	Num	Strength of medication
5	DISPENSE_AMOUNT	Num	Amount dispensed
6	NUMBER_OF_DAYS_SUPPLY	Num	Number of day supply
7	NDC9	Char	NDC Code (9 digit)
8	Product_Name	Char	Product name

Table E.4. Gabapentin/pregabalin data set

#	Variable	Type	Definition
1	STUDYID	Num	Study ID
2	DAYS_PHARM_INDEX	Num	Days from index to drug (gabapentin/pregabalin)
3	GIVE_CODE	Char	NDC Code (11 digit)
4	GIVE_STRENGTH	Num	Strength of medication
5	DISPENSE_AMOUNT	Num	Amount dispensed
6	NUMBER_OF_DAYS_SUPPLY	Num	Number of day supply
7	NDC9	Char	NDC Code (9 digit)
8	PRODUCT_NAME	Char	Product name and dose in mg

Table E.5. Visit data set

#	Variable	Type	Definition
1	STUDYID	Num	Study ID
2	DAYS_VISIT_INDEX	Num	Days from index to visit
3	VIS_TYPE	Char	Type of visit
4	DX_CODE	Char	ICD Code
5	DX_PRIORITY	Num	Dx priority
6	LOS	Num	Length of stay (discharge – admission +1); days

APPENDIX F. DETAILS OF DUPLICATE RECORDS REMOVAL

The observations were considered duplicates if they had the same opioid product (determined NDC) and the same number of day supply on the same pharmacy visit for the same study ID (Table F.1). The completeness of data was considered by number of day supply, dispense amount, and product strength. The completeness of these three variables varied differently for each duplicate. Some observations had all of these three variables while some had missing dispense amount, product strength, or both.

Table F.1. Example of duplicate records

Study ID	#Days from index to pharmacy	Day supply	Dispense amount	Product strength	NDC9	Unit MME	Product name
2795	270	10	60	.	00930058	5	Tramadol
2795	270	10	60	50	00930058	5	Tramadol
2795	270	10	.	.	00930058	5	Tramadol

To write SAS codes to remove the duplicate records, a unique number containing linked study ID, days from index to pharmacy, opioid product, and NDC code was created for each observation. From Table F.1, the unique number for this patient is 2795/270/Tramadol/930058. Thus, the three duplicate records above have the same unique number. Then the frequencies of each unique number are counted to find the number of duplicates. If this unique number appear twice in the data set, then there are 2 duplicates of the same unique number. The example for study ID 2795 in Table F.1 is considered 3 duplicates. After finding the frequencies of each unique number, there were 2, 3, and 4 number of duplicates in the full pharmacy data set. The patterns of duplicate records were then divided into 3 groups according to the number of duplicates, i.e. 2, 3, and 4. Then each group was explored separately to remove the duplicates. Each group was further divided to those with either the same or different day supply, unit strength, or dispense amount. The record with the most complete data was kept while those incomplete duplicates were removed.

From the example above, the second record with complete data was the only one record that was kept.

The method used to determine the most complete record was to add the values of the three variables (i.e. day supply, dispense amount, and strength) together for each duplicate and choose the record with the highest sum. From Table F.1, the sum of the three variables for the first, second, and third observations were 70, 120, and 10 respectively. Thus, the records with sum of 10 and 70 were removed and the second record which had the highest sum (120) was the record that was kept. Finally, after removal of 20,620 (1.2%) duplicate records, 1,726,294 observations remained in the pharmacy data set.

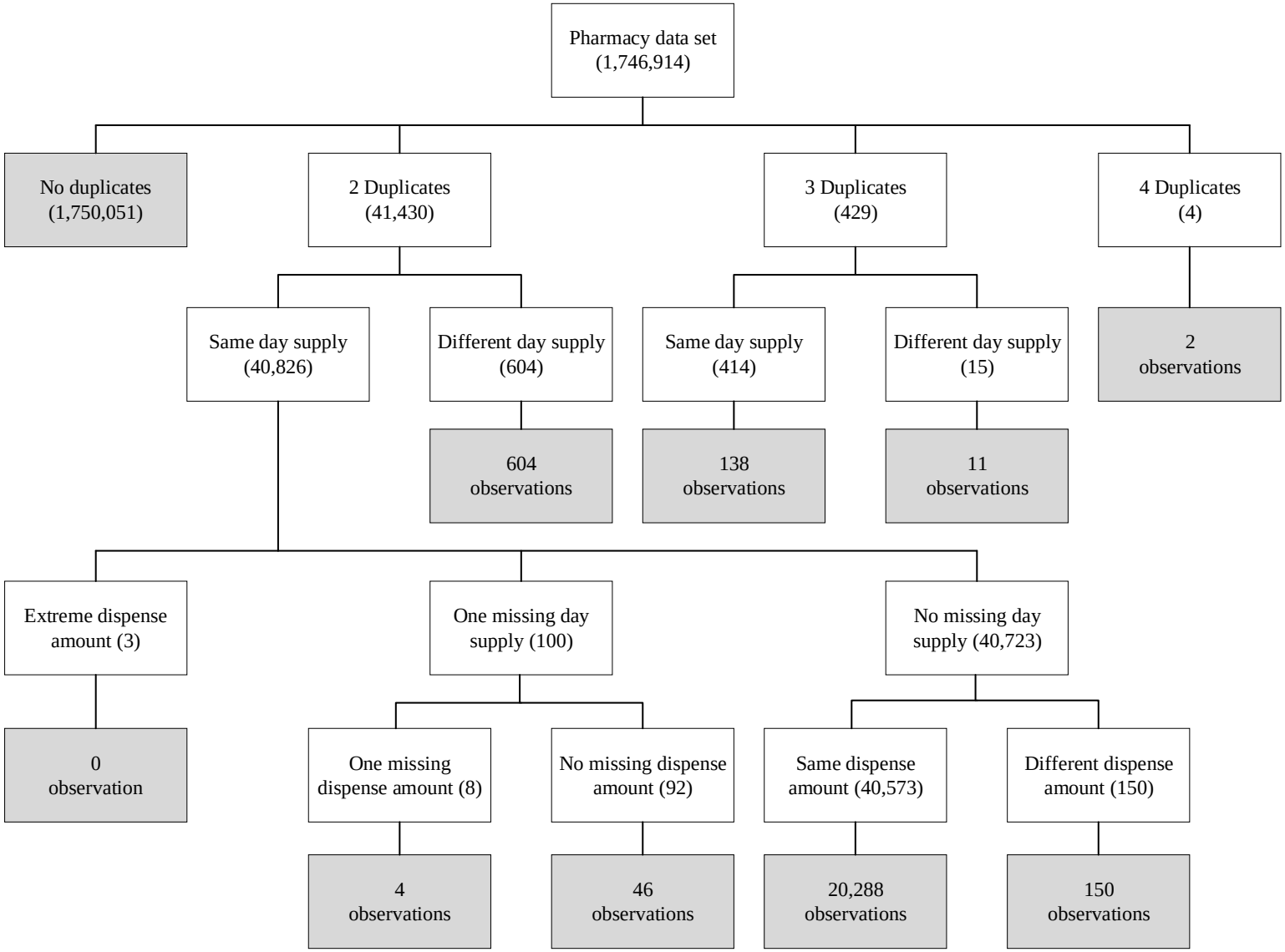

Figure F.1. Flow chart of strategies to remove duplicate records

APPENDIX G. SENSITIVITY ANALYSES

Table G.1. Factors associated with composite outcome of opioid abuse, dependence, and overdose

Variables	OR (95% CI)	P value
Age (years)	0.955 (0.952-0.959)	<0.0001
Sex		
Male	1.48 (1.32-1.65)	<0.0001
Female	Ref	Ref
Long term use		
Yes	3.39 (2.82-4.08)	<0.0001
No	Ref	Ref
Number of days in the study duration	1.000 (1.000-1.001)	<0.0001
Number of days supply	1.025 (1.018-1.031)	<0.0001
Opioid dose (MME/day)	1.003 (1.000-1.005)	0.0401
Concurrent short/long acting opioids		
Short + Long acting within 30 days	2.40 (2.00-2.87)	<0.0001
Short + Long acting not within 30 days	2.08 (1.23-3.31)	0.0036
Long acting only	2.25 (0.68-5.51)	0.1208
Short acting only	Ref	Ref
Concurrent medications with opioid		
Benzodiazepine	1.99 (1.71-2.32)	<0.0001
Gabapentin/Pregabalin	2.13 (1.77-2.57)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin within 30 days	2.76 (2.27-3.35)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin not within 30 days	2.53 (1.85-3.39)	<0.0001
None (opioid only)	Ref	Ref

Table G.2. Factors associated with all-cause mortality

Variables	HR (95% CI)	P value
Age (years)	1.087 (1.084-1.091)	<0.0001
Sex		
Male	1.59 (1.47-1.72)	<0.0001
Female	Ref	Ref
Race		
Caucasian	0.71 (0.63-0.81)	<.0001
Hispanic/Latino	1.11 (0.57-2.15)	0.7599
Asian	0.49 (0.18-1.32)	0.1577
Others	0.75 (0.60-0.95)	0.0146
African American	Ref	Ref
Number of days supply	1.010 (1.006-1.014)	<0.0001
Opioid dose (MME/day)	0.996 (0.994-0.999)	0.0056
Concurrent short/long acting opioids		
Short + Long acting within 30 days	1.88 (1.58-2.24)	<0.0001
Short + Long acting not within 30 days	1.56 (1.03-2.36)	0.0351
Long acting only	2.31 (1.04-5.17)	0.0409
Short acting only	Ref	Ref
Concurrent medications with opioid		
Benzodiazepine	1.09 (0.97-1.22)	0.1412
Gabapentin/Pregabalin	1.12 (0.99-1.26)	0.0861
Benzodiazepine + Gabapentin/Pregabalin within 30 days	1.49 (1.26-1.77)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin not within 30 days	0.76 (0.51-1.12)	0.1609
None (opioid only)	Ref	Ref

Table G.3. Factors associated with hospitalizations

Variables	RR (95% CI)	P value
Age group		
50+	1.78 (1.77-1.79)	<0.0001
<50	Ref	Ref
Sex		
Male	0.943 (0.937- 0.949)	<0.0001
Female	Ref	Ref
Race		
Caucasian	0.70 (0.69-0.71)	<0.0001
Hispanic/Latino	0.63 (0.60-0.66)	<0.0001
Asian	0.66 (0.62-0.70)	<0.0001
Others	0.64 (0.63-0.65)	<0.0001
African American	Ref	Ref
Long term user		
Yes	1.38 (1.37-1.40)	<0.0001
No	Ref	Ref
Duration in the study period (years)		
>2	1.42 (1.41-1.43)	<0.0001
≤2	Ref	Ref
Opioid dose (MME/day)		
>50	1.03 (1.02-1.03)	<0.0001
≤50	Ref	Ref
Concurrent short/long acting opioids		
Short + Long acting within 30 days	1.50 (1.48-1.52)	<0.0001
Short + Long acting not within 30 days	1.54 (1.48-1.61)	<0.0001
Long acting only	1.28 (1.17-1.39)	0.0017
Short acting only	Ref	Ref
Concurrent medications with opioid		
Benzodiazepine	1.28 (1.27-1.29)	<0.0001
Gabapentin/Pregabalin	1.50 (1.48-1.51)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin within 30 days	1.73 (1.71-1.76)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin not within 30 days	1.62 (1.58-1.66)	<0.0001
None (opioid only)	Ref	Ref

Table G.4. Factors associated with ED visits

Variables	RR (95% CI)	P value
Age group		
50+	0.676 (0.673-0.679)	<0.0001
<50	Ref	Ref
Sex		
Male	1.02 (1.01-1.02)	<0.0001
Female	Ref	Ref
Race		
Caucasian	0.54 (0.53-0.54)	<0.0001
Hispanic/Latino	0.70 (0.68-0.71)	<0.0001
Asian	0.30 (0.29-0.32)	<0.0001
Others	0.46 (0.45-0.46)	<0.0001
African American	Ref	Ref
Long term user		
Yes	1.46 (1.45-1.47)	<0.0001
No	Ref	Ref
Duration in the study period (years)		
>2	1.47 (1.46-1.48)	<0.0001
≤2	Ref	Ref
Opioid dose (MME/day)		
>50	0.811 (0.806-0.815)	<0.0001
≤50	Ref	Ref
Opioid day supply (days)		
>5	0.73 (0.71-0.74)	<0.0001
1-5	Ref	Ref
Concurrent short/long acting opioids		
Short + Long acting within 30 days	1.21 (1.19-1.22)	<0.0001
Short + Long acting not within 30 days	1.29 (1.26-1.33)	<0.0001
Long acting only	1.33 (1.25-1.41)	<0.0001
Short acting only	Ref	Ref
Concurrent medications with opioid		
Benzodiazepine	1.41 (1.40-1.42)	<0.0001
Gabapentin/Pregabalin	1.43 (1.42-1.44)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin within 30 days	2.00 (1.98-2.01)	<0.0001
Benzodiazepine + Gabapentin/Pregabalin not within 30 days	1.86 (1.83-1.89)	<0.0001
None (opioid only)	Ref	Ref

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