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Prescription Drug Monitoring Programs and Opioid Poisoning: Evaluating the Impact of Prescriber Use Mandates on Prescription Opioid Poisoning Emergency Department Visits

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Science at Virginia Commonwealth University.

by

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May, 2018

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Dedication

This dissertation is dedicated to my precious family: My mom "Dalal", my husband "Mohammad", and my three little angels "Ghala", "Dai", and "Abdulmohsen". You were with me in the ups and downs, you shared with me my happiness and sadness. May "Allah" bless you in your life. My Dad "Ali" I wish you was here, may "Allah" have mercy on you.

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List of Abbreviations

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ACPM: American College of Preventive Medicine

AFS: Ambulance Fee Schedule

AHRQ: Agency for Healthcare Research and Quality

APICC: Hospital-specific all payer inpatient cost to charge ratio

ARCOS: Automation of Reports and Consolidated Orders System

ARR: adjusted Risk Ratio

BJA: Bureau of Justice Assistance

BNE-NYSDOH: Bureau of Narcotics Enforcement- New York State Department of Health

CCR: Cost to Charge Ratio

CCS: Clinical Classifications Software

CDC: Centers for Disease Control and Prevention

CI: Confidence Interval

CINHAL: Cumulative Index to Nursing and Allied Health Literature

CMS: Centers for Medicare and Medicaid Services

COE: Center of Excellence

CPT: Current Procedural Terminology

CS: Controlled Substance

DAWN: Drug Abuse Warning Network

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DEA: Drug Enforcement Agency

DHMH: Department of Health and Mental Hygiene

DID: Difference in Difference

E-codes: External Cause of Injury codes

ED: Emergency Department

EPs: Emergency Providers

FDA: Food and Drug Administration

GAPICC: Group average all-payer inpatient cost to charge ratio

HB1: House Bill 1

HCPCS: Healthcare Common Procedure Coding System

HCUP: Healthcare Cost and Utilization Project

ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification

IRB: Institutional Review Board

I-STOP: Internet System for Tracking Over-Prescribing

KASPER: Kentucky All Schedule Prescription Electronic Reporting

MEC: Medical Examiners Commission

MeSH: Medical Subject Headings

MME: Morphine Milligram Equivalents

MPE: Multiple Provider Episode

MPFS: Medicare Physician Fee Schedule

MT: Medical Toxicologists

NAMCS: National Ambulatory Medical Care Survey

NAMSDL: National Alliance for Model State Drug Laws

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NEDS: Nationwide Emergency Department Sample

NMPO: Non-Medical Use of Prescription Opioids

NPDS: National Poison Data System

NSDUH: National Survey on Drug Use and Health

OR: Odds Ratio

PDAPS: Prescription Drug Abuse Policy System

PSR: Prevention Status Report

RADARS: Researched Abuse, Diversion and Addiction-Related Surveillance

SAMSHA: Substance Abuse and Mental Health Services Administration

SEDD: State Emergency Department Databases

SID: State Inpatient Databases

SPARCS: Statewide Planning and Research Cooperative System

TEDS: Treatment Episode Data Set

WHO: World Health Organization

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Abstract

PRESCRIPTION DRUG MONITORING PROGRAMS AND OPIOID POISONING: EVALUATING THE IMPACT OF PRESCRIBER USE MANDATES ON PRESCRIPTION OPIOID POISONING EMERGENCY DEPARTMENT VISITS

By Sarah A. Almanie, Ph.D.

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Science at Virginia Commonwealth University.

Virginia Commonwealth University, 2018.

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Introduction: Prescription drug monitoring programs (PDMPs) are one strategy established to curb the prescription opioid abuse epidemic. Prescriber use mandates has emerged as a promising practice to increase PDMPs impact on prescription opioid abuse; however, evidence of its effectiveness has not yet been established. Kentucky was the first state to implement comprehensive prescriber use mandates in July 2012.

Objective: To assess the relationship between prescriber use mandates policy and emergency department (ED) visits related to prescription opioid poisoning among adults in Kentucky and

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North Carolina. Secondary aim: to evaluate the economic impact of prescriber use mandates in Kentucky.

Methods: A controlled, pre-post study design. Data from the State Emergency Department Databases (SEDD) and the State Inpatient databases (SID) were used to identify prescription opioid poisoning ED visits among those ≥ 12 years old. Prevalence rate were estimated. Prescription opioid poisoning ED visits were characterized based on sociodemographic and clinical characteristics. Logistic regression was applied to compare occurrences of prescription opioid poisoning ED visits pre and post prescriber use mandates in Kentucky, and between Kentucky and North Carolina for the period 2011 to 2014. A cost of illness framework was applied to estimate direct medical costs associated with prescription opioid poisoning ED visits. The economic impact of prescriber use mandates was quantified based on logistic regression coefficient for the interaction term (state*time to implementation).

Results: There were 7,419 and 12,598 prescription opioid poisoning -related ED visits in Kentucky and North Carolina, respectively. Young and Middle age, male gender, white, having one or more chronic conditions, and psychiatric conditions (such as depression and drug abuse) were significantly associated with prescription opioid poisoning ED visits (*p*-value<0.05). The odds of having a prescription opioid poisoning ED visit in Kentucky were significantly lower compared to North Carolina in 2012, 2013, and 2014 compared to 2011 (OR = 0.9, 0.7, and 0.7 respectively). The total estimated direct medical costs were $13.77 and $24.37 million in Kentucky and North Carolina, respectively. In Kentucky, the economic impact of prescriber use mandates was estimated at - $2.3 million.

Conclusion: Prescriber use mandates is effective in reducing prescription opioid poisoning ED visits, and its economic impact is considerable.

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Chapter 1

Section 1.1: Introduction

Opioids and their related effects

Opioids are a class of drugs that include the illicit drug heroin as well as legal prescription pain relievers, including hydrocodone, oxycodone, morphine, and codeine.[1] Opioids can be naturally occurring (morphine), semi-synthetic (heroin), or synthetic (fentanyl). They are further classified as agonists, partial agonists, and antagonists based on their effect on opioid receptors.[2] Opioid agonists relieve pain by interacting with opioid receptors, thus, inhibiting the transmission of pain signals (codeine). In contrast, opioid antagonists block opioid receptors and have no functional response; naloxone is an example of an opioid antagonist that is used to reverse symptoms of opioid overdose. Opioids with partial agonist activity have some functional response when binding to opioid receptors (buprenorphine). Three major types of opioid receptors have been identified: mu, delta, and kappa, which are located in the central nervous system and the periphery.[3]

Opioids may also induce a number of behavioral effects, including euphoria, due to activation of reward regions in the brain.[1, 4] This may promote repeated use of opioids for pleasure, rather than pain relief. Continued opioid use may lead to abuse, dependence, addiction, and other related behaviors.

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The literature provides no consistent definition of opioid-related health behaviors like abuse, dependence, and addiction. According to the American College of Preventive Medicine (ACPM), abuse is defined as "self-administration of medications to alter one's state of consciousness."[5]

The World Health Organization (WHO) defines abuse as "persistent or sporadic excessive drug use inconsistent with or unrelated to acceptable medical practice."[6] Drug abuse is also defined in the literature as "a disease characterized by continued misuse of drugs even when faced with drug-related job, legal, health, or family difficulties."[7] Definitions of other related health behaviors are presented in Table 1.1.

Table 1. 1: Terms and definitions of opioid related behaviors

Term	Definition
Opioid use disorder	"A problematic pattern of opioid use that causes clinically significant impairment or distress"[1]
Misuse	"The use of prescription drugs without a prescription, or in a manner other than as directed by a doctor"[2]
Addiction	"A primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations"[3]
Physical dependence	"Adaptation to a drug that produces symptoms of withdrawal when the drug is stopped"[2]
Diversion	"Redirection of a prescription drug from its lawful purpose to illicit use; can be done with criminal intent"[4]
Non-medical use	"Intentional or unintentional use of legitimately prescribed medication in an un-prescribed manner for its psychic effect (either experimentation or recreationally)"[5]

1. Opioid overdose: prevent opioid use disorder. United States: Centers for Disease Control and Prevention; October, 2017. Available from: https://www.cdc.gov/drugoverdose/prevention/opioid-use-disorder.html.
2. Opioid overdose: commonly used terms. Centers for Disease Control and Prevention; August, 2017. Available from: https://www.cdc.gov/drugoverdose/opioids/terms.html.
3. Definitions Related to the Use of Opioids for the Treatment of Pain: Consensus Statement of the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine. United States: American Society of Addiction Medicine; 2001. Available from: https://www.asam.org/docs/default-source/public-policy-statements/1opioid-definitions-consensus-2-011.pdf.

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4. Passik SD. Issues in long-term opioid therapy: unmet needs, risks, and solutions. Mayo Clinic Proc. 2009; 84(7):593-601.
5. Use, Abuse, Misuse & Disposal of Prescription Pain Medication Clinical Reference United States: the American College of Preventive Medicine; 2011. Available from: www.acpm.org/?UseAbuseRxClinRef.

Based on the risk of abuse, the Food and Drug Administration (FDA) has classified opioids into one of the five federal schedules of controlled substances. Heroin is classified in Schedule I, which contains illegal drugs with the highest tendency of abuse. Prescription opioids, which have a lower risk of abuse than heroin, are classified in Schedules II to V depending on their specific risks. Although the use of prescription opioids is associated with abuse risk, opioids are widely accepted as pain relievers.

Prescription opioid abuse epidemic

The number of prescriptions for opioids in the United States has increased dramatically over the last two decades. According to the Quintiles IMS (Formerly IMS Health), the number of opioid prescriptions increased from 76 million in 1991 to 207 million in 2013.[8] Each day, more than 65 thousand of opioid prescriptions are dispensed.[9] In the United States, the use of prescription opioids varies largely among states, healthcare providers, and patients' characteristics.[10] The difference in opioid prescribing rates between states with the highest and lowest prescribing rate is about three fold. Among medical specialties, primary care physicians are responsible for almost half of opioid prescriptions dispensed.[11] Adults aged 40 years and older, women, and non-Hispanic white are prevalent users of prescription opioids. The commonly prescribed opioid analgesics are oxycodone, hydrocodone, morphine, and methadone.

Prescription opioid abuse has increased concurrently over the past two decades. Opioid abuse has reached epidemic levels in the United States, prompting the US Surgeon General to write a 2016 letter to all American physicians asking for help to solve the epidemic.[12] According to the

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National Survey on Drug Use and Health (NSDUH), about two million Americans abuse prescription opioids.[13] Almost four thousand people initiate non-medical use of prescription opioids on a single day.[9] The prevalence of abuse varies by age, sex, and other factors. Among people aged 12 years and older, young adults (18-25 years old) are the biggest abusers of prescription opioids.[14] Compared to women, men are more likely to abuse opioid analgesics.[14] The risk of abuse increases when patients obtain multiple prescriptions from multiple prescribers and/or pharmacies, a behavior known as doctor shopping or multiple provider episode (MPE).[15, 16] Other risk factors include high daily dose of opioid [>100 morphine milligram equivalents (MME)], patients with low income, and presence of a mental illness or a history of drug abuse.[17]

Prescription opioid abuse and related health and economic outcomes

The prescription opioid abuse epidemic is associated with significant negative health outcomes. Opioid overdose or poisoning is the most serious health outcome. The Centers for Disease Control and Prevention (CDC) defines overdose as "injury to the body that happens when a drug is taken in excessive amounts."[18] Opioids in high doses can lead to respiratory distress and death due to their impact on respiratory control regions in the brain. The World Health Organization (WHO) describes opioid overdose as a combination of three symptoms: pinpoint pupils, unconsciousness, and respiratory depression.[19] Opioid overdose is the leading cause of drug overdose deaths in the United States and was responsible for more than 15 thousands deaths in 2015.[20] The rate of opioid analgesic overdose deaths increased by more than fourfold from 2000 - 2014. Currently, half of opioid overdose deaths involve prescription opioids. The risk of opioid overdose increases with a high daily dose of opioid (>100 MME), use of long acting opioids, and the concurrent use of benzodiazepines.

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Additional negative health outcomes are associated with the prescription opioid abuse epidemic. According to the National Poison Data System (NPDS), a comprehensive poisoning surveillance database in the United States, more than 40 thousand exposure cases involved a single prescription opioid. Adults, aged 13 years and older, constituted more than 30% of total exposure cases.[21] Moreover, more than 360 thousands emergency department (ED) visits were attributed to non-medical use of prescription opioids in 2011.[22] The negative health impact of prescription opioid abuse become more serious when abusers of prescription opioids shift to heroin use due to its lower cost, ready availability in the black market, and higher level of induced euphoria. According to the Substance Abuse and Mental Health Services Administration (SAMSHA), four in five new heroin users have previously used prescription painkillers.[23]

The prescription opioid abuse epidemic has created a substantial economic burden. In a study by Birnbaum et al. in 2011, the annual cost of prescription opioid abuse in the United States was estimated at $55.5 billion. Of this cost, 46% was attributed to lost workplace productivity, 45% to health care costs, and 9% to spending on criminal justice.[24] In a more recent study by Inocencio et al, the total cost of prescription opioid poisoning was estimated at $16 billion. Emergency department (ED) visits shared 0.5 billion of the total estimated cost.[25]

The causes of the prescription opioid abuse epidemic are multifactorial. The rapid increase in the number of prescriptions written for opioids has increased accessibility to these medications. According to the CDC, about 259 million opioid prescriptions were written in 2012 alone.[26] Pill mills, or operations in which doctors prescribe large quantities of pills for little or no medical reason, have been one main driver for the massive increase in opioid prescriptions. In addition, increased social acceptability of prescription opioid use for pain relief and aggressive

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pharmaceutical marketing have facilitated the use of prescription opioids for first-line treatment of pain.

Combating the prescription opioid abuse epidemic

Controlling the prescription opioid abuse epidemic is complex and requires multifaceted efforts. The subjectivity of pain presents the first obstacle to limiting opioid prescribing. Patients have the right to receive adequate pain relief, but the severity of pain and the appropriateness of opioids to address that pain are difficult to determine and often depend on the prescriber's judgment. Doctor shopping behavior, or multiple provider episode (MPE), presents another obstacle to controlling this epidemic. MPE, defined as "the use of five or more prescribers and five or more pharmacies within three months"[27] makes it difficult for doctors, pharmacists, and the drug enforcement agencies to identify abusers and target them for interventions. Finally, efforts to control the opioid abuse epidemic must address the multiple pathways by which abusers can obtain prescription opioids. These pathways include taking or purchasing prescription opioids from relatives, friends, or the black market.[28] According to the NSDUH, more than half of non-medical users of prescription opioids obtain them from a friend or relative for free.[28] Due to the complexity of the prescription opioid abuse epidemic, policies or interventions developed at the federal or state level must ensure a balance between ensuring access to prescription opioids for patients who need them while minimizing the risk of abuse.

Opioid prescribing guidelines

One method for addressing the prescription opioid abuse epidemic is to decrease access to opioids for nontherapeutic use. Prescribers are the gate keepers of prescription opioids and thus, must ensure proper prescribing of opioids to patients. Several guidelines have been developed for

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prescribing opioids which provide recommendations on dosing threshold, cautious titration, and risk mitigation strategies. The most recent opioid prescribing guideline was published by the CDC in 2016 and provides recommendations for prescribing opioids for adults population (≥18 years old) with chronic non-cancer pain in primary care settings.[29]

Prescription Drug Monitoring Programs (PDMPs)

In 2011, the Federal Government identified PDMPs as one of four key areas of focus to prevent prescription drug abuse.[30] PDMPs are state-run electronic databases that collect information on the prescribing and dispensing of prescription opioids and other controlled substances. The pharmacy-reported prescription fill records contained in the PDMPs ease the tracking and analyzing of prescription data. PDMPs thereby help to identify improper prescribing, dispensing behavior, and doctor shopping. PDMPs cover controlled substances as defined by federal and state laws; most PDMPs monitor drug schedules II-V. PDMPs are primarily used by physician prescribers, nurses, and pharmacists. Other authorized entities, including law enforcement agencies and regulatory boards, may access prescribing data. States' PDMPs are operated mainly by pharmacy boards, departments of health, or law enforcement agencies. A sustained source of funding is essential to maintain PDMP functioning; state general funds are the major source of funding. Also, federal grants play an important role in supporting states PDMPs; the most common federal grant is Harold Rogers PDMP Grant Program.

PDMP use process

The PDMP use process begins when a patient comes to a physician office or other outpatient setting seeking a prescription for opioids. Before issuing the prescription, the physician must log in to the PDMP database to retrieve the patient's schedules II-V prescription history. The

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checkup step should be done for all new and established patients. If abuse behavior is suspected, opioids may not be prescribed. Otherwise, the prescription is issued and sent to the pharmacy. Before dispensing, the PDMP database should be double checked by the pharmacist to ensure safe and appropriate use of prescription opioids. When inappropriate use of opioids is suspected, the pharmacist may not dispense the prescription. The pharmacist is responsible for reporting all dispensed prescriptions for opioids to the PDMP program manager who stores the information on a database accessible to authorized parties. The transmission of prescribing data from pharmacy to the state PDMP database is done through an external vendor, where data are checked for any errors. The PDMP use process cycle continues whenever the same patient seeks another prescription for opioids. The PDMPs use process is summarized in Figure 1.1

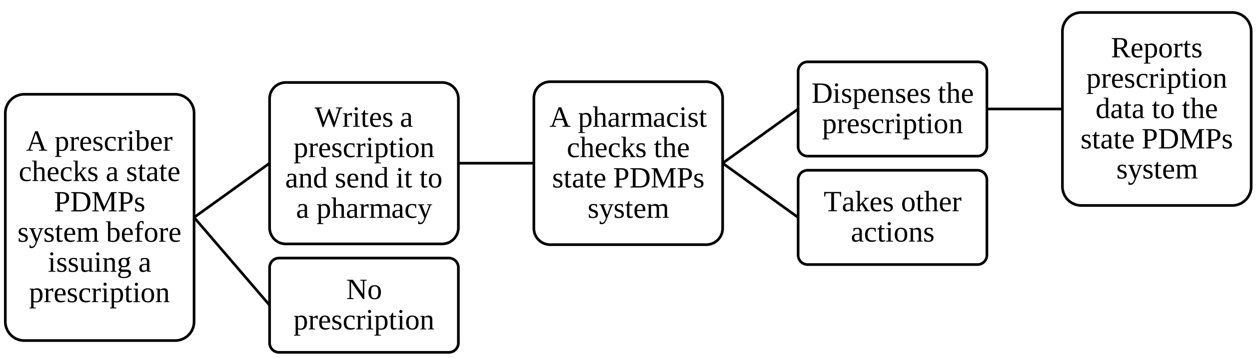

Figure 1. 1: PDMP use process

PDMP adoption

PDMPs are currently operational in all states. However, state PDMPs differ in practices pertaining data collection, analysis, user access, utilization, and user education. A PDMP practice is defined as “a database operation, or a particular policy that PDMP staff might adopt

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when carrying out its functions."[31] PDMPs practices can be used to evaluate the effectiveness of PDMPs.

PDMP effectiveness

The effectiveness of PDMPs has been questioned since their implementation. The impact of PDMPs on physician prescribing behavior, doctor shoppers, and health outcomes including overdose deaths and ED visits has been evaluated. The literature reveals inconsistent evidence on the effectiveness of PDMPs. However, a growing body of evidence suggests that PDMPs are effective tools.

The effectiveness of PDMPs may be influenced by the degree to which they conform with best practices related to data collection, analysis, utilization, user access, and education. In 2012, the Center of Excellence (COE) at Brandies University published a white paper proposing 35 potential best practices for PDMPs.[32] Most of the promising best practices proposed in the paper had no or weak evidence supporting their effectiveness and were suggested based primarily on expert opinion. As a result, more research on the effectiveness of PDMPs best practices is needed.

To be effective, PDMPs must be utilized by their intended users, which include prescribing physicians, nurses, and pharmacists. Currently, utilization of PDMPs is low and highly variable among different states and health care providers.[31, 33-35] Current efforts to improve PDMPs therefore focus on implementing best practices to maximize their utilization. At the 2016 National Prescription Drug Abuse and Heroin Summit, eight best practices were proposed to increase the use of PDMPs that focused on PDMPs utilization.[36] Recently, the National Alliance for Model State Drug Laws (NAMSDL) published a report advocating for these PDMP best practices.[31] Nevertheless, support for these practices only comes from case studies of selected

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states implementing one or more practices. Although its effectiveness is not yet supported by high-quality evidence, prescriber mandated utilization seems to be the most promising best practice.

Prescriber use mandates

Prescriber use mandates are defined as "state laws and regulations that require prescribers to view a patient's PDMP data under certain circumstances."[31] As of January, 2017, 32 states enacted laws requiring prescribers to check PDMPs in specific scenarios.[37]

States differ widely in how they require prescribers to check PDMPs.[38, 39] Some states have comprehensive rules regarding when and how frequently a prescriber should access PDMPs. For example, in Kentucky, prescribers are required to check PDMPs before prescribing some opioids and benzodiazepines for all patients and every three months thereafter. New York, Ohio and Connecticut have similarly comprehensive regulations. In contrast, Tennessee, Oklahoma, and other states do not require PDMP use for all patients and allow for longer follow-up intervals. In Delaware, North Dakota, and Utah the use of PDMPs is dependent upon a prescriber's judgment. Mandatory use of PDMPs has been opposed by prescribers nationwide for a number of reasons. Concerns surrounding technical issues with PDMPs systems have created some opposition to mandatory utilization laws.[40, 41] Many physicians assert that checking PDMPs unnecessarily adds to an already high work load and delays other important duties. Sustained funding for PDMPs is also a concern, as mandatory use may require additional staff to maintain the workflow of mandatory utilization.

Most of the currently available evidence of the effectiveness of mandatory PDMPs consists of analyses from selected states comparing utilization rates and opioid-related outcomes before and after the implementation of prescriber mandatory use regulations.[31, 38] A study by the University

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of Kentucky found that a prescriber use mandate policy sharply increased in prescriber utilization of the Kentucky All Schedule Prescription Electronic Reporting (KASPER) PDMP.[42] Improvements in opioid prescribing behavior, doctor shopping, and patients' health outcomes were also reported. Comparable results were documented for New York and Ohio, states that implemented similar comprehensive prescriber use mandates.[31] Although preliminary studies suggest that prescriber use mandates are effective, the strength of this evidence is limited by a lack of comparison with non-prescriber use mandates states. Only one study compared opioid overdose death rates in mandated states with non-mandated states and found a positive impact.[43] In addition to prescribers, pharmacists are other potential users of PDMPs. As of January 2017, 21 states require pharmacists to enroll in state PDMPs, and 11 states mandate pharmacist use of PDMPs prior to dispensing a controlled substance prescription. Evidence on the effectiveness of pharmacist PDMPs use mandate policies is lacking and more research is required to establish its value.

Other PDMP best practices

In addition to prescriber use mandates, NAMSDL report discusses seven more evidence-based practices that may increase prescriber utilization of PDMPs.[31] As the case with prescriber use mandates, evidence on the effectiveness of these practices is derived from case studies of selected states. The definitions of these best practices are presented in Table 1.2.

Table 1. 2: Evidence based practices to increase prescriber utilization of PDMPs[31]

Best practice	Definition
Delegate access	Allowing staff, such as a nurse, to access the PDMPs database on behalf of a provider
Unsolicited reports	Proactively send reports on prescription opioid utilization to healthcare providers, law enforcement agencies, and regulators to flag suspicious drug use or prescribing behavior

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Data timeliness	Uploading information into the database at set intervals, whether in real time, daily, weekly, or monthly
Streamlined enrollment	Simplifying prescriber enrollment to the PDMPs database
Educational and promotional initiatives	Efforts that promote the use of PDMPs, such as educating prescribers on PDMPs access and use
Health information technology (IT) integration	Combining PDMP data with other clinical data through technologies that are used to store, communicate, and analyze health information, such as electronic health records
Enhanced user interfaces	Implementing user-friendly technologies, such as dashboards and mobile applications that provide PDMPs data in easily understandable formats

Other strategies to curb opioid abuse epidemic

In addition to PDMPs, the report published by the Federal Government discussed three other plans to curb the prescription opioid abuse epidemic.[30] One is to implement educational programs to increase patients' awareness of the danger of abusing prescription opioids. In addition, health care providers should be trained on how to identify and respond to suspicious drug use behavior. Unused and expired prescription opioids are another risk for abusing opioids. Patients often keep unneeded medications at home making them readily available for family members and friends to use. Providing people with proper drug disposal methods is a way to reduce the risk of abuse. The last proposed plan develops enforcement actions against doctor shoppers and improper prescribing behavior.

The current research described in this dissertation evaluates the effectiveness of PDMPs by assessing the impact of mandated prescriber use of PDMPs on emergency department (ED) visits related to prescription opioid poisoning. This was measured by comparing ED visits within states

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before and after mandate implementation and between states with and without requirements for mandatory use. To our knowledge, no previous studies have evaluated the relationship between mandated prescriber PDMPs utilization and ED visits.

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Section 1.2: Conceptual Framework

This research uses Donabedian's structure-process-outcome quality framework to evaluate the effectiveness of PDMPs (Figure 1.2).[44] "Structure" refers to the presence of things associated with a quality initiative such as having a PDMP program and the potential best practices employed within the program. Simply having a PDMP program is unlikely to result in quality if people do not follow the policies and procedures within the program. Therefore, "process" describes the actions taken by program participants like checking the PDMP before prescribing or dispensing. The assumption is that quality occurs when people follow certain processes, although this may not be true when the structure is poorly designed and/or the processes are ineffective. Donabedian's framework argues although structure and process are important for measuring quality, "outcomes" or the end result of care are ideal for assessing the quality of healthcare. Positive health outcomes are desired and therefore will be used to assess the effectiveness of PDMP interventions.

The existence of PDMPs and policies mandating that prescribers use them (i.e., structure) is proposed as an intervention to improve their utilization (i.e., process) among prescribers. It is additionally proposed that this will reduce prescription opioid-related ED visits associated with opioid poisoning (i.e., outcomes). In addition, the economic impact of prescriber use mandates will be assessed.

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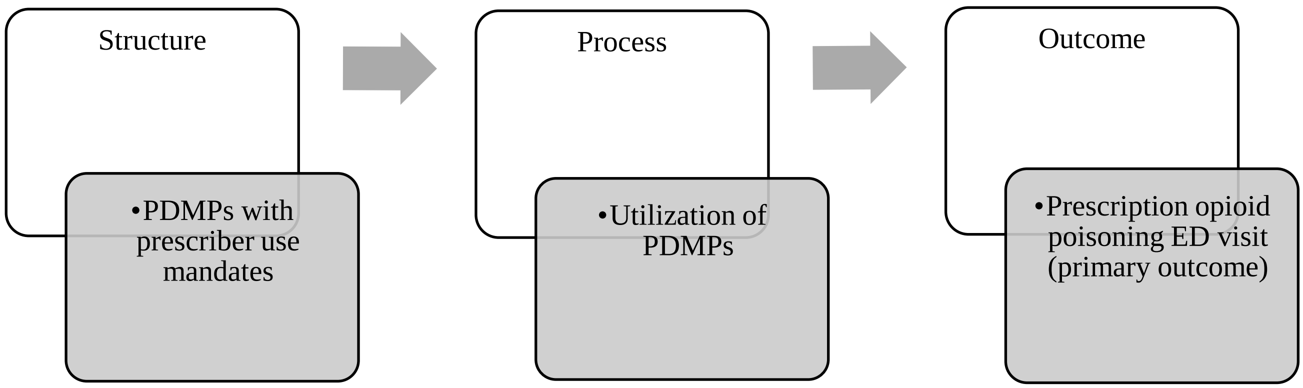

Figure 1. 2: The Donabedian model

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Section 1.3: Rationale

Mandated use of PDMPs by prescribers is a relatively new policy. A number of states have implemented prescriber use mandates, and these mandates contain differing stipulations on the scenarios requiring PDMPs utilization. These mandates have been enacted with the expectation that they will increase the low utilization rate of PDMPs and in turn, reduce inappropriate prescribing and adverse health outcomes associated with prescription opioid abuse. These expectations are supported by limited evidence of the association between prescriber use mandates and increased PDMPs utilization as well as reduced opioid prescribing rates, doctor shopping, and adverse health outcomes.[31, 32, 38]

PDMPs use mandates are opposed by many prescribers around the country and may be associated with unintended consequences on their prescribing behaviors.[40, 41] Thus, adopting prescriber use mandates is not a smooth process for policy makers, and stronger evidence of its effectiveness is needed to promote this policy.

The current literature provides a limited evidence on the impact of prescriber use mandates on prescription opioid abuse- related health outcomes. More rigorous study designs are needed to demonstrate or refute the effectiveness of prescriber use mandates. To our knowledge, none of the evidence has assessed the relationship between PDMPs and prescription opioid poisoning-related ED visits while specifically considering prescriber use mandates.

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Section 1.4: Objectives

The main objective of this research is to examine the impact of PDMP prescriber use mandates policy on ED visits related to prescription opioid poisoning among adults in the United States. The underlying concept of this research is study the relationship between prescriber use mandates and prescription opioid abuse-related health outcomes. The population of interest is ambulatory (out-patient) individuals aged 12 years and older who receive their opioids from prescribers in outpatient settings including physician offices and EDs. Four specific aims fall under the main objective.

Specific aim I:

A. To identify and select states with laws or regulations mandating prescriber use of PDMPs.
B. To identify comparison state(s) without mandatory use policies.

Specific aim II:

Among Kentucky and North Carolina residents:

A. To determine the prevalence of prescription opioid poisoning ED visits.
B. To characterize prescription opioid poisoning ED visits based on socio-demographic and clinical characteristics.
C. To examine associations between patients' sociodemographic and clinical characteristics and prescription opioid poisoning ED visits.

Specific aim III:

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A. To compare occurrences of prescription opioid poisoning ED visits pre and post prescriber use mandates in Kentucky.
B. To compare occurrences of prescription opioid poisoning ED visits in Kentucky and North Carolina, after prescriber use mandate implementation.

Specific aim IV:

A. To estimate the direct medical costs associated with prescription opioid poisoning ED visits in Kentucky and North Carolina.
B. To estimate the economic impact of prescriber use mandates in Kentucky.

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Chapter 2

Literature Review on Prescription Drug Monitoring Programs (PDMPs)

A comprehensive literature review on PDMPs was completed in April 2017. A search of PubMed/MEDLINE (limited to English) and Cumulative Index to Nursing and Allied Health Literature (CINHAL) was conducted, using different combinations of keywords and Medical Subject Headings (MeSH) terms. A predetermined inclusion and exclusion criteria were used to screen for eligible studies. The following inclusion and exclusion criteria were considered in the literature search:

Inclusion criteria:

The literature search considered original studies that:

a. Assessed the impact of PDMPs implementation on outcomes related to prescriber, patient, or health outcomes.
b. Assessed PDMPs utilization among prescribers.
c. Evaluated the impact of prescriber use mandates on opioid prescribing, doctor shopping, or health outcomes.
d. Examined the influence of adopting other PDMPs best practices on PDMPs effectiveness.

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Exclusion criteria:

Studies with one or more of the following criteria were excluded:

a. Conducted outside the United States.
b. Considered veterans or cancer patients as the study population. The current research considers prescription opioid abuse among the general population. Veterans or cancer patients have different characteristics and thus, were excluded.
c. Assessed prescribers' knowledge, opinion, or perception toward PDMPs or PDMPs best practices.
d. Examined PDMPs utilization solely among pharmacists.
e. Descriptive studies: these include studies that utilize PDMPs data to describe patterns of opioid abuse, identify risk factors and risky prescriber and patient behaviors.

Search terms used are summarized in Table 2.1. Titles and abstracts of articles were checked for inclusion and exclusion criteria. The original 885 articles were reduced to 37 after applying inclusion and exclusion criteria and eliminating duplicates. Similar articles to the included studies were also reviewed, yielding 5 studies. A total of 42 studies were included for discussion. The literature search is summarized in Figure 2.1.

Table 2. 1: Search terms history

Search term	**Eligible studies**	
	PubMed	CINHAL
Prescription drug monitoring program	42	35
Prescription drug monitoring program AND emergency room visits	3	5
Prescription drug monitoring program AND (prescriber mandate OR mandatory use OR mandates OR provider mandate)	7	3

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“Analgesics, opioid” [Mesh] AND (prescriber mandate OR mandatory use OR mandates OR provider mandate) AND (monitor OR control OR manage)	2	0
Total unique eligible studies		37

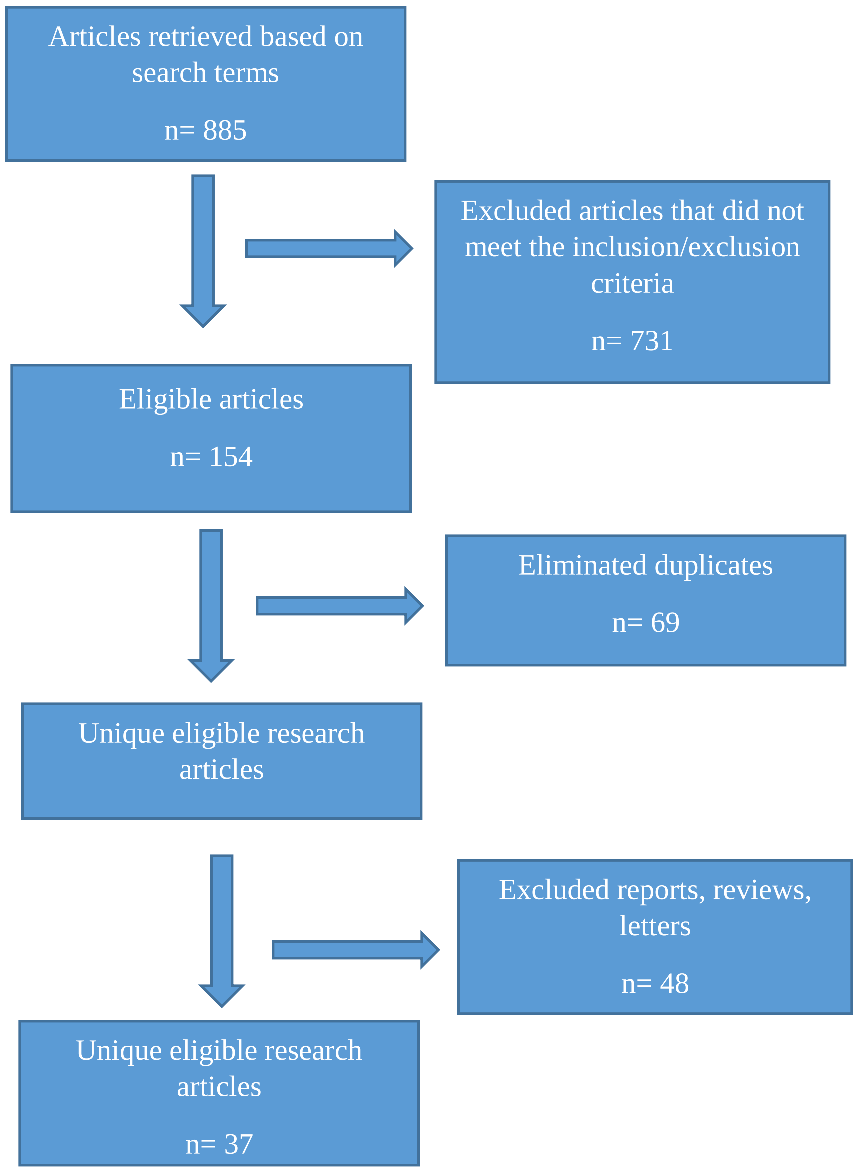

Figure 2. 1: Flow chart summary of literature search

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Overview of the literature

Prescription opioid abuse has reached epidemic levels in the United States. Concurrently, the number of opioid overdose deaths and related emergency room visits has dramatically increased. In response to the epidemic, the federal government released in 2011, the Prescription Drug Abuse Prevention Plan that includes actions in four major areas to combat the epidemic. Increased utilization of prescription drug monitoring programs (PDMPs) was one major area. PDMPs are state run electronic databases that track prescribing and dispensing data and thus, help identify doctor shoppers and improper prescribing behaviors. The effectiveness of PDMPs have been assessed through their impact on doctor shoppers, opioid prescribing behavior, and health outcomes like overdose deaths. The existing literature found mixed evidence on the effectiveness of PDMPs, however, there is a growing body of literature that supports their effectiveness. Studies have shown that PDMPs are effective if utilized. A recent report from the National Alliance for Model State Drug Laws (NAMSDL) indicated that utilization of PDMPs is low and highly variable among the states and healthcare providers within a state.[31] The low and inconsistent utilization of PDMPs makes it difficult to evaluate their effectiveness.

To be effective, PDMPs must be utilized by prescribers, dispensers, and other intended users. Correspondingly, many states implemented laws, regulations, or policies that mandate prescribers and/or dispensers to check the system before issuing a controlled substance prescription. Case studies from Kentucky, New York, and Ohio showed that prescriber use mandates increase PDMPs utilization and are effective in reducing doctor shopping and opioid prescribing.[31] However, higher levels of evidence are needed to approve the effectiveness of this policy.

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The aim of the literature review was to evaluate PDMPs effectiveness with a focus on the impact of prescriber use mandates. The search terms identified studies in three related areas:

a. Studies that assessed prescriber utilization of PDMPs. These studies were considered, because PDMPs utilization is part of their effectiveness.
b. Studies that assessed the impact of PDMPs on patient behavior, prescriber behavior, or health outcomes.
c. Studies that specifically evaluated the impact of prescriber use mandates on patient behavior, prescriber behavior, or health outcomes.

Part 1: Literature review on prescriber utilization of PDMPs

A total of 17 studies have evaluated prescriber utilization of PDMPs in different medical settings. Five studies focused on emergency providers' usage of PDMPs. One study included only primary care physicians, and another study assessed PDMPs utilization among dentists. The remaining ten studies evaluated PDMPs utilization among pharmacists, dentists, and/or physicians in different specialties. Studies are summarized in Table 2.2.

Poon et al. conducted a mixed method study to assess usability of PDMPs among emergency providers (EPs) in Massachusetts.[45] The first part of the study involved quantitative analysis of PDMPs usability compared to three other commonly performed tasks in the ED. Accessing PDMPs took a longer time and required more mouse clicks compared to other tasks. In addition, PDMPs were the most difficult task compared to others (mean = 4.29 on a 1–7 scale). In terms of frequency of use, PDMPs were less frequently utilized compared to two other tasks (mean = 2.41 on a 1–5 scale). The second part of the study involved semi-structured interviews with EPs to identify barriers to use PDMPs. Difficulty in accessing the system, retrieving patient's history, and analyzing patient information were common barriers.

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In a similar study by Young et al., EPs in Florida were surveyed about their utilization of PDMPs.[46] The findings of the study indicated low and infrequent use of the system. Only 3% of providers check PDMPs before issuing a controlled substance prescription; almost half of them check the system only when misuse is suspected. As low as 12% of EPs use PDMPs most of the time. Among frequent users, the chief complaint when using PDMPs is the frequent time out of the system (55%). Common barriers among all other users included frequent need to renew the password (68%) and difficulty in accessing the system (52%).

A third survey was conducted by Fleming et al.[47] The study evaluated emergency physicians' utilization of PDMPs in Texas and included those with PDMP accounts and non-registrants. Among all physicians, 76% were non-PDMP users; among users, 83% utilized PDMP (≤20%) of the time.

The fourth survey of EPs was by Wang et al. who investigated PDMPs utilization among pediatric emergency physicians.[48] The study included physicians from 21 states, assessing their knowledge about the state PDMP and identifying barriers to use the system. Thirty percent of physicians were not aware of their state PDMPs. Among those who registered with the state PDMPs, almost 60% rarely use the system and 35% have never used it. However, these findings may not be nationally representative to pediatric emergency physicians in the United States due to the small sample size (n= 47). In accordance with previous studies, the most common barrier to using PDMPs were difficulty to access the system; insufficient time and forgetting to check the system were also reported as common barriers.

The last survey was conducted by Perrone et al. and assessed PDMPs utilization among medical toxicologists (MTs).[49] The survey utilized a nationally representative sample of MTs (n=205), most of whom practiced emergency medicine for a significant portion of their clinical practice.

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The survey responses indicated variable knowledge and utilization of PDMPs. Most MTs had some knowledge about their state PDMPs, but more than 25% did not access it. Among all surveyed MTs, 50% have used the state PDMPs with 30% of them utilizing it daily. Most respondents complained about the time lag between data entry and retrieving patient information. Also, being unaware of the PDMPs existence and lack of registration to the system prevented MTs from accessing the state PDMPs.

PDMPs utilization was also assessed among primary care physicians. A study by Rutkow et al. included a national representative sample of primary care physicians in the United States.[50] Authors found that approximately one quarter of surveyed physicians were unaware of their state PDMPs. Fifty three percent of all physicians have used PDMPs. Among those with existing knowledge of their state PDMPs, 87% have used the system. However, only 23% check the system when abuse behavior is not suspected. Information on frequency of using PDMPs was not provided in the study. Among barriers to use the system, the lengthy period of the process was the most common.

Dentists are another group of prescribers who significantly contributed to the prescription opioid epidemic. Almost 12% of immediate release opioids are prescribed by dentists.[51] A study by McCauley et al. examined dentists use of PDMPs as an opioid abuse risk mitigation strategy in South Carolina.[52] About 62% have never used the system. Among users, only 12% of dentists check PDMPs before issuing an initial prescription of opioid each time. For refill prescriptions, about 15% of dentists use PDMPs each time; however, more than 36% have never used it. Most dentists were unaware of the PDMPs existence (72%) and one third did not know how to access the system.

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The remaining studies (n =10) involved prescribers with different specialties to evaluate and compare their utilization of PDMPs. Most of the studies (n =7) were conducted in single states, one study compared PDMPs utilization between Connecticut (CT) and Rhode Island(RI), and two studies included national representative samples.

Three studies focused on PDMPs utilization among prescribers in Oregon.[53-55] The first study compared PDMP users (n=619) to non-users (n=439).[53] Most PDMP users were primary care physicians (56.4%), followed by emergency physicians (17.2%). Among non-users, physicians in other specialties constituted the largest group (27.5%), followed by surgical specialties (20.7%). Also, the study identified high and low frequency PDMP users (≥ or < four times in three month periods, respectively). Among high frequency users, 50% use the system ten or more times a month, compared to 10% of low frequency users. Almost all physicians reported checking PDMPs when abuse behavior is suspected and/or early refill is requested. Only one third of respondents use PDMPs whenever a controlled substance is prescribed.

A mixed method study in Oregon assessed PDMP registration, use, and barriers to use among clinicians with different specialties.[54] In 2013, using Oregon's PDMP registry, authors found that 25% of all licensed prescribers had PDMP accounts; 45% of accounts were attributed to medical doctors. Among controlled substance prescribers, 36% were registered with PDMPs. Of these prescribers, 50% of osteopathic physicians and nurse practitioners had active PDMPs accounts, compared to 36% of medical doctors. Among medical doctors, the number of PDMPs queries have been almost doubled from 2012 to 2013. The average number of queries per user have increased from 14 to 16 queries per month. When surveyed about reasons for not registering and barriers using PDMPs, prescribers were divided into three groups: frequent users (> one query per month, n= 358), infrequent users (≤ one query per month + one query to PDMP, n= 261), and

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non-registrants (n= 439). Almost half of non-registrants were not aware that they could register. Among the three groups, time constraints were reported as the most common barriers to using PDMPs, followed by an inability to delegate PDMPs access to other medical staff. A sample of prescribers who were PDMP users was further studied by Leichtling et al.[55] In this study, clinicians were interviewed to identify patterns of PDMP use. Most PDMP users were regular users with 78% accessing PDMPs ten or more times a month. Authors compared patterns of PDMP use among short and long term prescribers. Long term prescribers used PDMPs routinely compared to their counterparts who were less frequent users. However, long term prescribers checked PDMPs more frequently for new patients than existing patients. Conversely, short term prescribers depend more on their clinical judgment and suspected abuse behavior, when deciding to use the system.

A survey by Rittenhouse et al. measured PDMPs utilization among medical doctors, nurse practitioners, and pharmacists in Arkansas.[56] The sample had an equal distribution of the three groups of providers; similarly, PDMPs utilization was evenly distributed among the three groups in terms of frequency of accessing the system. Accessing PDMPs varied from daily use (21.1%) to less than three times a month (26.2%). Most medical doctors and nurse practitioners accessed PDMPs when abuse behavior was suspected (91% and 87%, respectively); less percentage use the system with any involvement of controlled substance prescription (36% and 45%, respectively).

A similar survey in Maryland evaluated PDMPs registration and use among primary care, pain, and emergency providers (EPs).[57] The sample included three groups of providers: registered users (46%), registered non-users (28%), and non-registrants (26%). PDMP users included prescribers with at least one PDMPs access in the 18 month period preceding the survey. Among

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non-registrants, about one third were not aware of the state PDMPs or lacked knowledge of how to register. Among registered non-users and non-registrants with PDMPs access, 69% and 49% respectively, have ever used the system in their practice. More than 70% of prescribers (including registered users, non-users, and non-registrants) found the system easy to access. In a multivariable regression model, physicians who wrote opioid prescriptions for more than 50 patients accessed the PDMPs three times as often as those prescribing opioids for less than ten patients monthly (IRR = 3.00, 95% CI = (1.07–8.43)). Common barriers to using PDMPs for registered physicians were: multiple IDs for same the patient, system slowness, and missing data. No data on frequency of use or drivers to use PDMPs were reported in the study.

An older study in Ohio (2011) revealed a significant difference in PDMPs awareness and utilization among physicians with different specialties.[58] The study found that 84% of all survey respondents were aware of the Ohio PDMPs; however, only 59% used it. Among all specialties, pediatric physicians were least aware of the PDMPs (67%). Emergency medicine had the highest proportion of utilization compared to pediatric physicians (p-value ≤ 0.001). The study did not report figures on frequency of utilization. Almost all physicians (91%) reported concerns about drug abuse that drive accessing the system; no significant difference, in reasons to use PDMPs, between different specialties were noted.

Another survey in Ohio compared PDMPs utilization among attending and resident physicians (n=25 and 70, respectively).[59] The study found that almost all attending physicians (96%) and most resident physicians (81%) were aware of the system. However, about one third of attending physicians and half of the resident physicians do not utilize PDMPs. Most PDMP users utilized the system to address concerns about prescription drug abuse. Unlike most previous studies, the current study did not assess frequency of PDMP use among different specialties.

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Green et al. conducted a survey among prescribers in CT and RI.[60] The study found significant differences in PDMPs utilization among prescribers in the two states (44% and 16.3% have ever used the system, respectively, p-value = <0.0001). Prescribers in CT used the PDMPs more frequently compared to those in RI (p-value <0.0001). Almost 35% of CT prescribers accessed the PDMPs weekly or more often, compared to 3.3% in RI. More than two thirds of prescribers in both states did not use PDMPs, because they were not aware of their existence (68% in CT, 84% in RI). The second reported barrier to using PDMPs in CT and RI was a lack of knowledge of how to use the system and lack of internet access, respectively.

The last two studies assessed PDMP utilization among nationally representative samples of prescribers.[61, 62] The first study was carried by Fleming et al.[61] The study involved PDMP administrators from 15 states to evaluate prescribers, pharmacists, and law enforcement personnel utilization of PDMPs. Authors found that prescribers had the highest rate of requests per population of 100,000, followed by pharmacists and law enforcement personnel. Also, it was found that availability of online access and fast turnover of PDMP requests increased utilization. The study did not evaluate frequency of PDMP use among prescribers with different specialties or assessed barriers to use.

Hildebran et al. conducted a qualitative study including 35 prescribers from nine states.[62] Prescribers with different specialties were interviewed to identify patterns of PDMP use. Most clinicians reported checking PDMPs for clinical purposes, others use it for administrative requirements. Examples of clinical use included verifying prescription history and coordinating with other prescribers when suspected prescribing behavior is noted. Consistency for using PDMPs were varied among specialties. Long term prescribers checked PDMPs more consistently for their patients compared to emergency providers. Barriers to using PDMPs were also

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identified; patient satisfaction rating was one important barrier. Some organizations evaluated prescribers based on patient satisfaction; utilizing PDMPs may delay treatment sessions or forbid an opioid prescription, adversely affecting patient satisfaction. Also, lack of training on how to access PDMPs was another reported barrier.

Summary of part I literature review:

Studies of PDMPs utilization revealed low and inconsistent use of the system among prescribers in different states. The literature also documented variation in PDMP use among prescribers with different specialties. Most of the encountered surveys had a low response rate (≤50%) and small sample size. Thus, findings of the studies may not be generalized to the whole population of prescribers. PDMP utilization was assessed in terms of frequency of accessing the system and reasons that drive access of the system. Studies used different terms to describe PDMP users. Some studies considered prescribers who used the system at least one time in the past as PDMP users. Other studies classified prescribers as frequent or infrequent users based on their frequency of checking the system in a defined period of time. Many studies agreed that most prescribers check the system when abuse behavior is suspected; fewer prescribers use PDMP with every controlled substance prescription. Studies also shared common barriers for using PDMPs including difficulty in accessing the system, lack of knowledge of the system's existence, and time constraints. The low and inconsistent utilization among prescribers may adversely affect PDMP effectiveness. PDMPs must be utilized sufficiently to have a powerful impact on the prescription opioid abuse epidemic.

The second part of the literature review evaluates the effectiveness of PDMPs through assessing their impact on prescription opioid abuse risk measures, opioid prescribing, and health outcomes related to prescription opioid abuse.

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Table 2. 2: Summary of included studies (prescriber utilization of PDMPs)

Author	Study design and sample	Sample size	Outcome measure of interest	Period	Setting and data source	Related findings
Poon et al[45] 2016	- Mixed method study - Emergency physicians (EPs)	17	- Time and number of mouse clicks required to complete the PDMP task compared to three commonly performed tasks in the ED - Ease of use	5 months	One large urban academic medical center in MA	- PDMPs require more time and greater number of mouse clicks - PDMPs are more difficult to use compared to other tasks
Young et al[46] 2017	-Web based survey -EPs	88	- Utilization of PDMP	5 weeks	Florida	- Most EPs (99%) are aware of PDMPs, 21% rarely use it - Only 3% use it with every CS prescription
Fleming et al[47] 2014	- Survey - EPs	76	- PDMP utilization	_	Emergency medicine conference in Texas	-76% do not use PDMPs as a screening tool - Most users (83%) utilize PDMPs ≤ 20% of the time
Wang et al[48] 2016	- Web based Survey - Pediatric EPs	47	- PDMP utilization	_	21 states	- 60% rarely use the system - 35% have never used it
Perrone et al[49] 2012	-Web based survey - Medical toxicologists (MTs)	205	- PDMP utilization	2 months	35 states	- More than 25% do not access PDMPs - 50% have ever used PDMPs - only 30% access it daily
Rutkow et al[50] 2015	- Mail survey - Primary care physicians	420	- PDMP utilization	18 weeks	51 states	- 53% of all physicians have used PDMPs -77% check the system only when abuse behavior is suspected
McCauley et al[52] 2015	-Web based survey - Dentists	86	-PDMP utilization	_	South-Carolina	- 38% have ever used PDMPs

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						- 27% use PDMPs all the times for initial and refill opioid prescriptions
Irvine et al[53] 2014	-Mail survey - Clinicians with DEA license	1,058 (PDMP users and non-users)	-PDMP utilization	_	-Oregon -PDMP registry	- 95% access PDMPs when abuse or diversion is suspected - Less than 50% check it for every new patient or every time they prescribe a CS
Deyo et al[54] 2014	- Mixed method study - Clinicians with DEA	- 612 PDMP frequent users - 503 infrequent users - 1,789 non-registrants	- PDMPs registration and use	_	-Oregon -PDMP registry	- 25% of all licensed prescribers had PDMPs accounts - 36% of CS prescribers were registered with PDMPs - Among medical doctors, number of PDMPs queries have almost doubled in 2013
Leichtling et al[55] 2017	- Qualitative telephone interviews -Clinicians registered with Oregon PDMP	33	- Pattern of PDMP use	_	Oregon	- Most of PDMP users were regular users - Long term prescribers used PDMPs routinely compared to short term prescribers - Short term prescribers depend more on their clinical judgment and suspected abuse behavior, as a driver to use PDMPs
Rittenhouse et al[56] 2015	-Web based survey - Medical doctors, nurse practitioners, and pharmacists	1541	-PDMPs utilization	30 days	Healthcare practices in all 75 Arkansas counties	- PDMPs access varied from daily access (21.1%) to < 3 times a month (26.2%) - Most medical doctors and nurse practitioners accessed PDMPs when abuse behavior is suspected
Lin et al[57] 2016	-Mail survey - Primary care, pain, and EPs	405 (105 non-registrants, 114 registered non-users, 186 registered users)	-PDMP registration and use	4 months	- Maryland - Maryland (DHMH)	- 85% of all prescribers with PDMPs access have ever used the system in their practice - Physicians who wrote opioid prescriptions for more than 50 patients accessed the PDMPs three times as often as those prescribing opioids for less than 10 patients monthly (IRR = 3.00, 95 % CI = 1.07–8.43)

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Feldman et al[58] 2011	- Survey - Physicians with different specialties	95	-Awareness and utilization of state PDMPs	3 months	One academic medical center in Ohio	-84% of all survey respondents were aware of Ohio PDMPs, 59% used PDMPs - Emergency medicine had the highest proportion of utilization compared to pediatric physicians (p-value ≤0.001)
Feldman et al[59] 2012	- Survey -Attending and resident physicians	- 70 resident physicians and 25 attending physicians	-Utilization of state PDMPs and reasons for accessing the system	3 months	One academic medical center in Ohio	- One third of attending physicians and half of resident physicians do not utilize PDMPs - Most of PDMP users utilized the system to address concerns about prescription drug abuse
Green et al[60] 2012	-Web based and mail survey - All providers licensed to prescribe scheduled medications with an email address	1,385 prescribers (998 in CT and 375 in RI)	-PDMPs utilization	6 months	CT and RI	- Prescribers in CT used PDMPs more frequently compared to those in RI (p-value <0.0001) -More than 60% of prescribers in both states did not use PDMPs because they were not aware of its existence
Fleming et al[61] 2013	-Web based survey - Operational PDMPs Administrators	15	-PDMP utilization	3 months	15 states	-Prescribers had the highest rate of requests per 100,000 population -Availability of online access and fast turnover of PDMPs requests increase utilization
Hildebran et al[62] 2014	-Qualitative study (online focus groups and telephone interviews) - Prescribers	35	-Pattern of PDMP use	_	9 states	- Most clinicians reported checking PDMPs for clinical purposes, followed by administrative requirements - Long term prescribers checked PDMPs more consistently for their patients compared to emergency providers

CS: controlled substance.
DEA: drug enforcement agency.
DHMH: Department of Health and Mental Hygiene.

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Part II: Literature review on PDMP effectiveness

This part of the literature review is divided into three parts. The first part discusses studies that evaluate PDMPs impact on prescription opioid abuse risk measures. The second part reviews studies on the impact of PDMPS on opioid prescribing. The last part discusses studies assessing the impact of PDMPS on health outcomes related to prescription opioid abuse.

PDMP impact on prescription opioid abuse risk measures:

A total of seven studies assessed the impact of PDMPs on a variety of prescription opioid abuse risk measures.[62-69] The studies compared changes in abuse risk measures by analyzing longitudinal data or evaluating changes in measures before and after implementing PDMPs. One of the encountered studies was a randomized clinical trial in a managed care organization. The remaining studies had a quasi-experimental study design with a control group. Four studies assessed differences in abuse risk measures between PDMPs and non-PDMPs states. Three studies examined changes in single states. Following is a review for studies that evaluated PDMPs effectiveness, arranged in a sequential manner based on date of data collection. Studies are summarized in Table 2.3.

Reisman et al.[63] conducted an ecological study examining the impact of PDMPs on opioid shipment and inpatient admission rate over the period of 1997 – 2003. The study compared changes in the two outcome measures between PDMPs (13 states) and non-PDMPs states (36 states). Both groups demonstrated increase in opioid shipment (except for codeine). However, a significant reduction in the rise of oxycodone shipment was noted in PDMPs states compared to non-PDMPs states (p-value= 0.019). Also, increase in rate of opioid inpatient admissions was

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lower in PDMPs states compared to non-PDMPs states, however, no information on the significance of this result was reported.

A study by Brady et al.[64] assessed the impact of state PDMPs on per capita dispensing of opioids. To account for variation in opioid potency, the amount of each drug dispensed was converted into Morphine Milligram Equivalents (MME). Authors examined the overall effect of PDMPs on per capita dispensing of opioid as well as state specific impact of PDMPs, using state quarter as the unit of analysis. The amount of MME dispensed increased significantly over the study period. However, no significant difference in MME dispensed per capita was found between state quarters with and without PDMPs (p-value = 0.68). State specific impact of PDMPs showed a great variation. Nine states had significant reduction in MME dispensed per capita between state quarters with and without PDMPs. No significant difference was found in 14 states. Eight states had significant increase in MME dispensed. Also, results were not significant when PDMPs characteristics were considered. Type of PDMPs operating agency, having statutory requirements for committee oversight of the PDMPs, and having laws that explicitly do not require prescribers to check the system were not significantly associated with changes in MME dispensed per capita. Differences in other PDMPs characteristics adopted by different states may explain variation in states' specific impact of PDMPs.

Reifler et al.[65] (2003 – 2009)

Reifler et al. evaluated PDMPs effectiveness by examining their impact on opioid intentional exposures and opioid treatment admission rate in PDMPs and non-PDMPs states. The study utilized data from poison centers and opioid treatment databases which report both measures on a quarterly basis. Over the period of 2003 – 2009, opioid intentional exposures and opioid treatment admissions showed an increasing trend over time for PDMPs and non-PDMPs states.

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However, quarterly increase in intentional exposures in PDMPs states was significantly less than non- PDMPs states (0.2% vs 1.9%, respectively, p-value = 0.036). Opioid treatment admissions increased per quarter by 2.6% in PDMPs states compared to 4.9% in non-PDMPs states (p-value 0.058). Also, PDMPs characteristics were considered in additional analyses. PDMPs that have been active for long time, provide data directly to health care providers, and cover controlled substance at least through schedule IV were considered as superior PDMPs. Increase in opioid treatment admissions were significantly less in superior PDMPs states compared to others (p-value= 0.027); however, no significant difference was found for opioid intentional exposure rate (p-value = 0.086).

Gonzalez et al.[66] (2009 – 2010)

A randomized clinical trial by Gonzalez et al. examined the impact of a managed care PDMPs on prescription opioid abuse measures. Patients with at least three prescribers and three dispensed prescriptions in a three month period were identified. Prescribers in both groups received letters indicating an increasing trend of prescription opioid use. Prescribers in the intervention group received an additional medical report (intervention) providing data for each controlled substance dispensed during the three month period. Three outcome measures were assessed: change in number of opioid prescribers, number of pharmacies, and number of opioid prescriptions filled. The outcome measures were compared between the first month and 12 month following the intervention. A greater reduction in number of prescribers, number of pharmacies, and number of prescriptions filled was noted in the intervention group compared to the control group. The study did not report information on the significance of the observed difference.

Young et al.[67] (2010 – 2011)

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Young et al. conducted a study to assess the impact of PDMPs proactive reports on a number of patient opioid abuse risk measures. In January 2010, Massachusetts PDMPs started to send proactive reports to prescribers whose patients met the multiple prescriber episode criteria (utilizing four or more prescribers and four or more pharmacies in a six month period). However, not all prescribers were notified due to system limitations. The current study utilized a controlled pre – post study design. The intervention group included patients whose prescribers were sent proactive reports. The control group was represented by patients who met the multiple prescriber episode criteria, without informing their prescribers. Participants in the control group were matched on demographics and baseline prescription history using propensity score matching. The two groups were assessed for differences in abuse risk measures in the baseline period (before January 2010); no significant differences were found. However, following proactive reports, significant reductions in abuse risk measures were reported for the intervention group relative to the control group. The intervention group had significant reduction in number of schedule II opioid prescriptions ($P < 0.01$), number of prescribers visited ($P < 0.01$), number of pharmacies used ($P < 0.01$), dosage units ($P < 0.01$), total days' supply ($P < 0.01$), total MME ($P < 0.01$), and average daily MME ($P < 0.05$) compared to the control group.

Surratt et al.[68] (2009 – 2012)

A study in Florida examined changes in prescription opioid diversion rate following a comprehensive legislation to regulate pain clinic and PDMPs implementation in Florida. Change in diversion rate per 100,000 population was assessed on a quarterly basis over a three year period (2009 – 2012). A significant reduction in rate of diverted cases was noted for oxycodone, methadone, and morphine (p-value: 0.03, 0.001 and 0.05, respectively) following the implementation of the policies. Diversion rate for other opioids either remained stable over the

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study period or did not significantly change. The study did not isolate the impact of pain clinic laws (effective in late 2010) from Florida PDMPs (effective in late 2011). Thus, the observed change in diversion rates cannot be attributed to Florida PDMPs only.

Ali et al.[69] (2004 – 2014)

A study by Ali et al. assessed PDMPs impact on non-medical use of prescription opioids (NMPO), utilizing the National Survey of Drug Use and Health data (2004 – 2014). The study evaluated the impact of PDMPs existence alone or with prescribers' mandatory enrollment/access policy on four outcomes related to NMPO. States with operational PDMPs and states with an additional requirement of prescribers' enrollment/access did not significantly differ from other states in: past year NMPO use, past year prescription opioid dependence, and past year initiation of NMPO. However, states with PDMPs only or with additional prescriber enrollment/access requirements had significantly fewer days of NMPO compared to other states (p-value <0.05 and <0.01, respectively). Also, states with operational PDMPs were associated with 56% reduction in doctor shopping ($\geq$ two prescribers) compared to non-PDMPs states (p-value ≤ 0.05). Further reduction in doctor shopping (80%) was noted in states with additional requirement of prescriber use mandates (p-value ≤ 0.05).

Summary of PDMP impact on prescription opioid abuse risk measures:

The literature on PDMPs effectiveness on a variety of prescription opioid abuse risk measures is inconsistent. Four studies found that having operational PDMPs significantly reduced oxycodone shipment, prescription opioid intentional exposures, days of prescription opioid supply, and doctor shopping.[63-65, 69] However, PDMPs did not positively impact other abuse risk measures including per capita dispensing of opioid, treatment admission rate, and last year non-medical

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use of prescription opioids. Three studies were conducted in single states and reported positive impact of PDMPs on prescription opioid abuse risk measures.[66-68]

The inconsistency in the reported findings can be related to differences in PDMPs characteristics adopted by different states. Also, the presence of other policies implemented at similar times to PDMPs can impact the assessment of PDMPs effectiveness. State level unmeasured confounders is another contributing factor that should be considered when evaluating differences in outcome measures among the states.

Table 2. 3: Summary of included studies (PDMP impact on prescription opioid abuse risk measures)

Author	Study design and sample	Sample size	Unit of analysis	Outcome measure of interest	Period	Setting and data source	Related findings
Reisman et al[63] 2009	- Ecologic cohort study - PDMPs and non-PDMPs states	- 14 PDMP states - 36 non-PDMPs states	-State	- Rate of prescription opioid shipments - Rate of inpatient admissions for prescription opioid abuse	1997–2003	-ARCOS - TEDS	- PDMPs and non-PDMPs states demonstrated increase in opioid shipment (except for codeine) - A significant reduction in the rise of oxycodone shipment was noted in PDMPs states compared to non-PDMPs states (p-value= 0.019) - Increase in rate of opioid inpatient admissions was lower in PDMPs states compared to non-PDMPs states (no p-value)
Brady et al[64] 2014	-Ecologic cohort study - PDMPs and non-PDMPs states	- 2,040 state quarters (619 state quarters with active PDMPs)	-State quarter	- Per capita dispensing of opioid (MME)	1999 - 2008	-ARCOS	- No significant difference in MME dispensed per capita was found between state quarters with and without PDMPs (p-value = 0.68) - State specific impact of PDMPs showed a great variation
Reifler et al[65] 2012	-Ecologic cohort study	_	-State quarter	- Opioid intentional exposures and opioid	2003-2009	RADARS	- Opioid intentional exposures and opioid treatment admissions showed an

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	-PDMPs and non-PDMPs states			treatment admission rate			increasing trend over time for PDMPs and non-PDMPs states - Quarterly increase in intentional exposures in PDMPs states was significantly less than non- PDMPs states (0.2% vs 1.9%, respectively, p-value = 0.036) - Opioid treatment admissions increased per quarter by 2.6% in PDMPs states compared to 4.9% in non-PDMPs states (p-value 0.058)
Gonzalez et al[66] 2012	Randomized clinical trial - Patients who received opioid prescriptions from three or more prescribers at three or more pharmacies in a three month identifica-tion period	Intervention group (242 patient) -Control group (220 patient)	Patient	Change in: - Number of opioid prescribers - Number of pharmacies - Number of opioid prescriptions filled	2009 - 2010	-A managed care organiza-tion in New York	- A greater reduction in number of prescribers, number of pharmacies, and number of prescriptions filled was noted in the intervention group compared to the control group (no p-value)
Young et al[67] 2017	-Controlled pre-post - Patients who received schedule II prescriptions (with at least one opioid) from four or more prescribers at four or more pharmacies in a six-month identifica-tion period	Intervention group (84 patient) - Control group (504)	Patient	- Seven opioid abuse risk measures	2010 - 2011	MA	- Compared to the control group, the intervention group had significant reduction in: - Number of schedule II opioid prescriptions ($P < 0.01$) - Number of prescribers visited ($P < 0.01$) -Number of pharmacies used ($P < 0.01$) - Dosage units ($P < 0.01$) -Total days' supply ($P < 0.01$) -Total MME ($P < 0.01$) -Average daily MME ($P < 0.05$)

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Surratt et al[68] 2014	Longitudinal ecologic study	- 219	- Year quarter	- Quarterly change in prescription opioid diversion rate per 100,000 population	2009 - 2012	- Florida -RADARS	- Significant reduction in rate of diverted cases was noted for oxycodone, methadone and morphine (p-value: 0.03, 0.001 and 0.05, respectively - Diversion rate for other opioids either remained stable over the study period or did not significantly change
Ali et al[69] 2017	Longitudinal ecologic study - Civilian population (12≥ years old)	- 507,000	-State	- Four outcome measures related to NMPO	2004 - 2014	NSDUH	- Significant association between PDMPs implementation and reduction in 'doctor shopping' behavior - No significant associations between PDMPs implementation on nonmedical use/initiation/dependence of opioids

ARCOS: Automation of Reports and Consolidated Orders System.
TEDS: Treatment Episode Data Set.
RADARS: Researched Abuse, Diversion and Addiction-Related Surveillance.
MME: Morphine Milligram Equivalents.
NSDUH: National Survey on Drug Use and Health.
NMPO: Non-Medical use of Prescription Opioid.

PDMPS impact on opioid prescribing:

PDMPS impact on opioid prescribing was assessed in eight studies.[70 - 77] Five were conducted in single states; the remaining studies compared opioid prescribing in PDMP and non-PDMP states. Three studies examined changes in opioid prescribing among emergency providers (EPs), while others were more general and included prescribers from other ambulatory care settings. Studies are summarized in Table 2.4.

Three studies evaluated changes in opioid prescribing in Florida. The first study by Rutkow et al. assessed the impact of pain clinic laws and PDMPS on opioid prescribing and use.[70] The study followed a comparative interrupted times series design over the period 2010 to 2012; Georgia was selected as the comparator state. Four outcome measures were evaluated: total opioid

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volume, average MME per transaction, number of days supplied, and total number of opioid prescriptions. Authors found modest, but a statistically significant reduction in monthly opioid volume and mean MME per transaction in Florida compared to Georgia (p-value <0.05 for both measures). No significant difference was found in monthly number of days supplied and total number of opioid prescriptions dispensed. The impact of policies was further examined among groups of prescribers and patient stratified based on volume of opioid prescribing and use. Significant reduction in total opioid volume and average MME per prescription was limited for prescribers and patients with the highest baseline opioid prescribing and use. The study examined the impact of pain clinic laws and PDMPS jointly and findings supported the effectiveness of the policies. Nevertheless, the magnitude of the impact was modest and the statistical significance could be related to the large sample size. Further evidence is needed to support the effectiveness of PDMPs. Findings of the current study were further analyzed in another study by Chang et al.[71]

The new study examined impact of PDMPs implementation and pain clinic laws on high risk prescribers.[71] The latter was defined as prescribers in the top fifth percentile of opioid volume during four consecutive calendar quarters in the pre-intervention period. The current study compared seven prescriber related outcomes in Florida and Georgia using a comparative interrupted times series analysis. The impact of policies was assessed by comparing differences in level and monthly trend of the outcomes. Among high risk prescribers, the policies had no significant impact on the level of any of the outcomes. A slight, but statistically significant increase in monthly trend of average days' supply was reported (p-value<0.05). In contrast, significant reduction in the monthly trend of the number of patients receiving opioids, MME per transaction, total opioid volume, and number of filled opioid prescriptions was found (p-value

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<0.05 and <0.01). Despite this significant impact, opioid prescribing remained highly concentrated among high risk prescribers after implementation of the policies. In other words, high risk prescribers continued to account for the high proportion of opioid volume and opioid prescriptions in the post as the pre-implementation period. The impact of policies on the seven outcomes were also examined among low risk prescribers and no significant change in level or trend of the outcomes was documented.

The third study in Florida was conducted among emergency providers (EPs).[72] The study utilized a pre – post study design with a historical control group. Prescribers in the intervention group were notified of their patients' prescription history using reports from Florida PDMPs. The average number of controlled substance prescribed per patient was compared between patients in the intervention group (in February 2014) and the historical control group (in December 2013). Results from the Poisson regression model indicated non-significant difference in average number of controlled substance prescribed per patient between the two groups. Thus, authors concluded that Florida PDMPs did not influence EPs prescribing of controlled substances. However, there are clear limitations that could affect findings of the study. Authors did not use propensity score matching or other statistical methods when selecting the historical control group and thus, comparison between the two groups might not be acceptable. Also, in the Poisson regression model, only age, sex and chief complaint were included as confounders, while other possible confounders were left uncontrolled. The study also investigated PDMPs utilization among twenty five prescribers in the ED; one third were registered to use PDMPs and more than two thirds rarely or never accessed the system.

Further assessment of the impact of PDMPs on opioid prescribing in emergency care settings was conducted in Ohio.[73] EPs were surveyed about their likelihood to prescribe opioid analgesics

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for patients presented with non-acute injury. PDMPs data were presented to EPs and prescribers' likelihood to prescribe opioid was re-assessed after reviewing patients' prescription fill history. Among all providers, opioid prescribing decisions were altered for 41% of patients; 61% resulted in fewer or no opioids prescribed. The study indicated positive impact of PDMPs on opioid prescribing in the ED; however, two thirds of patients were treated by only four providers. Thus, findings may not be representative to the general population of EPs.

In North Carolina, Ringwalt et al. examined the relationship between prescribers' utilization of PDMPs and opioid prescribing, utilizing PDMPs data for the period between 2009 – 2011.[74] Over the study period, an increasing trend in the number of providers with PDMPs queries and days of access was found. However, the trend of opioid prescriptions and patients filling opioid prescriptions remained stable. Linear regression models found that increasing prescriber utilization of PDMPs was not associated with significant reduction in the proportion of patients or opioid prescriptions filled.

The remaining three studies included prescribers from multiple states and compared differences in opioid prescribers after PDMP implementation or use.[75 - 77]

A survey by Pomerleau et al. assessed the impact of PDMPs utilization on opioid prescribing among EPs.[75] The survey included 443 EPs from seven emergency centers across the United States. About 60% of EPs were registered in the state PDMPs and 50% use it less than once per shift. The relationship between PDMPs and opioid prescribing was tested in four case scenarios. Decisions to prescribe opioid in each scenario were compared between PDMP users and non-users using Chi-square test. No significant association was found between the two groups. Authors concluded that PDMPs have no impact on opioid prescribing among EPs, which is contrary to previous studies. To assess the impact of PDMPs on an outcome, regression analysis

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should be used controlling for possible confounders. Using only Chi-square test does not reflect the actual impact of PDMPs on opioid prescribing and this may explain the non-significant findings of the current study.

Another study by Bao et al. evaluated PDMPs impact on opioid prescribing in ambulatory care settings during the period between 2001 – 2010.[76] Visits after PDMP implementation were compared to visits in states without PDMPs. The overall effect of PDMPs on the rate of opioid prescribing was examined, as well as, the effect of time since implementation. A 30% reduction in schedule II opioid prescribing was found after PDMPs implementation (p-value<0.001). However, the reduction in the prescribing of any opioid was not significant. The impact of PDMPs on schedule II opioid prescribing showed significant results considering time since PDMP implementation. Furthermore, the reduction in rate of schedule II opioid prescribing remained significant up to two years after implementation. However, decline in rate of other opioid prescribing was not significant after six months of implementation.

The last study examined changes in opioid prescribing among Medicare population with part D coverage.[77] The study utilized difference in difference modeling to compare opioid prescribing pre and post PDMP implementation in states with and without PDMPs. Two independent variables were included in the models: presence of PDMPs with online access and presence of a statute that explicitly does not require PDMPs access. The main outcome measure was percent change in days of opioid supply. Presence of PDMPs with online access was associated with a significant, but limited decrease in days' supply for all opioids, oxycodone only, and hydrocodone only (p-value <0.01). A significant increase in days' supply for schedule IV was also found (p-value <0.05). States where a statute did not explicitly require PDMP access were associated with significant increase in days' supply for all opioids, hydrocodone only, oxycodone

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only, and schedule IV opioids. Findings of the current study were significant, but limited in magnitude. The reported significance may also be related to the large sample size and not due to the actual impact of PDMP.

Summary of PDMP impact on prescribing:

Studies show inconsistent evidence on the impact of PDMPs on opioid prescribing. Studies in Florida did not isolate the impact of PDMPs from pain clinic laws, so any observed effect cannot be attributed to PDMPs implementation only. In addition, the positive impact of PDMPs reported in few studies are either not generalizable, could not be validated, or statistically but not clinically significant. More evidence is needed to support PDMPs effectiveness. In general, there is an increasing trend of opioid prescribing in PDMP and non-PDMP states. This suggests that PDMPs should not be the only policy to combat the prescription opioid abuse epidemic.

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Table 2. 4: Summary of included studies (PDMPs impact on prescribing)

Author	Study design and sample	Sample size	Unit of analysis	Outcome measure of interest	Period	Setting and data source	Related findings
Rutkow et al[70] 2015	- Comparative interrupted times series - Patients	2.6 million	-Patient	- Four outcomes measures related to opioid prescribing	2010 - 2012	- Florida (intervention state), Georgia (control state) - IMS Health's LRx Lifelink database	- Modest, but, statistically significant reduction in monthly opioid volume and mean MME per transaction in Florida compared to Georgia (p-value <0.05 for both measures) - No significant difference in monthly number of days supplied and total number of opioid prescriptions dispensed
Chang et al[71] 2016	- Comparative interrupted times series - Prescribers	For Florida: - High risk prescribers (1526) - Low risk prescribers (36,939)	Prescriber	- Seven prescriber related outcomes	2010 - 2012	- Florida (intervention state), Georgia (control state) - IMS Health's LRx Lifelink database	- Significant reduction in the monthly trend of: (- Number of patients receiving opioids - MME per transaction -Total opioid volume, and - Number of filled opioid prescriptions) in Florida compared to Georgia - A slight, but significant increase in monthly trend of average days' supply (p-value <0.05) - No significant differences among low risk prescribers
McAllister et al[72] 2015	- Pre – post design - Patients (≥18 years old) treated at ED	Interventio n group (356 patient) - Historical control group (354 patient)	Patient	- Change in average number of CS prescribed per ED visit	2013 and 2014	- ED of a tertiary care, urban university teaching hospital in Florida	- No significant difference in average number of controlled substance prescribed per patients between the two groups

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Baehren et al[73] 2010	- Pre – post design (using survey as data collection method) -Patients presented at the ED with painful conditions	- 179 patient - 18 provider	Prescriber	- Change in opioid analgesics prescribing for patients presented with non-acute injury	June - July 2008	Ohio	- Opioid prescribing decisions were altered in 41% of patients - 61% resulted in fewer or no opioids prescribed
Ringwalt et al[74] 2015	Longitudinal ecologic study	_	Per six months/per 1000 persons	-PDMPs utilization and its impact on: - Rate of patients filling opioid prescription - Rate of opioid prescriptions filled	2009 - 2011	NC	- Increasing trend in number of providers with PDMPs queries and days of access - However, no significant reduction in proportion of patients filling opioid prescriptions or opioid prescriptions filled
Pomerleau et al[75] 2017	-Web based survey - EPs	443	_	- PDMPs registration and use - Opioid prescribing	August – October 2014	- Seven emergency centers across the United States	- 60% of EPs were registered in state PDMPs - 50% use it less than once a shift - PDMPs utilization did not significantly impact opioid prescribing
Bao et al[76] 2016	- Pre – post design - Patients (≥ 18 years old) presented to an office based visit with pain	26,275 ambulatory care office visits	Visit	- Having at least one Schedule II opioid analgesic (dichotomous) - Having at least one opioid of any kind prescribed or continued at a pain-related ambulatory care visit (dichotomous)	2001 – 2010	- 24 states with online access PDMPs - NAMCS	a. Impact of PDMP existence: - 30% reduction in schedule II opioid prescribing following PDMPs implementation (p-value<0.001) - Non significant reduction in the prescribing of any opioid b. Impact of PDMP considering time since implementation:

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							- Significant reduction in schedule II prescribing up to two years following implementation - Significant reduction in the prescribing of any opioid for the first six months following implementation
Yarbough CR[77] 2017	-Controlled before and after - Medicare population with part D coverage	451,583 physician year observatio-ns	-Physician	-Percent change in days of opioid supply	2010 – 2013	-ProPublica - CMS	- States with online access PDMPs had significant reduction in days' supply for all opioids (p-value <0.01) - However, a significant increase in days' supply for schedule IV was found (p-value <0.05)

IMS Health's LRx Lifelink database: an individual level claims database that represents 65% of retail prescription transactions in the United States.
MME: Morphine Milligram Equivalents.
CS: controlled substance.
EPs: emergency providers.
NAMCS: National Ambulatory Medical Care Survey.
ProPublica: a non-profit news organization.
CMS: Centers for Medicare and Medicaid Services.

PDMPs impact on prescription opioid related-health outcomes:

The existing literature examined PDMPs impact on prescription opioid related overdose deaths and emergency room visits. Five studies assessed the impact of PDMPs on overdose deaths,[78 - 82] and one evaluated the impact on ED visits.[83] The reviewed studies assessed PDMPs effectiveness by comparing the rate of overdose deaths or ED visits in PDMPs and non-PDMPs states over a period of time. One study was conducted in Florida and evaluated changes in overdose deaths following PDMPs implementation. Studies are summarized in Table 2.5.

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An early study by Paulozzi et al. examined PDMPs impact on overdose deaths over the period 1999 – 2005.[78] The study compared opioid overdose mortality rate and MME consumption rate (per 100,000 population) in PDMPs and non-PDMPs states. PDMPs implementation was not associated with significant reductions in opioid overdose mortality or MME consumption rate per state-year (p-value = 0.34, 0.55, respectively).

Over a similar period of time, Li et al. conducted a study comparing the number of drug overdose deaths per state per quarter year (i.e. state-quarter) in 31 PDMPs states and 20 non-PDMPs states during the period 1999 – 2008.[79] A state-quarter was coded having PDMP if the state implemented the PDMP any time during the quarter year. State-quarters with PDMP were associated with a 11% increase in drug overdose deaths compared to state-quarters without PDMPs (adjusted risk ratio = 1.11; 95% CI: 1.02–1.21). Also, the impact of PDMPs varied among the states. PDMP implementation was associated with a significant reduction in drug overdose mortality in three states, a significant increase in 17 states, and no impact in 11 states. The impact of PDMPs characteristics was also examined. The increase in overdose mortality was more pronounced in state-quarters with PDMPs monitored by a pharmacy board or those without an expectation on practitioners to access the system.

A later study by Patrick et al. evaluated the impact of PDMPs implementation on opioid overdose deaths in 34 states.[80] The study compared the annual rate of deaths per 100,000 population pre and post PDMPs implementation over the period 1999 – 2013. Unlike previous studies, results from linear regression analysis found a significant decline in the annual rate of opioid overdose deaths following PDMPs implementation (p-value<0.001). The impact of PDMPs characteristics was also examined. States with PDMPs that monitor four or more drug schedules and update data on a weekly basis had a significantly lower rate of opioid overdose

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deaths compared with other state PDMPs (p-value <0.05 and <0.001, respectively). However, no significant impact of PDMPs registration or use mandates was found.

The significant impact of PDMPs on overdose mortality was also documented in a recent study by Pardo.[81] The study compared the opioid overdose death rate in PDMPs and non-PDMPs states. Unlike previous studies, the current study considered PDMP strength when assessing its impact on overdose deaths. PDMP strength was measured based on the adoption of 11 characteristics or policies related to PDMPs operation. A score (a continuous number) was given for each state-year to represent PDMPs strength for the state-year; stronger PDMPs (i.e. more policies adopted) received higher scores. States without operational PDMPs received a score of zero. The regression model also controlled for the type of administrating agency and the presence of other regulatory policies including naloxone access and pain clinic laws. Results of the regression model were significant; with every one point increase in the PDMPs score, overdose deaths decreased by 1.5% (p-value ≤ 0.05). However, when scoring on quartiles, only PDMPs scores in the third quartiles were associated with a significant reduction in overdose deaths compared to non-PDMPs states. PDMPs scores in the fourth quartile were not significant. Findings of the current study suggest that PDMPs strength matters when assessing PDMPs effectiveness. The non-significant impact of PDMPs with scores in the fourth quartile may indicate that increasing the number of PDMPs policies may negatively influence the effectiveness of PDMPs.

Also, a recent study in Florida supports PDMPs effectiveness in reducing overdose mortality.[82] The study examined changes in oxycodone-caused deaths following PDMPs implementation. The study utilized an interrupted time series design and examined changes from 2003 to 2012. Authors compared the monthly number of oxycodone-caused deaths before and after PDMPs

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implementation in 2010. The model controlled for multiple confounders including pain clinic laws and other regulatory policies implemented at a similar time to PDMPs. The impact of PDMPs and the rate of PDMPs query by health care providers on oxycodone-related mortality were examined. PDMPs were associated with a 25% decline in the number of deaths (p-value = 0.008). Significant results were also reported for the impact of the rate of PDMPs query. With every increase of one query per health care provider, the number of oxycodone deaths decreased by 0.23 persons per month (p-value = 0.002). However, the impact of PDMPs on opioid (excluding oxycodone) caused deaths was not significant (p-value 0.7).

The last study assessed the impact of PDMPs on the prescription opioid related ED visits and the findings were not significant.[83] The study compared the rate of ED visits per quarter year between PDMPs and non-PDMPs states during the period 2004 – 2011. The main outcome measure included ED visits related to misuse and non-misuse of prescription opioids. For all opioid related visits, the rate of ED visits did not significantly differ between states with and without PDMP (p-value = 0.74). Results for ED visits related to prescription opioid misuse or abuse were also not significant (p –value = 0.57). Findings of the current study suggest PDMPs ineffectiveness. However, authors did not consider differences in PDMPs characteristics or policies among states, which may have a huge impact on the reported findings.

Summary of PDMP impact on health outcomes:

As discussed earlier, old studies that examined the PDMPs impact on prescription opioid overdose deaths showed mixed evidence of PDMPs effectiveness. Later studies provided more evidence supporting the positive impact of PDMPs on reducing overdose mortality. Overdose deaths may not be a good measure for opioid safety; many factors may contribute to death. Furthermore, documentation for the reason of death may not be accurate and thus, may not truly

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represent deaths due to prescription opioid overdose. Most studies did not consider differences in PDMP characteristics among states, which may have a profound effect on PDMPs effectiveness. Only one study considered PDMP strength and the results were significant.

Prescription opioid related ED visits is a better indicator for opioid safety. Only one study examined PDMP impact on ED visits and the results were not significant. More studies are needed to examine the impact of PDMPs on ED visits.

Table 2. 5: Summary of included studies (PDMPs impact on prescription opioid related-health outcomes)

Author	Study design and sample	Sample size	Unit of analysis	Outcome measure of interest	Period	Setting and data source	Related findings
Paulozzi et al[78] 2011	- Ecologic study	357 state year (247 without active PDMPs and 110 with PDMPs)	State-year	- Rate of prescription opioid overdose death - Rate of MME consumption	1999 - 2005	- PDMPs and non-PDMPs states -CDC (multiple cause of death mortality files) - ARCOS	PDMPs implementation was not associated with significant reduction in overdose death or MME consumption rate
Li et al[79] 2014	- Ecologic study	2040 state quarter (619 with active PDMPs)	State-quarter	- Rate of drug overdose deaths	1999 - 2008	PDMPs (31) and non-PDMPs (20) states -CDC (multiple cause of death mortality files)	- Overall, implementation of PDMPs was associated with an 11% increase in drug overdose mortality (ARR = 1.11; 95% CI = 1.02–1.21) - PDMPs impact on drug overdose mortality varied greatly across states
Patrick et al[80] 2016	- Ecologic study (interrupted time-series)	_	State-year	- Annual rate of opioid-related overdose deaths (per 100,000 population)	1999 – 2013	- 34 states with active PDMPs - CDC (multiple cause of death	- Significant decline in annual rate of opioid overdose deaths following PDMPs implementation (p-value <0.001)

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						mortality files)	
Pardo B[81] 2017	- Ecologic study	816 state year	State-year	- Rate of opioid overdose death	1999 - 2014	- PDMPs and non-PDMP states - CDC (multiple cause of death mortality files) - PDAPS	- Significant impact of PDMPs considering its strength: - With every one point increase in PDMPs score, overdose deaths decreased by 1.5% (p-value ≤ 0.05)
Delcher et al[82] 2015	- Interrupted time-series	120 monthly counts of oxycodone-caused mortality	Month	- Monthly counts of oxycodone-caused mortality	2003 - 2012	- Florida - Florida MEC	- PDMPS was associated with 25% decline in number of deaths (p-value = 0.008) - With every increase of one PDMPS query per health care provider, number of oxycodone deaths decrease by 0.23 persons per month (p-value = 0.002) - PDMPS did not significantly impact other opioid related deaths (p-value= 0.7)
Maughan et al[83] 2015	- Ecologic study	_	Quarter year	-Rate of ED visits (per 100,000 population)	2004 - 2011	- DAWN	- Rate of prescription opioid related ED visits did not significantly differ between states with and without PDMPs (p -value = 0.57)

MME: Morphine Milligram Equivalents.
ARR: adjusted Risk Ratio.
CDC: Centers for Disease Control and Prevention.
ARCOS: Automation of Reports and Consolidated Orders System.
State-quarter: Per state per quarter year.
PDAPS: Prescription Drug Abuse Policy System.
MEC: Medical Examiners Commission.
DAWN: Drug Abuse Warning Network.

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Part III: literature review on prescriber mandates

As seen in the previous studies (part I and II literature review), the literature provided inconsistent evidence of the effectiveness of PDMPs. Studies on PDMPs utilization showed low and irregular use of the system; this negatively impacted the expected benefit of PDMPs. Prescriber use mandates are a relatively new policy directed to increase PDMPs utilization among prescribers. The impact of the policy on increasing PDMPs effectiveness (by increasing its utilization) has not been fully studied. This part of the literature review discusses studies on prescriber use mandates and its impact on the prescription opioid abuse epidemic.

A total of four studies have investigated the impact of prescriber use mandates on opioid prescribing and opioid related overdose deaths.[84-87] Two studies were conducted in New York and two studies included multiple states. Studies are summarized in Table 2.6.

Brown et al. conducted a study to examine the impact of the Internet System for Tracking Over-Prescribing (I-STOP) on opioid prescribing and related morbidity.[84] I-STOP is an extension of New York PDMPs with the additional requirement of prescriber use mandates. The study examined changes in the trend of opioid prescriptions filled per year, quarterly MME supply, and opioid related overdoses before and after I-STOP implementation. Following the introduction of I-STOP, quarterly MME supply significantly increased (p-value= 0.006), although the number of opioid prescriptions filled appeared to have a negative trend. More data points are required to confirm the impact of I-STOP on reducing the number of opioid prescriptions filled. Prescription opioid related overdose (as measured by number of ED visits and inpatient admissions) showed an increasing trend before I-STOP implementation and leveled off following I-STOP. However, differences in slope between pre and post I-STOP periods were not significant (p-value =0.37). The study findings indicated that I-STOP did not significantly change the opioid prescription

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trend in NY. A leveling off in prescription opioid morbidity following I-STOP is promising given the national increasing trend of opioid morbidity and mortality.

In addition to the previous study, Rasubala et al. assessed the impact of I-STOP on dentists prescribing of opioids.[85] The study examined changes in the odds of opioid prescribing in the period following I-STOP implementation compared to the pre-I-STOP period. Results were significant; the odds of receiving an opioid analgesic decreased by almost 60% following I-STOP compared to the pre-I-STOP period (OR = 0.42, 95% CI: 0.35, 0.51, p-value <0.05). Also, there was a significant reduction in the total number of opioid prescriptions following I-STOP implementation (p-value <0.05). A number of study limitations have been noted. The regression model was not clear and results were not shown. Authors did not control for confounders like demographics or, if they did so, the included covariates were not reported in the study.

In a more generalizable study, Dowell et al. evaluated the impact of PDMPs prescriber mandatory access and pain clinic laws in 38 states and the District of Colombia.[86] The study compared rate of opioid prescribing (in MME per state resident) and overdose deaths in states with prescriber use mandates and pain clinic laws and those without the policies over the period 2006 - 2013. A significant reduction in the rate of opioid prescribing and overdose deaths was observed in states with both policies compared to controls (p-value <0.05). States who implemented pain clinic laws also adopted prescriber use mandates at similar times and thus, the impact of prescriber mandates only could not be isolated.

A more recent study by Wen et al. examined the impact of prescriber mandates on the rate of opioid prescribing among Medicaid enrollees for the period 2011- 2014.[87] The study differentiated mandates into registration mandates only, use mandates only, and registration and use mandates. The main outcome measure was the total number of opioid prescriptions filled per

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100 enrollees per quarter year. Results from linear regression models indicated that states with PDMPs registration mandates had a significant reduction in the rate of schedule II opioid prescribing compared to states without any mandates (p-value <0.05). Significant reductions in the rate of schedule II opioid prescribing were also reported for states with PDMPs registration and use mandates (p-value <0.05). However, PDMP use mandates only had a limited impact on the rate of schedule II opioid prescribing (results were not significant at a 0.05 level of significance). Further analysis differentiated weak and strong (i.e. comprehensive mandates without prescriber judgment) mandates, however, no significant impact of any type of mandates was found.

As seen in the previous studies, prescriber use mandates have a limited impact on opioid prescribing and prescription opioid related overdose deaths. More studies are needed to prove the effectiveness of the new policy.

Table 2. 6: Summary of included studies (PDMPs prescriber use mandates)

Author	Study design and sample	Sample size	Unit of analysis	Outcome measure of interest	Period	Setting and data source	Related findings
Brown et al[84] 2017	Interrupted time series	_	- Year quarter -Year	- Changes in trend of: - Quarterly MME supply - Quarterly Opioid related morbidity - Yearly opioid prescriptions filled per year	2010 - 2015	- NY - ARCOS - BN-NYSDOH - SPARCS	-Following ISTOP implementation: - Significant increase in quarterly MME (P-value= 0.006) - Prescription opioid related morbidity leveled off (no significant difference from pre-ISTOP period) - Number of opioid prescription filled showed a negative trend

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Rasubala et al[85] 2015	- Pre – post design - Dentists	6204 visits	Dentist visit	-Odds of receiving opioid - Number of opioid prescription	(12/ 2012– 02/2013) and (12/ 2013 – 02/ 2014)	- A dental urgent care in NY - Patient records	- Following ISTOP implementation: - Odds of receiving an opioid analgesic decreased by almost 60% (OR = 0.42, 95% CI: 0.35, 0.51) - Significant reduction in total number of opioid prescriptions (Chi-square test, p-value <0.05)
Dowell et al[86] 2016	- Ecologic study (difference in difference model)	312 state year	State year	-Rate of opioid prescribing-g (in MME per state resident) - Rate of prescripti-on opioid overdose deaths (per 100,000 state resident)	2006 – 2013	-Prescriber mandates and non-prescriber mandates states (total 39 states) - CDC (multiple cause of death mortality files) - IMS Health's National Prescriptio-n Audit	- Significant reduction in rate of opioid prescribing and overdose deaths was observed in states with prescriber mandates compared to controls (p-value <0.05)
Wen et al[87] 2017	- Ecologic study -Medicaid enrolls	736 state quarter	Year quarter	-Rate of opioid prescribe-ng (per 100 enrollee per quarter year)	2011- 2014	- CMS (Medicaid State Drug Utilization Files)	- Significant reductions in rate of schedule II opioid prescribing for state PDMPs with both registration and use mandates (p-value <0.05). – No significant reduction in rate of schedule II opioid prescribing for state with use mandates only

ARCOS: Automation of Reports and Consolidated Orders System.
BNE-NYSDOH: Bureau of Narcotics Enforcement- New York State Department of Health.
SPARCS: Statewide Planning and Research Cooperative System.
MME: Morphine Milligram Equivalents.
CDC: Centers for Disease Control and Prevention.
CMS: The Centers for Medicare and Medicaid Services.

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Overview of the literature

Prescription Drug Monitoring Programs (PDMPs) have been adopted by all states (except Missouri). However, the effectiveness of these systems has not been fully demonstrated. Earlier studies provided inconsistent evidence on PDMPs effectiveness. However, there is a growing body of literature to support their positive impact on the prescription opioid abuse epidemic. Studies have shown that PDMP utilization is low and variable among healthcare providers; this may explain the inconsistent findings reported in the literature. In addition, studies examining the impact of PDMPs on prescription opioid related health outcomes have selected overdose death as the outcome measure even though it may not be a good indicator for PDMP effectiveness. Only one study has selected ED visits as a measure for prescription opioid safety, and results were not significant.

In the proposed research, PDMPs effectiveness will be examined in terms of their impact on prescription opioid poisoning related ED visits. Also, the impact of prescriber use mandates on increasing PDMPs utilization will be considered. The connection between prescriber use mandates and their impact on ED visits can be explained by the Donabedian model discussed in Chapter 1.

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Chapter 3

Methods and results for specific aim 1:

A. To identify and select states with laws or regulations mandating prescriber use of PDMPs.

B. To identify and select comparison state(s) without mandatory use policies.

Section 3.1-Methods

Data source

Three data sources were used to identify states with or without PDMPs prescriber use mandate policies, the Center of Excellence (COE) at Brandeis University, the National Alliance for Model State Drug Laws (NAMSDL), and the Prevention Status Report (PSR) from the CDC. The COE at Brandeis University is the first comprehensive source of information on PDMPs.[88] Established in 2010, the COE is a joint project between the Bureau of Justice Assistance (BJA) and Brandeis University, and it was created to evaluate PDMPs effectiveness. One major use of the CEO data is to disseminate information on PDMPs best practices or policies in order to enhance their effectiveness in combating the prescription opioid abuse epidemic.

The NAMSDL is another valuable source of information on PDMPs.[89] NAMSDL is a non-profit organization that drafts model drug and alcohol laws, policies, and regulations. NAMSDL also

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compares state policies and regulations related to alcohol and substance abuse prevention and treatment. For example, in December 2016, NAMSDL published a report on eight evidence based practices to optimize prescriber utilization of PDMPs.[31] The report discussed states' adoption of the policies and preliminary findings on their impact on prescription opioid abuse as well as prescriber use mandates policy. Compared to the COE, the NAMSDL provided more information on the type of prescriber use mandates adopted by the states. States were classified based on the level of prescriber requirements to check the PDMPs.

Lastly, the PSR was utilized. First published by the CDC in February 2012, PSR provides information on states adoption of PDMPs prescriber use mandates.[90] The PSR focuses on two PDMP policies: state requirement for prescriber comprehensive PDMP use and timely data submission to PDMP. The CDC used a three-level rating scale (green, yellow, red) to describe the extent of state adoption of these policies. The rating scale is based on data from the COE at Brandeis University and NAMSDL supported by emerging evidence and/or expert opinion. The green rating is the highest level rating and is given to states with comprehensive prescriber use mandates, defined as "requiring prescribers to consult the PDMP before initially prescribing opioids and benzodiazepines, and at least every three months thereafter."[90] The latest PSR assessment of state adoption of prescriber use mandates was conducted on October 31, 2015; however, it does not provide information on timing of policy implementation. Table 3.1 describes the three-level rating scale.

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Table 3. 1: Requirements for comprehensive use of state PDMPs[90]

Rating	State PDMP use requirement
Green	Prescribers are required to consult the PDMP before initial opioid and benzodiazepine prescriptions and at least every three months thereafter
Yellow	Prescribers are required to consult the PDMP before initial opioid prescriptions and again within one year
Red	Prescribers are not required to consult the PDMP before initial opioid prescriptions, OR such a requirement does exist but there is no required subsequent check and/or the policy includes subjective standards or broad exceptions

Selection of eligible states

Using the COE, NAMSDL and PSR, an overall assessment of states adoption of PDMPs prescriber use mandates was conducted. As of 2017, the COE classified 39 states as "mandate states". As of 2015, the NAMSDL identified 13 states with requirements for comprehensive prescriber use and 15 states with requirements for prescribers to check the system in narrower circumstances; the remaining 22 states were classified as non-mandates states.[31] Comprehensive prescriber use mandates require all prescribers to check the state PDMPs with just a few exceptions. Based on the PSR, only four states were classified as comprehensive prescriber use mandates, four states had non-comprehensive mandates, and all other states were non-mandated. For the current study, the selection of mandates and non-mandates states was based on the three-level rating scale. States with green rating (comprehensive prescriber use mandates) were considered as gold standards and represented the intervention state(s) in order to examine the full impact of the prescriber use mandates policy. Comparator states were selected from states who received a red rating. The HCUP State Emergency Department Databases (SEDD) and the State Inpatient Databases (SID) provide information on treat and release ED visits and ED visits that

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resulted in hospital admission. The SEDD and the SID are the only available databases that provide ED visits on the state level and were selected as the source of data for the current study.[91]

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Section 3.2-Results

States with prescriber use mandates policy

States require prescribers to check PDMPs based on specific scenarios — which varies significantly based on the situation. In July 2012, Kentucky was the first state that implemented a comprehensive prescriber use mandate policy followed by New York, Ohio, and Connecticut. New Jersey, Oklahoma, Rhode Island, and Tennessee received a yellow rating from the CDC while all other states were rated red. States with comprehensive mandate policies were considered as intervention states. To select an intervention state, the state should have available data on prescription opioid poisoning ED visits at least one year before and one year after the policy implementation. Out of the four states that received green rating from the CDC, only Kentucky and New York have ED visits data available in the HCUP. However, the latest available data for New York were in 2014 and the mandates policy was implemented in August 2013. The after mandates period was not sufficient to examine the impact of the policy. Thus, Kentucky was selected as the intervention state. The comparator state was selected from states that received red rating in the PSR. The selection was based on geographic proximity to Kentucky and availability of data in the HCUP. ED visits data were not available for the seven neighboring states. The closest state with available data was North Carolina, which was selected as the comparator state. Table 3.2 summarizes information on states adoption of prescriber use mandates policy and availability of ED visits data in the HCUP.

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Table 3.2: States adoption of prescriber use mandates policy and availability of ED visits data in the SEDD and the SID[92]

State	Intervention vs. comparator state[a]	Effective date of policy[b]	Data in the SEDD	Data in the SID	Eligibility for the current study	Rationale
Kentucky	**Intervention**	7/20/2012	2008 - 2015	2000 - 2015	**Eligible**	Implemented comprehensive mandates and has available ED visits data before and after 2012
New York	Intervention	8/27/13	2006 - 2014	1999 - 2014	Not eligible	ED visits data are not available one year after August 2013
Ohio[c,d]	Intervention/ comparator	4/1/15	Not available	Not available	Not eligible	ED visits data are not available
Connecticut[d]	Intervention	10/1/2015	Not available	Not available	Not eligible	ED visits data are not available
West Virginia[d]	Comparator	-	Not available	2000 - 2014	Not eligible	ED visits data are not available in the SEDD
Virginia[d]	Comparator	-	Not available	Not available	Not eligible	ED visits data are not available
Tennessee[d]	Comparator	-	Not available	Not available	Not eligible	ED visits data are not available
Indiana[d]	Comparator	-	Not available	Not available	Not eligible	ED visits data are not available
Missouri[d]	Comparator	-	Not available	Not available	Not eligible	ED visits data are not available
Illinois[d]	Comparator	-	Not available	Not available	Not eligible	ED visits data are not available
North Carolina	**Comparator**	-	2000 - 2015	2007 - 2015	**Eligible**	- A non-mandates state. -Geographically close to Kentucky - Has available ED visits data one year before and one year after 2012

a. States with green rating were considered as intervention states, states with red rating were considered as reference.
b. NAMSDL report.
c. Ohio is a neighboring state to Kentucky and it implemented mandates policy in 2015, thus, it could be considered as intervention state (if ED data were available) or a comparator state.
d. A neighboring state to Kentucky.

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Chapter 4

Methods and results for specific aim 2:

Among Kentucky and North Carolina residents:

A. To determine the prevalence of prescription opioid poisoning ED visits.
B. To characterize prescription opioid poisoning ED visits based on socio-demographic and clinical characteristics.
C. To examine associations between patients' sociodemographic and clinical characteristics and prescription opioid poisoning ED visits.

Section 4.1-Methods

Study Setting

All prescription opioid poisoning ED visits in Kentucky and North Carolina for the years 2011 to 2014.

Data source

Data from the State Emergency Department Databases (SEDD) and the State Inpatient Databases (SID) were used for the current study.[91] Both SEDD and SID are part of the family of databases and software tools developed for the Healthcare Cost and Utilization Project (HCUP). The

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SEDD is a longitudinal dataset that contains information on emergency visits at hospital-affiliated EDs that do not result in hospitalization, and clinical, socio-demographic, and resource utilization information. Currently, 22 states release their ED data through the SEDD; however, not all variables are available for each year data was collected.

To analyze all ED visits, data from the SEDD need to be combined with the SID. The SID records ED visits that result in hospital admissions and contains information about patients initially seen in the ED and then admitted to the hospital. The SID includes inpatient discharges from community hospitals per state per year. Currently, 31 states have their inpatient data available through the SID. Similar to the SEDD, the SID includes clinical, socio-demographic, and resource utilization variables for each inpatient discharge. Both the SEDD and the SID for Kentucky and North Carolina were used in the current study.

Sample

The inclusion and exclusion criteria considered to determine the final study samples are listed below. Figure 4.1 illustrates the sample selection process.

Inclusion criteria:

a. Patients had to be at least 12 years of age.
b. ED visits with all listed diagnosis of prescription opioid poisoning were considered. There are up to 25 diagnosis variable in the SEDD and the SID (DX1 to DX25), an indicator variable of prescription opioid poisoning event was created using all 25 variables.
c. Intentional, unintentional, and prescription opioid poisoning events with undetermined intent were considered. Patients may have the intention to abuse prescription opioid,

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however, they may develop a poisoning event unintentionally. Since there is no clear guidance on how to classify intention of opioid poisoning, all intentions were considered for this study. The variables (ECODE1 to ECODE7) were utilized to identify poisoning intention.

Exclusion criteria:

a. Prescription opioid poisoning ED visits for patients with cancer were excluded. Cancer patients are considered a special population due to severity of pain and complexity of their medical condition. PDMPs are intended to capture doctor shoppers; therefore, including cancer patients does not reflect the population of interest. Single level Clinical Classifications Software (CCS) was used to identify patients with cancer diagnosis. A list of CCS for cancer is available in Appendix A.
b. Opioid poisoning ED visits for patients who were not residents in Kentucky or North Carolina. Prescriber use mandates policy is state specific and thus, including non-residents may bias the evaluation of the policy.
c. Fatal prescription opioid poisoning events. Death might not be a good indicator for prescription opioid poisoning because many factors can contribute to a patient's death.
d. Heroin related poisoning events because illicit drugs are not covered under PDMPs.

Identification of prescription opioid poisoning events

Opioid poisoning events were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. External Cause of Injury codes (E-codes) are an extension of ICD-9-CM codes used to specify intent of opioid poisoning. Description of ICD-9-CM codes and E-codes related to opioid poisoning is available in Table 4.1.

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Table 4. 1: ICD-9-CM codes and E-codes for opioid poisoning

ICD-9-CM code	**Description**
965.00	Poisoning by opium (alkaloids), unspecified
965.02	Poisoning by methadone
965.09	Poisoning by other opiates
E-code	**Description**
E850.1	Accidental poisoning by methadone
E850.2	Accidental poisoning by other opiates and related narcotics
E950.0	Suicide and self-inflicted poisoning by analgesics, antipyretics, & antirheumatics
E980.0	Poisoning by analgesics, antipyretics & antirheumatics, undetermined whether accidentally or purposely inflicted

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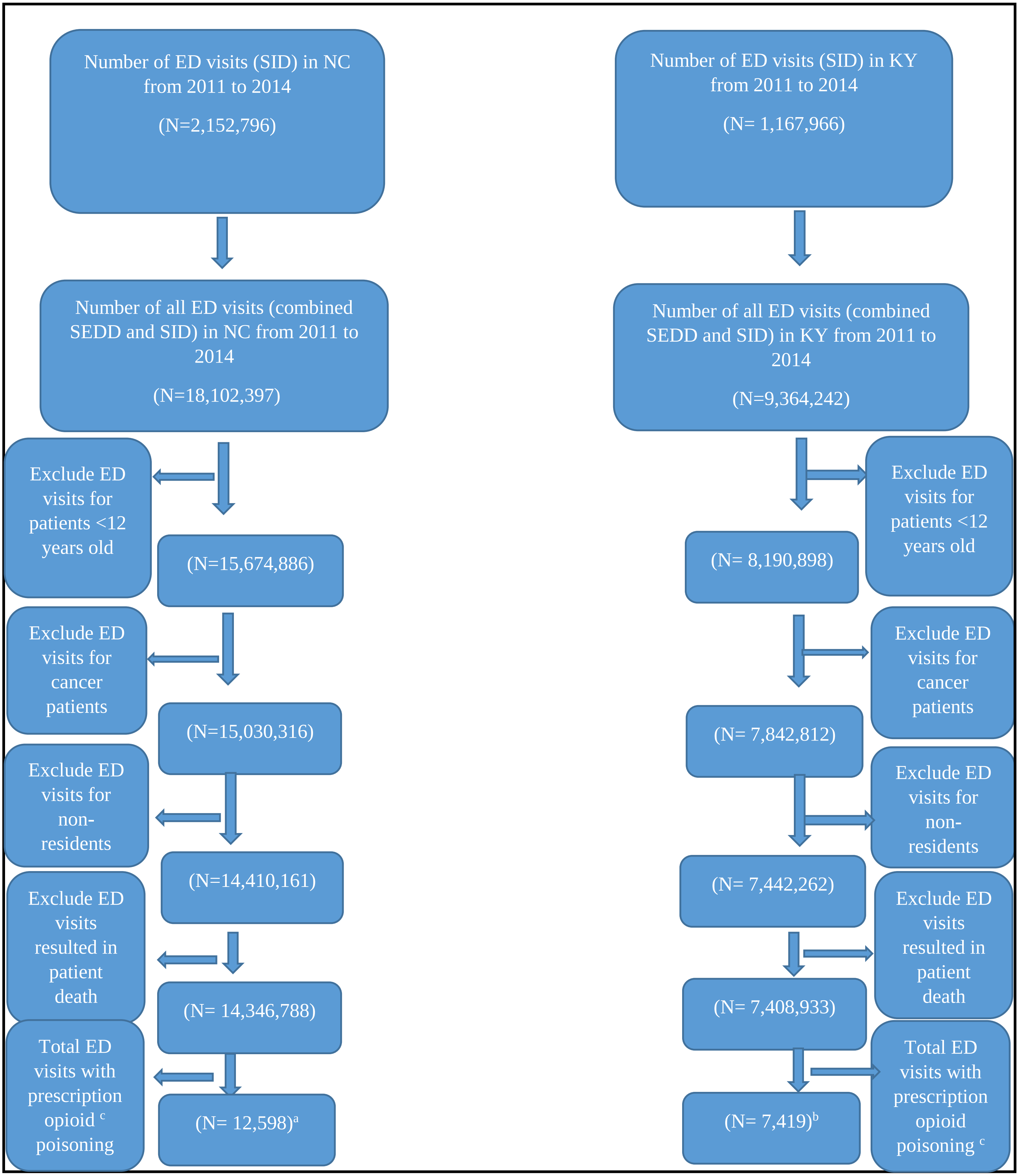

Figure 4. 1: Sample flow chart for specific aim 2

a. Final sample size for NC from 2011 to 2014, b. Final sample size for KY from 2011 to 2014, c. based on ICD-9-CM codes in Table 4.1

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Variables

Clinical Variables

In the SEDD and the SID, the variable (DXn) represents patient's diagnosis based on ICD-9-CM codes. There are up to 25 listed diagnosis for each patient discharge abstract (DX1 to DX25). An indicator variable was created to identify prescription opioid poisoning event using all listed diagnoses. For the SID, the first listed diagnosis is the principle diagnosis responsible for hospital admission; however, in the SEDD, the first listed diagnosis is the main condition, symptom, or problem responsible for the ED visit. The first listed diagnosis in the SEDD and the SID cannot be substituted, if missing, with the second, third, or any following diagnosis. However, starting from the first secondary diagnosis, the diagnoses are shifted to eliminate blank secondary diagnoses.

Number of chronic conditions was recoded into six categories based on the Agency for the Healthcare Research and Quality (AHRQ) classification.[93] Number of chronic conditions was selected because it is a risk factor for opioid poisoning. The more chronic conditions the patient has, the higher is the risk of having a prescription opioid poisoning event.

Other risk factors for opioid poisoning include pre-existing conditions of psychoses, depression, alcohol, and drug abuse. Indicator variables for each condition was created based on ICD-9-CM codes. An indicator variable for each condition was created using all listed diagnoses (DX1 to DX25). A description of ICD-9-CM codes for depression, psychoses, alcohol abuse, and drug abuse is available in Table 4.2.

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Table 4. 2: ICD-9-CM codes for depression, psychoses, alcohol abuse, and drug abuse[94]

Comorbidity	ICD-9-CM code
Depression	296.2, 296.3, 296.5, 300.4, 309.x, 311
Psychoses	293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x
Alcohol abuse	265.2, 291.1, 291.2, 291.3, 291.5, 291.6, 291.7, 291.8, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0, 571.0, 571.1, 571.2, 571.3, 980.x, V11.3
Drug abuse	292.x, 304.x, 305.2, 305.3, 305.4, 305.5, 305.6, 305.7, 305.8, 305.9, V65.42

Sociodemographic variables

Age was categorized into five groups based on the literature related to opioid poisoning.[95, 96] Other sociodemographic variables available in the SEDD and the SID include gender, race, ethnicity, insurance, median household income, and patient's location (urban/rural). A description of all original variables and recoded variables used in this study is available in Table 4.3.

Table 4. 3: Description of variables included for specific aim 2

Variable name in the SEDD and the SID	Description	Name of the recoded variable in this study	Description
DX1 – DX25	ICD-9-CM codes[a]	Poisoning_indicator	1 = yes 0 = no
NCHRONIC	Number of chronic conditions	New-nchronic	0 = no chronic conditions 1= 1 chronic condition 2= 2 chronic conditions 3= 3 chronic conditions 4= 4 chronic condition 5 ≥ 5 chronic conditions
DX1 – DX25	ICD-9-CM codes[b]	Depression	1 = yes 0 = no
DX1 – DX25	ICD-9-CM codes[b]	Psychoses	1 = yes 0 = no
DX1 – DX25	ICD-9-CM codes[b]	Alcohol	1 = yes

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			0 = no
DX1 – DX25	ICD-9-CM codes[b]	Drug_abuse	1 = yes 0 = no
AGE	Age in years	New_age	1 = (12 -17) 2= (18-15) 3= (26-34) 4= (35-50) 5 >50
FEMALE	Indicator of sex	New_female	1 = female 2= male
RACE	Race and ethnicity	New_race	1 = white 2= black 3= Hispanic 4= other
PAY1	Expected primary payer	New_pay1	1 = Medicare 2 = Medicaid 3= private insurance 4= self-pay 5= others
MEDINCSTQ	Median household income state quartile for patient ZIP Code	New_medincstq	1= first quartile(poor) 2= second quartile (lower-average) 3= thirds quartile (higher-average) 4= fourth quartile (rich)
PL_UR_CAT4	Patient location: urban-rural 4 categories	New_pl_ur_cat4	1= urban 2= rural

a. Description of ICD-9CM codes for opioid poisoning considered in the study is available in Table 4.1.
b. Description of ICD-9CM codes for depression, psychoses, alcohol abuse and, drug abuse is available in Table 4.2.

Statistical analyses

Prevalence

Annual prevalence of prescription opioid ED visits in Kentucky and North Carolina were estimated using the following equation:

$$\text{Prevalence} = \frac{\text{number of prescription opioid poisoning ED visits per state per year}}{\text{Estimate of the resident population in that state/year}}$$

Number of prescription opioid poisoning ED visits were obtained from the SEDD and the SID.

Estimates of the resident population in Kentucky and North Carolina are available from the

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United States Census Bureau.[97] Estimates for residents of 12 years of age and older were calculated and used for this study. Also, total four years (2011 -2014) prevalence in Kentucky and North Carolina was reported using the following equation: [98]

$$\text{Total prevalence} = \frac{\text{total number of prescription opioid poisoning ED visits in each state over the period 2011-2014}}{\text{Estimate of the average resident population in that state over the same period}}$$

Annual prevalence rates by age group were also calculated and compared to examine changes in prescription opioid poisoning ED visits among different age groups:

$$\text{Prevalence by age group} = \frac{\text{number of prescription opioid poisoning ED visits in each age group per state}}{\text{Estimate of the resident population in that age group/state}}$$

Prevalence estimates of prescription opioid poisoning ED visits among all ED visits in Kentucky and North Carolina were calculated as follows:

$$\text{Prevalence among all ED visits} = \frac{\text{number of prescription opioid poisoning ED visits per state per year}}{\text{Total number of all ED visits in that state/year}}$$

Descriptive statistics

Descriptive statistics were used to describe basic sociodemographic and clinical characteristics of prescription opioid poisoning ED visits in each state over the 2011 – 2014 period. Age as a continuous variable was described by mean and standard deviation; frequencies and percentages were used to describe all categorical variables reported in Table 4.3. Prescription opioid poisoning ED visits were described by age group and intent of poisoning. Bivariate analyses using Chi-square test and/or Fisher's exact test were applied to examine associations between patients' sociodemographic and clinical characteristics and prescription opioid poisoning ED visits in each state. This study was qualified for exemption by Virginia Commonwealth University Institutional Review Board (IRB) (ID: HM20009965).

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Section 4.2-Results

Aim 2A: To determine the prevalence of prescription opioid poisoning ED visits in Kentucky and North Carolina.

Kentucky

Over the four-year period, a total of 7,419 prescription opioid poisoning ED visits were reported among people aged 12 years and older. The total (four year) prevalence rate of prescription opioid poisoning ED visits was 199.6 per 100,000 population. The prevalence of prescription opioid poisoning ED visits by year is reported in Table 4.4. There was 26.1% decrease in the prevalence of prescription opioid poisoning ED visits from 2011 to 2014.

The total and annual prevalence rate of prescription opioid poisoning ED visits among different age groups was examined (Table 4.5). The total prevalence rate was higher in adults 26-34 years old and 35-50 years old, 68.4 and 65.5 per 100,000 population, respectively, compared to other age groups. There was an overall reduction in the annual rate of prescription opioid poisoning ED visits in people ≤ 50 years of age. The decrease in the annual prevalence rate was greater among 18 to 25 years old and 26 to 34 years old compared to other age groups. On the other hand, there was 0.7% increase in the prevalence of prescription opioid poisoning ED visits among people greater than 50 years old from 2011 to 2014.

The annual prevalence rate of prescription opioid ED visits among all ED visits is reported in Table 4.6. There was 26.1% reduction in annual rate of non-fatal prescription opioid ED visits from 2011 – 2014.

North Carolina

Over the four-year period, a total of 12,598 prescription opioid poisoning ED visits were reported among people aged 12 years and older. Total (four years) prevalence rate of prescription

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opioid poisoning ED visits was 151.94 per 100,000 population. The prevalence of prescription opioid poisoning ED visits by year is reported in Table 4.4. There was 3.2% increase in the prevalence of prescription opioid poisoning ED visits from 2011 to 2014.

The total and annual prevalence rate of prescription opioid poisoning ED visits among different age groups was assessed (Table 4.7). The total prevalence rate was higher in adults 26-34 years old and 35-50 years old, 43.18 and 42.12 per 100,000 population, respectively, compared to other age groups. The annual prevalence rate of prescription opioid poisoning ED visits increased in children 12 to 17 years old, adults 26 to 34 years, and >50 years. On the other hand, there was reduction in annual prevalence rate of prescription opioid poisoning ED visits in adults 18 to 25 years old and 35 to 50 years.

The annual prevalence rate of prescription opioid ED visits among all ED visits is reported in Table 4.6. The annual prevalence rate of prescription opioid ED visits (per 100,000 ED visits) was stable over the years 2011 – 2014.

Table 4. 4: Annual prevalence rate of prescription opioid-poisoning ED visits (per 100,000 population) by state

State	KY	NC
2011	59.31	36.29
2012	54.94	37.68
2013	41.67	39.49
2014	43.82	37.45
Percent change 2011 - 2014	-26.12	3.20

Note: KY= Kentucky; NC = North Carolina

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Table 4. 5: Annual and total prevalence rate of prescription opioid poisoning ED visits (per 100,000 population) by age group in Kentucky

Age (in years)	2011	2012	2013	2014	Percent change 2011 - 2014	Total prevalence rate
12 - 17	19.00	14.00	12.56	11.71	-38.40	14.25
18 - 25	62.15	58.3	32.2	34	-45.3	46.50
26 - 34	94	77	48.3	54.2	-42.3	68.43
35 - 50	78	69	58	56.3	-27.8	65.46
>50	43	46.5	39	43.3	0.7	43.00

Table 4. 6: Annual prevalence rate of prescription opioid poisoning ED visits (per 100,000 ED visits) by state

State	KY	NC
2011	117	86.8
2012	109.4	87.1
2013	87.2	90.5
2014	86.5	86.8
Percent change 2011 - 2014	-26.1	0

Note: KY= Kentucky; NC = North Carolina

Table 4. 7: Annual and total prevalence rate of prescription opioid poisoning ED visits (per 100,000 population) by age group in North Carolina

Age (in years)	2011	2012	2013	2014	Percent change 2011 - 2014	Total prevalence rate
12 - 17	12.7	14.0	11.1	14.7	15.7	13.12
18 - 25	41.9	38.6	37.2	38.3	-8.6	39.00
26 - 34	43.0	39.7	45.5	44.5	3.5	43.18
35 - 50	41.1	42.4	44.6	40.3	-1.9	42.12
>50	34.3	39.2	41.6	41.2	20.1	39.14

Aim 2B: To characterize prescription opioid poisoning ED visits based on socio-demographic and clinical characteristics.

Kentucky

Sociodemographic characteristics

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The mean age was 43 years (SD=15.9). More than two thirds of prescription opioid ED visits were related to adults 35 to 50 years old and >50 years. Children 12 to 18 years old were the least group among all age groups. More females were involved compared to males (54.1% and 45.9%, respectively). The majority of prescription opioid poisoning ED visits involved whites (93.9%). About one third of prescription opioid poisoning ED visits were related to people with low income. Most of ED visits were paid by Medicare or Medicaid (29.1% and 27.0%, respectively). Descriptions of all sociodemographic are reported in Table 4.8.

Clinical characteristics

Prescription opioid poisoning ED visits were more common in people with at least one chronic condition. One third of prescription opioid poisoning ED visits involved people with five or more chronic conditions. About one quarter of ED visits were related to patients diagnosed with depression. Other psychiatric conditions like psychoses, drug abuse, and alcohol abuse were rarely reported (Table 4.8).

Table 4. 8: Sociodemographic and clinical characteristics of prescription opioid poisoning ED visits in Kentucky from 2011 – 2014

Sociodemographic variable	**N (%)**
Age (in years)	
0-17	195 (2.63)
18-25	902 (12.16)
26-34	1393 (18.78)
35-50	2445 (32.96)
>50	2484 (33.48)
Gender	
Male	3406 (45.91)
Female	4013 (54.09)
Race	
White	6967 (93.91)
Black	262 (3.53)
Hispanic	113 (1.52)
Other	77 (1.04)
Primary expected payer	
Medicare	2150 (29.09)
Medicaid	1994 (26.98)

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Private insurance	1294 (17.51)
Self-pay	1411 (19.09)
Other	543 (7.35)
Median household income	
Poor	2487 (34.42)
Lower average	1789 (24.76)
Higher average	1647 (22.79)
Rich	1303 (18.03)
Patient location	
Urban	3838 (51.90)
Rural	3557 (48.10)
Clinical variable	N (%)
No. of chronic conditions	
0	834 (11.24)
1	1092 (14.72)
2	1095 (14.76)
3	953 (12.85)
4	829 (11.17)
≥5	2616 (35.26)
Psychoses	
Yes	3 (0.04)
No	7416 (99.96)
Alcohol abuse	
Yes	61 (0.82)
No	7358 (99.18)
Drug abuse	
Yes	6 (0.08)
No	7413 (99.92)
Depression	
Yes	1815 (24.46)
No	5604 (75.54)

Sociodemographic and clinical characteristics were further examined by age group. Results are summarized in Tables 4.9. Prescription opioid poisoning ED visits were more common in males 35 to 50 years old and in females >50 years. Although females were the predominant group across all ages, males had a higher percentage among young adults (18-25 and 26-34 years old). Among white, black, Hispanic, and others prescription opioid poisoning ED visits were more common in adults 35 to 50 years old and >50 years compared to other age groups. Low income patients had the highest proportion of prescription opioid poisoning ED visits among all age groups; however, they were most common in middle age adults (35 to 50 years old). With the

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exception of patients 35 to 50 years old, urban areas had higher prevalence of prescription opioid poisoning ED visits as compared to rural. Medicaid was the most common primary payer for patients 12 to 17 years old and 35 to 50 years (60% and 31.6%, respectively). Among young adults (18- 25 and 26-34 years old), private insurance was the most prevalent payer (31.8% and 34.1%, respectively). Medicare was the primary source of payment for two thirds of prescription opioid ED visits for patients >50 years old.

Among patients with zero to three chronic conditions, one third of prescription opioid poisoning ED visits were related to people 35 to 50 years old. Two thirds of patients 35 to 50 years old had five or more chronic conditions. Prescription opioid poisoning ED visits for patients with depression and alcohol abuse were more common in those 35 to 50 years old and > 50 years.

Table 4. 9: Sociodemographic and clinical characteristics of prescription opioid poisoning ED visits by age group in Kentucky from 2011 – 2014

Characteristics	**Age (in years) n (%)**				
	0 – 17	18 – 25	26 – 34	35 – 50	>50
Gender					
Male	95 (1.28)	523 (7.05)	742 (10.00)	1102 (14.85)	944 (12.72)
Female	100 (1.35)	379 (5.11)	651 (8.77)	1343 (18.10)	1540 (20.76)
Race					
White	164 (2.21)	817 (11.01)	1309 (17.64)	2326 (31.35)	2351 (31.69)
Black	22 (0.30)	55 (0.74)	39 (0.53)	64 (0.86)	82 (1.11)
Hispanic	6 (0.08)	16 (0.22)	27 (0.36)	33 (0.44)	31 (0.42)
Other	3 (0.04)	14 (0.19)	18 (0.24)	22 (0.30)	20 (0.27)
Primary expected payer					
Medicare	0 (0.00)	22 (0.30)	104 (1.41)	576 (7.79)	1448 (19.59)
Medicaid	115 (1.56)	219 (2.96)	432 (5.84)	769 (10.40)	459 (6.21)
Private insurance	58 (0.78)	255 (3.45)	194 (2.62)	415 (5.61)	372 (5.03)
Self-pay	17 (0.23)	284 (3.84)	472 (6.39)	508 (6.87)	130 (1.76)
Other	5 (0.07)	114 (1.54)	183 (2.48)	169 (2.29)	72 (0.97)
Median household income					
Poor	63 (0.870	264 (3.65)	492 (6.81)	866 (11.98)	802 (11.10)
Lower average	41 (0.57)	210 (2.91)	318 (4.40)	585 (8.10)	635 (8.79)
Higher average	37 (0.51)	192 (2.66)	307 (4.25)	525 (7.27)	586 (8.11)
Rich	52 (0.72)	213 (2.95)	242 (3.35)	393 (5.44)	403 (5.58)

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Patient location					
Urban	105 (1.42)	535 (7.23)	735 (9.94)	1187 (16.05)	1276 (17.25)
Rural	90 (1.22)	361 (4.88)	649 (8.78)	1249 (16.89)	1208 (16.34)
No. of chronic conditions					
0	66 (0.89)	159 (2.14)	209 (2.82)	235 (3.17)	165 (2.22)
1	55 (0.74)	221 (2.98)	301 (4.06)	343 (4.62)	172 (2.32)
2	36 (0.49)	227 (3.06)	292 (3.94)	348 (4.69)	192 (2.59)
3	18 (0.24)	137 (1.85)	208 (2.80)	363 (4.89)	227 (3.06)
4	9 (0.12)	91 (1.23)	164 (2.21)	281 (3.79)	284 (3.83)
≥ 5	11 (0.15)	67 (0.90)	219 (2.95)	875 (11.79)	1444 (19.46)
Alcohol abuse					
No	195 (2.63)	901 (12.14)	1385 (18.67)	2421 (32.63)	2456 (33.10)
yes	0 (0.00)	1 (0.01)	8 (0.11)	24 (0.32)	28 (0.38)
Drug abuse					
No	195 (2.63)	901 (12.14)	1392 (18.76)	2442 (32.92)	2483 (33.47)
yes	0 (0.00)	1 (0.01)	1 (0.01)	3 (0.04)	1 (0.01)
Depression					
No	151 (2.04)	718 (9.68)	1123 (15.14)	1842 (24.83)	1770 (23.86)
yes	44 (0.59)	184 (2.48)	270 (3.64)	603 (8.13)	714 (9.62)
Psychoses					
No	195 (2.63)	902 (12.16)	1392 (18.76)	2445 (32.96)	2482 (33.45)
yes	0 (0.00)	0 (0.00)	1 (0.01)	0 (0.00)	2 (0.03)

Also, sociodemographic and clinical characteristics were described by intent of poisoning. Results are summarized in Tables 4.10. Accidental prescription opioid poisoning constituted 51% of all visits. On the other hand, intentional represented more than half visits in children 12 to 17 years old (53.5%). Among all other age groups, accidental prescription opioid poisoning was more common. Females had a higher proportion of accidental and intentional opioid poisoning as compared to males (58.1%, 54.5%) and (41.9%, 45.6%), respectively.

Table 4. 10: Sociodemographic and clinical characteristics of prescription opioid poisoning ED visits by intent of poisoning in Kentucky from 2011-2014

Characteristics N (%)	**Intent of poisoning**		
	Unintentional (N= 3370)	Intentional (N= 1678)	Undetermined (N=1571)
Age (in years)			
0 – 17	47 (0.71)	92 (1.39)	33 (0.50)
18 – 25	348 (5.26)	251 (3.79)	203 (3.07)
26 – 34	535 (8.08)	324 (4.89)	349 (5.27)

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35 – 50	1006 (15.20)	626 (9.46)	550 (8.31)
>50	1434 (21.66)	385 (5.82)	436 (6.59)
Gender			
Male	1535 (23.19)	703 (10.62)	782 (11.81)
Female	1835 (27.72)	975 (14.73)	789 (11.92)
Race			
White	3174 (47.95)	1544 (23.33)	1497 (22.62)
Black	113 (1.71)	82 (1.24)	41 (0.62)
Hispanic	50 (0.76)	35 (0.53)	16 (0.24)
Other	33 (0.50)	17 (0.26)	17 (0.26)
Primary expected payer			
Medicare	1225 (18.58)	328 (4.97)	390 (5.91)
Medicaid	835 (12.66)	465 (7.05)	509 (7.72)
Private insurance	526 (7.98)	414 (6.28)	215 (3.26)
Self-pay	565 (8.57)	329 (4.99)	349 (5.29)
Other	210 (3.18)	130 (1.97)	104 (1.58)
Median household income			
Poor	1052 (16.33)	498 (7.73)	661 (10.26)
Lower average	853 (13.24)	424 (6.58)	328 (5.09)
Higher average	772 (11.99)	389 (6.04)	311 (4.83)
Rich	614 (9.53)	328 (5.09)	211 (3.28)
Patient location			
Urban	1828 (27.71)	876 (13.28)	665 (10.08)
Rural	1534 (23.25)	797 (12.08)	897 (13.60)
No. of chronic conditions			
0	381 (5.76)	130 (1.96)	192 (2.90)
1	466 (7.04)	254 (3.84)	256 (3.87)
2	457 (6.90)	281 (4.25)	245 (3.70)
3	382 (5.77)	258 (3.90)	198 (2.99)
4	351 (5.30)	223 (3.37)	173 (2.61)
≥ 5	1333 (20.14)	532 (8.04)	507 (7.66)
Alcohol abuse			
No	3346 (50.55)	1667 (25.19)	1549 (23.40)
Yes	24 (0.36)	11 (0.17)	22 (0.33)
Drug abuse			
No	3367 (50.87)	1677 (25.34)	1569 (23.70)
Yes	3 (0.05)	1 (0.02)	2 (0.03)
Depression			
No	2625 (39.66)	1062 (16.04)	1275 (19.26)
Yes	745 (11.26)	616 (9.31)	296 (4.47)
Psychoses			
No	3370 (50.91)	1677 (25.34)	1570 (23.72)
Yes	0 (0.00)	1 (0.02)	1 (0.02)

North Carolina

Sociodemographic characteristics

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The mean age was 44.5 years (SD =17.2). Prescription opioid poisoning ED visits were more common in adults >50 years old (39%). Children 12 to 18 years old had the least proportion of prescription opioid ED visits among all other age groups. More females were involved compared to males (56.6% and 43.4%, respectively). The majority of prescription opioid poisoning ED visits involved whites (81.4%). About one third of prescription opioid poisoning ED visits were related to people with low income. Medicare was the most common primary payer (29.2%) followed by private insurance (23.8%), self-pay (22.5%), and Medicaid (21.4%). More than two thirds of prescription opioid poisoning ED visits belonged to patients living in urban areas. Description of all sociodemographic is reported in Table 4.11.

Clinical characteristics

Prescription opioid poisoning ED visits were more common in people with at least one chronic condition. More than one third of prescription opioid poisoning ED visits involved people with five or more chronic conditions. About one quarter of ED visits were related to patients diagnosed with depression. Other psychiatric conditions including psychoses, drug abuse and alcohol abuse constituted ≤1% of total prescription opioid poisoning ED visits (Table 4.11).

Table 4. 11: Sociodemographic and clinical characteristics of prescription opioid poisoning ED visits in North Carolina from 2011-2014

Sociodemographic variable	**n (%)**
Age (in years)	
0-17	403 (3.20)
18-25	1723 (13.68)
26-34	1973 (15.66)
35-50	3587 (28.48)
>50	4911 (38.99)
Gender	
Male	5465 (43.39)
Female	7131 (56.61)
Race	
White	10212 (81.44)
Black	1600 (12.76)
Hispanic	226 (1.80)

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Other	502 (4.00)
Primary expected payer	
Medicare	3663 (29.18)
Medicaid	2680 (21.35)
Private insurance	2984 (23.77)
Self-pay	2823 (22.49)
Other	403 (3.21)
Median household income	
Poor	3806 (31.23)
Lower average	3433 (28.17)
Higher average	3088 (25.34)
Rich	1861 (15.27)
Patient location	
Urban	8213 (65.78)
Rural	4272 (34.22)
Clinical variable	
No. of chronic conditions	
0	1137 (9.03)
1	1738 (13.80)
2	1815 (14.41)
3	1708 (13.56)
4	1524 (12.10)
≥5	4676 (37.12)
Psychoses	
Yes	11 (0.09)
No	12587 (99.91)
Alcohol abuse	
Yes	128 (1.02)
No	12470 (98.98)
Drug abuse	
Yes	44 (0.35)
No	12554 (99.65)
Depression	
Yes	3044 (24.16)
No	9554 (75.84)

Description of sociodemographic and clinical characteristics by age group is available in Table 4.12. Prescription opioid poisoning ED visits were more common in males and females >50 years old (33.8% and 42.9%, respectively). Although females were the predominant group across all ages, males had a higher proportion among young adults (18-25 and 26-34 years old). Among white, black, and others prescription opioid poisoning ED visits were more common in adults 35 to 50 years old and >50 years compared to other age groups. Hispanics had similar proportions

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among all adult age groups (i.e. ≥18 years old). Among patients with high income, one quarter of prescription opioid poisoning involved children 12 to 18 years old. Medicaid was the most common primary payer for patients 12 to 17 years old and 35 to 50 years (51.7% and 26.5%, respectively). Among young adults (18- 25 and 26-34 years old), private insurance was the most prevalent primary payer (38.3% and 48.3%, respectively). Medicare was the primary source of payment for about half of prescription opioid ED visits for patients >50 years old.

Prescription opioid ED visits with one chronic condition were more common in children 12 to 17 years old, adults 18 to 25 years, and 26 to 34 years. About two thirds of patients 35 to 50 years old had five or more chronic conditions. Prescription opioid poisoning ED visits with existing diagnosis of depression, alcohol abuse, and drug abuse were more common in patients > 50 years old (Table 4.12).

Table 4. 12: Sociodemographic and clinical characteristics of prescription opioid poisoning ED visits by age group in North Carolina from 2011 to 2014

Characteristics	**Age (in years) n (%)**				
	0 – 17	18 – 25	26 – 34	35 – 50	>50
Gender					
Male	188 (1.49)	940 (7.46)	1035 (8.22)	1453 (11.54)	1848 (14.67)
Female	215 (1.71)	782 (6.21)	938 (7.45)	2134 (16.94)	3062 (24.31)
Race					
White	267 (2.13)	1329 (10.60)	1641 (13.09)	2907 (23.18)	4067 (32.43)
Black	85 (0.68)	259 (2.07)	225 (1.79)	452 (3.60)	579 (4.62)
Hispanic	24 (0.19)	48 (0.38)	50 (0.40)	51 (0.41)	53 (0.42)
Other	26 (0.21)	73 (0.58)	52 (0.41)	161 (1.28)	190 (1.52)
Primary expected payer					
Medicare	0 (0.00)	34 (0.27)	131 (1.04)	801 (6.38)	2697 (21.49)
Medicaid	208 (1.66)	419 (3.34)	486 (3.87)	946 (7.54)	621 (4.95)
Private insurance	154 (1.23)	526 (4.19)	331 (2.64)	845 (6.73)	1128 (8.99)
Self-pay	23 (0.18)	657 (5.23)	945 (7.53)	872 (6.95)	325 (2.59)
Other	17 (0.14)	78 (0.62)	64 (0.51)	111 (0.88)	133 (1.06)
Median household income					
Poor	114 (0.94)	453 (3.72)	562 (4.61)	1065 (8.74)	1611 (13.22)

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Lower average	94 (0.77)	469 (3.85)	557 (4.57)	996 (8.17)	1317 (10.81)
Higher average	89 (0.73)	449 (3.68)	487 (4.00)	887 (7.28)	1176 (9.65)
Rich	101 (0.83)	300 (2.46)	298 (2.45)	521 (4.28)	641 (5.26)
Patient location					
Urban	289 (2.31)	1197 (9.59)	1322 (10.59)	2349 (18.82)	3055 (24.47)
Rural	112 (0.90)	512 (4.10)	628 (5.03)	1205 (9.65)	1815 (14.54)
No. of chronic conditions					
0	117 (0.93)	245 (1.94)	242 (1.92)	278 (2.21)	255 (2.02)
1	143 (1.14)	450 (3.57)	403 (3.20)	432 (3.43)	310 (2.46)
2	64 (0.51)	397 (3.15)	391 (3.10)	528 (4.19)	435 (3.45)
3	44 (0.35)	283 (2.25)	338 (2.68)	530 (4.21)	513 (4.07)
4	20 (0.16)	171 (1.36)	235 (1.87)	523 (4.15)	574 (4.56)
≥ 5	15 (0.12)	177 (1.41)	364 (2.89)	1296 (10.29)	2824 (22.42)
Alcohol abuse					
No	403 (3.20)	1721 (13.66)	1970 (15.64)	3546 (28.15)	4829 (38.33)
Yes	0 (0.00)	2 (0.02)	3 (0.02)	41 (0.33)	82 (0.65)
Drug abuse					
No	401 (3.18)	1716 (13.62)	1966 (15.61)	3579 (28.41)	4891 (38.83)
Yes	2 (0.02)	7 (0.06)	7 (0.06)	8 (0.06)	20 (0.16)
Depression					
No	312 (2.48)	1351 (10.72)	1567 (12.44)	2692 (21.37)	3632 (28.83)
Yes	91 (0.72)	372 (2.95)	406 (3.22)	895 (7.10)	1279 (10.15)
Psychoses					
No	403 (3.20)	1723 (13.68)	1971 (15.65)	3580 (28.42)	4909 (38.97)
Yes	0 (0.00)	0 (0.00)	2 (0.02)	7 (0.06)	2 (0.02)

Sociodemographic and clinical characteristics were further analyzed based by intent of opioid poisoning. Results are reported in Table 4.13. More than half of non-fatal prescription opioid poisoning were accidental. Intentional prescription opioid poisoning ED visits were more common among children 12 to 17 years old. In contrast, accidental poisoning was more common for all adult age groups. Female had a higher proportion of ED visits across all intent as compared to men.

Table 4. 13: Sociodemographic and clinical characteristics of prescription opioid poisoning ED visits by intent of poisoning in North Carolina from 2011 – 2014

Characteristics	**Intent of poisoning n (%)**		
	Unintentional (N=6130)	Intentional (N=3065)	Undetermined (N=1822)
Age (in years)			

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0 – 17	130 (1.18)	180 (1.63)	61 (0.55)
18 – 25	693 (6.29)	564 (5.12)	292 (2.65)
26 – 34	871 (7.91)	557 (5.06)	346 (3.14)
35 – 50	1580 (14.34)	1044 (9.48)	527 (4.78)
>50	2855 (25.92)	720 (6.54)	596 (5.41)
Gender			
Male	2756 (25.02)	1219 (11.07)	845 (7.67)
Female	3372 (30.61)	1846 (16.76)	977 (8.87)
Race			
White	5023 (45.79)	2393 (21.81)	1509 (13.76)
Black	725 (6.61)	491 (4.48)	205 (1.87)
Hispanic	84 (0.77)	64 (0.58)	38 (0.35)
Other	271 (2.47)	107 (0.98)	60 (0.55)
Primary expected payer			
Medicare	2137 (19.48)	520 (4.74)	474 (4.32)
Medicaid	1222 (11.14)	715 (6.52)	430 (3.92)
Private insurance	1359 (12.38)	924 (8.42)	331 (3.02)
Self-pay	1214 (11.06)	772 (7.04)	537 (4.89)
Other	173 (1.58)	119 (1.08)	46 (0.42)
Median household income			
Poor	1906 (17.84)	875 (8.19)	572 (5.35)
Lower average	1680 (15.73)	819 (7.67)	485 (4.54)
Higher average	1452 (13.59)	754 (7.06)	480 (4.49)
Rich	907 (8.49)	526 (4.92)	227 (2.12)
Patient location			
Urban	3861 (35.32)	2116 (19.36)	1167 (10.68)
Rural	2230 (20.40)	913 (8.35)	643 (5.88)
No. of chronic conditions			
0	616 (5.59)	184 (1.67)	194 (1.76)
1	812 (7.37)	459 (4.17)	297 (2.70)
2	763 (6.93)	540 (4.90)	303 (2.75)
3	764 (6.93)	496 (4.50)	235 (2.13)
4	741 (6.73)	443 (4.02)	189 (1.72)
≥ 5	2434 (22.09)	943 (8.56)	604 (5.48)
Alcohol abuse			
No	6076 (55.15)	3043 (27.62)	1800 (16.34)
Yes	54 (0.49)	22 (0.20)	22 (0.20)
Drug abuse			
No	6108 (55.44)	3055 (27.73)	1814 (16.47)
Yes	22 (0.20)	10 (0.09)	8 (0.07)
Depression			
No	4906 (44.53)	1988 (18.04)	1467 (13.32)
Yes	1224 (11.11)	1077 (9.78)	355 (3.22)
Psychoses			
No	6129 (55.63)	3056 (27.74)	1822 (16.54)
Yes	1 (0.01)	9 (0.08)	0 (0.00)

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Aim 2C: To examine associations between patients' sociodemographic and clinical characteristics and prescription opioid poisoning ED visits in Kentucky and North Carolina.

Bivariate analyses were performed using Chi-square test to examine the relationship between various sociodemographic/clinical characteristics and prescription opioid poisoning ED visits. In Kentucky, with the exception of patient location and psychoses, all variables were statistically significant (p-value<0.0001). The largest coefficients were associated with number of chronic conditions, depression, and age (Chi-square = 5514.9, 5233.3, and 444.7, respectively). In North Carolina the results were similar, where with the exception of only psychoses, all variables were significantly associated with prescription opioid poisoning ED visits. The largest coefficients were associated with number of chronic conditions, race, and depression (Chi-square = 10840.8, 8994.5, and 2980.6, respectively).

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Chapter 5

Methods and results for specific aim 3:

A. To compare occurrences of prescription opioid poisoning ED visits pre and post prescriber use mandates in Kentucky.

B. To compare occurrences of prescription opioid poisoning ED visits in Kentucky and North Carolina, after prescriber use mandate implementation.

Section 5.1-Methods

Study design

Controlled pre-post study design. Kentucky and North Carolina represented the intervention state and the control (comparator) state, respectively. Figure 5.1 describes the study design.

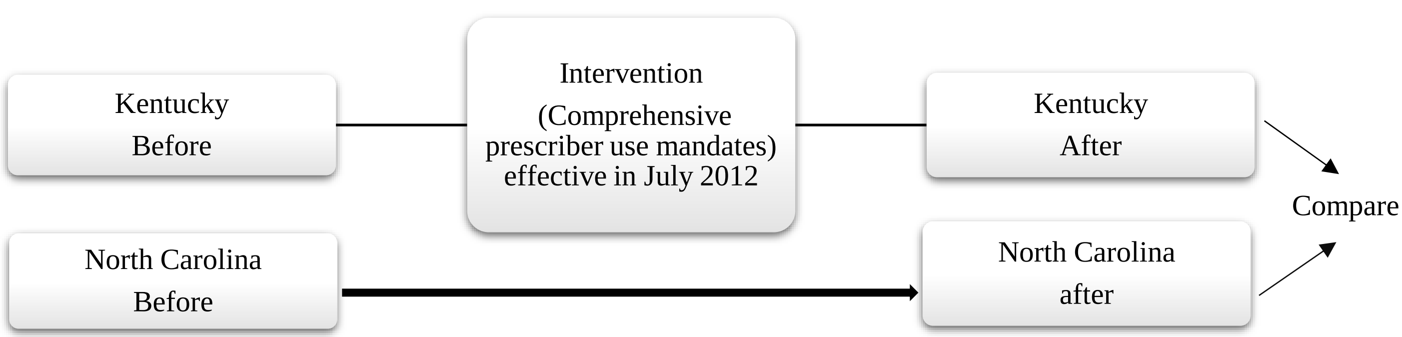

Figure 5. 1: Controlled pre-post study design

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Study settings

Prescription opioid poisoning ED visits in Kentucky and North Carolina for the period 2011 to 2014.

Data source

The SEDD (treat and release ED visits) and the SID (ED visits that resulted in hospital admission) for Kentucky and North Carolina. See section 4.1

Sample

Prescription opioid poisoning ED visits in Kentucky were compared between the years (2011, 2012), (2011, 2013), and (2011, 2014). In addition, comparisons were made between Kentucky and North Carolina utilizing the same sets of years. Sample selection process for specific aim 3A and 3B, including exclusion criteria is illustrated in Figure 5.2 and 5.3, respectively.

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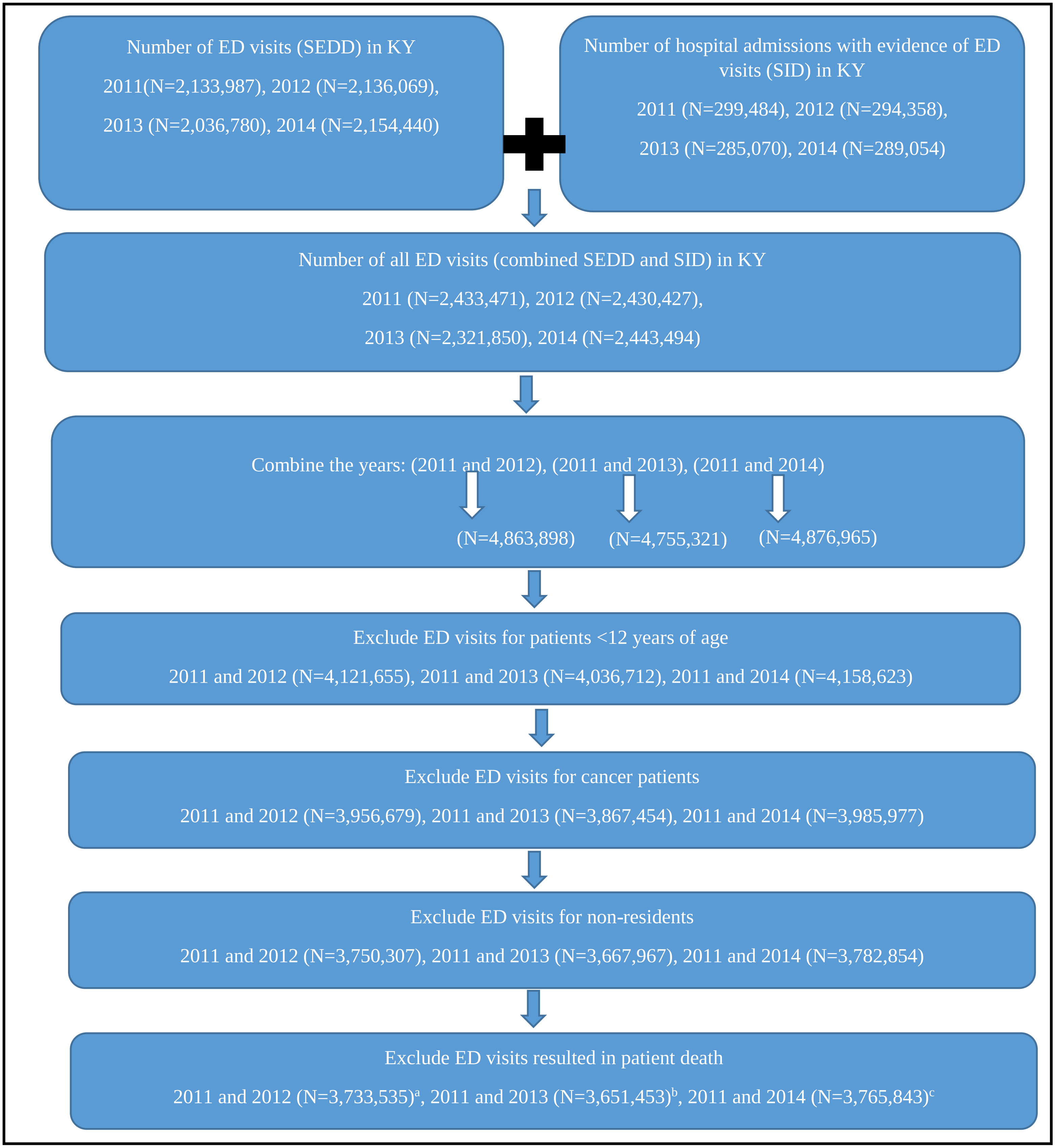

Figure 5. 2: Sample flow chart for specific aim 3A (Kentucky only)

a. Final sample size for the years 2011 and 2012, b. Final sample size for the years 2011 and 2013
c. Final sample size for the years 2011 and 2014

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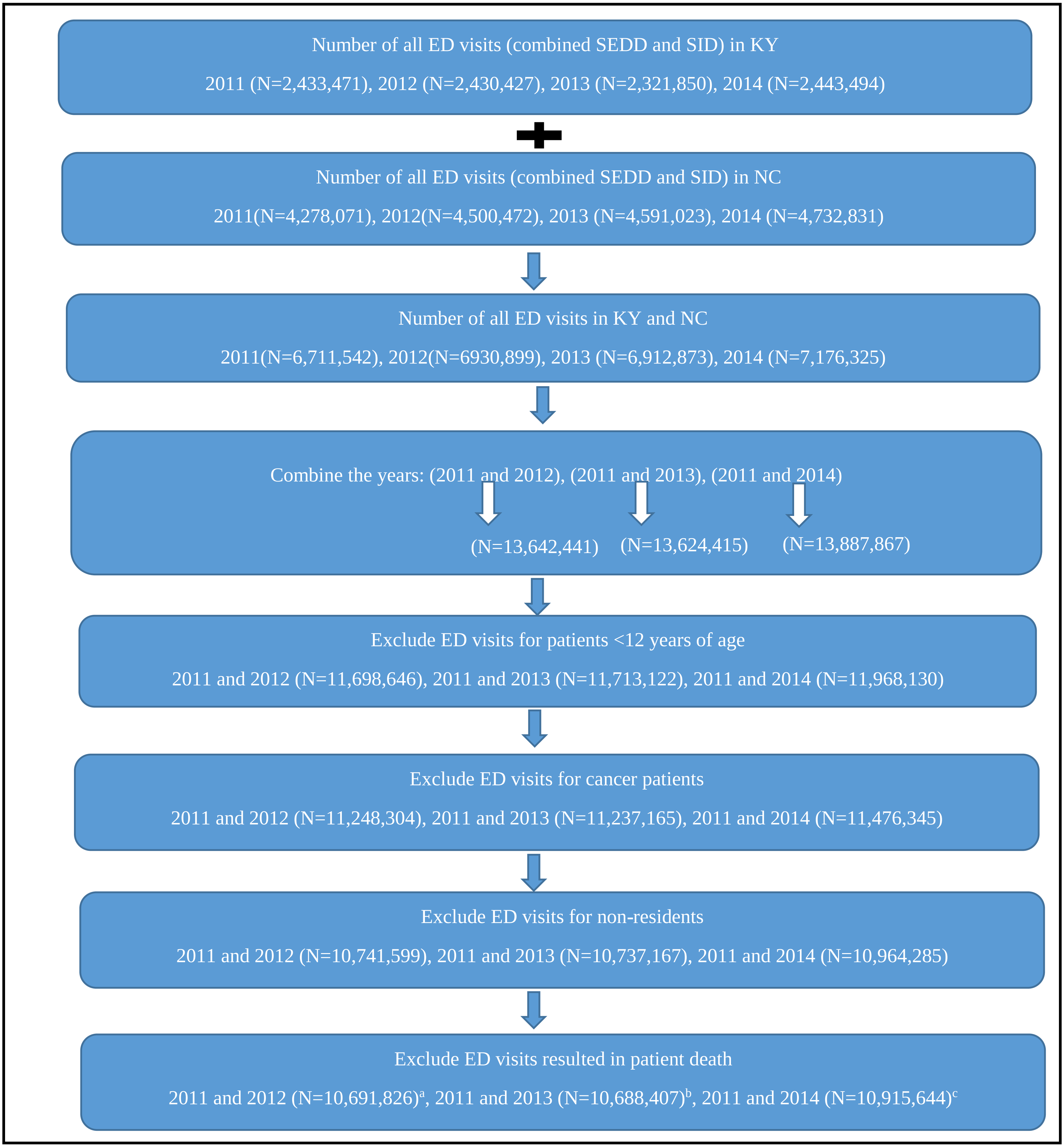

Figure 5. 3: Sample flow chart for specific aim 3B (Kentucky and North Carolina)

a. Final sample size for the years 2011 and 2012, b. Final sample size for the years 2011 and 2013
c. Final sample size for the years 2011 and 2014

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Variables

Main predictor and outcome variables for specific aims 3A and 3B are listed in Table 5.1. Other sociodemographic and clinical variables considered for specific aim 3 are similar to specific aim 2 (Table 4.3). The unit of analysis is the ED visit.

Table 5. 1: Main predictor and outcome variables for specific aims 3A and 3B

Aim	Main predictor variable	Type of variable	Outcome variable	Type of variable
3A	Post	Dichotomous variable: 1 = post mandates (i.e. second half of 2012, 2013, and 2014), 0 = pre-mandates (i.e. 2011 and first half of 2012)	Poisoning_indicator	Dichotomous variable: 1 = yes, 0= no
3B	Mandates*post	Interaction term of two dichotomous variables. Mandates: 1= Kentucky, 0= North Carolina. Post: 1= post mandates (i.e. second half of 2012, 2013 and, 2014), 0 = pre-mandates (i.e. 2011 and first half of 2012)	Poisoning_indicator	Dichotomous variable 1 = yes, 0= no

Statistical analyses

Specific aim 3A:

Multivariable logistic regression analysis was used to examine the impact of prescriber use mandates on prescription opioid poisoning ED visits in Kentucky. A stepwise selection with 0.05 level of significance was used to identify confounders to include in the final model. Three models were created to compare ED visits before and after prescriber use mandates

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implementation in Kentucky. The mandates policy became effective in July 2012, the first set of comparison was made for the years 2011 and 2012. The subsequent set of comparisons included the years (2011, 2013) and (2011, 2014).

Specific aim 3B:

Multivariable logistic regression was used to assess changes in prescription opioid poisoning ED visits relative to prescriber use mandates, in Kentucky and North Carolina. A difference in difference (DID) framework was applied to analyze the casual effect of prescriber use mandates policy on prescription opioid poisoning ED visits. The DID framework is a common analytical technique used to evaluate the impact of policy change.[99, 100] It estimates the difference in changes of an outcome variable over time between the intervention and control group. Three sets of comparison models were conducted including the years (2011, 2012), (2011, 2013), and (2011, 2014). Each model compared the occurrences of prescription opioid poisoning ED visits in Kentucky and North Carolina. The main outcome measure was the occurrence of prescription opioid poisoning ED visit (a binary variable). The main predictor variable was an interaction term of state with time relative to policy implementation. The logistic regression analysis with DID framework can be explained by the following equation:

$$\text{Logit (poisoning\_indicator=1)} = \beta_0 + \beta_1 \text{ mandates} + \beta_2 \text{ post} + \beta_3 \text{ (mandates*post)} + \beta_{(4-n)} X_{(4-n)}$$

- Mandates is a dummy variable for prescriber mandates (1= Kentucky, 0= North Carolina).

- Post is a dummy variable for post mandates period (1= post mandates (i.e. second half of 2012, 2013 and, 2014), 0= pre-mandates (i.e. 2011 and first half of 2012)).

- β_3 is the DID estimator which represents the true effect of mandates:

β_3= (KY post - KY pre) - (NC post - NC pre).

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- $X_{(4-n)}$ are the potential confounders considered in the final model, n = number of confounders.

Scenario analyses

Scenario analyses were performed for specific aim 3B to test the impact of two inclusion criteria on the final estimates:

a. Including only ED visits with prescription opioid poisoning listed as the first diagnosis (variable: DX1). This ensured that prescription opioid poisoning was the main diagnosis or chief compliant responsible for the ED visit or the hospital stay and thus, eliminate overestimation of the study sample.
b. Including only ED visits with unintentional prescription opioid poisoning. The population of interest was patients who abuse prescription opioid and developed a poisoning event as a result of the abuse behavior. Thus, suicide attempts and poisoning events with undetermined intent may not reflect the intended population.

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Section 5.2-Results

Aim 3A: To compare occurrences of prescription opioid poisoning ED visits pre and post prescriber use mandates in Kentucky.

Three logistic regression models were conducted to examine the impact of prescriber use mandates on occurrences of prescription opioid poisoning ED visits. Table 5.2 summarizes results of the logistic regression analysis for the years 2011 and 2012. The final model included the variables listed in Table 5.2 and the interaction term of age with number of chronic conditions. All covariates had a significant relationship with opioid poisoning ED visits (i.e. *p*-value<0.05). Holding all other variables constant, the odds of having an opioid poisoning ED visit in 2012 was 11% (95% CI= 6.0% - 17.0%) less compared to 2011.

Table 5. 2: Adjusted logistic regression for prescription opioid poisoning ED visits in (KY 2011-2012)

	OR	95% CI Lower limit	95% CI Upper limit	Wald Chi-Square (*p*-value)
Year				
2011*	-	-	-	-
2012	0.89	0.83	0.94	10.9668 (0.0009)
Age (in years)				
12 -17	2.57	1.06	6.22	4.3458 (0.0371)
18 -25	2.87	2.06	4.01	38.6180 (<.0001)
26 -34	3.27	2.68	3.98	139.0875 (<.0001)
35 -50	2.34	2.06	2.65	177.6008 (<.0001)
>50*	-	-	-	-
Sex				
Female*	-	-	-	-
Male	1.23	1.16	1.31	42.4909 (<.0001)
Race				
White*	-	-	-	-
Black	0.30	0.25	0.35	190.9968 (<.0001)
Hispanic	0.57	0.38	0.87	6.7231 (0.0095)
Other	0.95	0.71	1.26	0.1326 (0.7157)

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Primary expected payer				
Medicare*				-
Medicaid	1.29	1.17	1.42	24.4983 (<.0001)
Private insurance	0.97	0.88	1.07	0.3761 (0.5397)
Self-pay	1.35	1.22	1.50	31.9044 (<.0001)
Other	1.46	1.28	1.66	32.8242 (<.0001)
Median household income				
Poor*	-	-	-	-
Lower average	0.87	0.80	0.94	11.1926 (0.0008)
Higher average	0.77	0.71	0.84	38.2778 (<.0001)
Rich	0.85	0.78	0.94	11.4361 (0.0007)
No. of chronic conditions				
0	0.19	0.15	0.23	210.6224 (<.0001)
1	0.26	0.21	0.33	142.2541 (<.0001)
2	0.38	0.31	0.46	87.3323 (<.0001)
3	0.49	0.40	0.60	50.1801 (<.0001)
4	0.78	0.66	0.94	7.3415 (0.0067)
5*	-	-	-	-
Drug abuse				
No	0.05	0.01	0.20	16.8625 (<.0001)
Yes*	-	-	-	-
Depression				
No	0.40	0.37	0.44	518.7315 (<.0001)
Yes*	-	-	-	-

Note: OR= odds ratio; CI= confidence interval
* Reference category

The following models for years 2011, 2013 and 2011, 2014 included the same covariates as the final model above. The second logistic regression model compared occurrences of prescription opioid poisoning ED visits between the years 2011 and 2013. Results of the adjusted analysis are summarized in Table 5.3. All covariates were statistically significant (i.e. *p*-value <0.05). Holding all other variables constant, the odds of having an opioid poisoning ED visit in 2013 was 33% (95% CI= 28.0% - 37.0%) less compared to 2011.

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Table 5. 3: Adjusted logistic regression for prescription opioid poisoning ED visits (KY 2011-2013)

	OR	95% CI Lower limit	Upper limit	Wald Chi-Square (*p*-value)
Year				
2011*	-	-	-	-
2013	0.67	0.63	0.72	140.1676 (<.0001)
Age (in years)				
12 -17	3.90	1.84	8.27	12.5565 (0.0004)
18 -25	2.16	1.45	3.21	14.3199 (0.0002)
26 -34	3.02	2.30	3.53	91.1886 (<.0001)
35 -50	2.41	2.12	2.74	180.7251 (<.0001)
>50*	-	-	-	-
Sex				
Female*	-	-	-	-
Male	1.20	1.12	1.28	28.0746 (<.0001)
Race				
White*	-	-	-	-
Black	0.33	0.27	0.39	155.9573 (<.0001)
Hispanic	1.20	0.95	1.53	2.3506 (0.1252)
Other	0.70	0.45	1.10	2.4134 (0.1203)
Primary expected payer				
Medicare*	-	-	-	-
Medicaid	1.20	1.08	1.34	11.3530 (0.0008)
Private insurance	0.90	0.80	1.00	4.0724 (0.0436)
Self-pay	1.35	1.21	1.50	28.8509 (<.0001)
Other	1.28	1.11	1.48	11.8466 (0.0006)
Median household income				
Poor*	-	-	-	-
Lower average	0.90	0.82	0.98	6.0363 (0.0140)
Higher average	0.84	0.77	0.92	14.0983 (0.0002)
Rich	0.94	0.86	1.04	1.4479 (0.2289)
No. of chronic conditions				
0	0.20	0.16	0.25	180.8271 (<.0001)
1	0.26	0.20	0.33	127.9302 (<.0001)
2	0.36	0.28	0.44	83.0225 (<.0001)
3	0.51	0.42	0.63	41.2326 (<.0001)
4	0.82	0.69	0.99	4.2864 (0.0384)
5*	-	-	-	-
Drug abuse				
No	0.05	0.01	0.20	17.1835 (<.0001)
Yes*	-	-	-	-
Depression				

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No	0.40	0.37	0.43	470.7818 (<.0001)
Yes*	-	-	-	-

Note: OR = odds ratio; CI = confidence interval
*Reference category

The third regression model compared occurrences of prescription opioid poisoning ED visits between the years 2011 and 2014. Results of the adjusted analysis are summarized in Table 5.4. All covariates were statistically significant (i.e. *p*-value <0.05) except for drug abuse. Holding all other variables constant, the odds of having an opioid poisoning ED visit in 2014 was 35.0% (95% CI= 30.0%- 39.0%) less compared to 2011.

Table 5. 4: Adjusted logistic regression for prescription opioid poisoning ED visits (KY 2011-2014)

	OR	**95% CI**		**Wald**
		Lower limit	**Upper limit**	**Chi-Square (*p*-value)**
Year				
2011*	-	-	-	-
2014	0.65	0.61	0.70	86.9103 (<.0001)
Age category (years)				
12 -17	2.61	1.16	5.85	5.3772 (0.0204)
18 -25	2.17	1.51	3.13	17.2781 (<.0001)
26 -34	2.53	2.05	3.12	74.8696 (<.0001)
35 -50	2.06	1.81	2.34	124.9205 (<.0001)
>50*	-	-	-	-
Sex				
Female*	-	-	-	-
Male	1.21	1.13	1.29	31.5105 (<.0001)
Race				
White*	-	-	-	-
Black	0.33	0.28	0.39	160.7185 (<.0001)
Hispanic	0.94	0.70	1.27	0.1589 (0.6901)
Other	0.73	0.51	1.05	2.8720 (0.0901)
Primary expected payer				
Medicare*	-	-	-	-
Medicaid	1.33	1.20	1.47	31.4368 (<.0001)
Private insurance	0.96	0.86	1.06	0.6929 (0.4052)
Self-pay	1.42	1.26	1.60	33.5470 (<.0001)
Other	1.38	1.19	1.61	17.5406 (<.0001)
Median household income				
Poor*	-	-	-	-

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Lower average	0.86	0.79	0.94	11.7200 (0.0006)
Higher average	0.78	0.71	0.85	32.3057 (<.0001)
Rich	0.92	0.83	1.01	3.3122 (0.0688)
No. of chronic conditions				
0	0.19	0.15	0.24	200.2151 (<.0001)
1	0.24	0.19	0.30	148.4039 (<.0001)
2	0.33	0.27	0.42	98.5405 (<.0001)
3	0.46	0.37	0.56	57.2555 (<.0001)
4	0.70	0.59	0.85	13.8377 (0.0002)
5*	-	-	-	-
Drug abuse				
No	0.51	0.19	1.36	1.8345 (0.1756)
Yes*	-	-	-	-
Depression				
No	0.40	0.37	0.44	470.2845 (<.0001)
Yes*	-	-	-	-

Note: OR= odds ratio; CI= confidence interval
*Reference category

<u>Aim 3B: To compare occurrences of prescription opioid poisoning ED visits in Kentucky and North Carolina, after prescriber use mandate implementation</u>

Logistic regression model (KY and NC 2011-2012)

All variables listed in Table 4.3 were considered for inclusion in the model. The selection of these variables was based on the existing literature, which supports their association with opioid abuse. The logistic regression model was used to assess changes in prescription opioid poisoning ED visits relative to prescriber use mandates, in Kentucky and North Carolina for the years 2011 and 2012. A stepwise selection with 0.05 level of significance was applied. The stepwise selection works by removing or adding variables during the various steps of model building. The stepwise selection resulted in a model not including the interaction term (state*post), the state variable, and the variables: psychoses, alcohol abuse, and patient location. This means that these variables were not significantly associated with prescription opioid poisoning ED visits.

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The interaction term (state*post) and the state variable were forced as regressors in the final model. Variables sometimes need to be forced into regression equations because they are necessary to conduct the analysis. The resultant model experienced poor fit (Pearson Goodness-of-Fit Statistic: Value/DF=1.76, *p*-value <0.0001).

To enhance model fit, a PROC GENMOD procedure was used with logit link function; the resultant models did not show any improvement. The PROC GENMOD procedure conducts a generalized linear model, which is a large class of models containing logistic regression model and others. The advantage of PROC GENMOD is the possibility of using other links to improve the fit of the model. Also, adding interaction terms of age with all other covariates did not improve model fit. However, single inclusion of the interaction term of age with number of chronic conditions showed a better model fit (based on -2 Log L).

The final model included the variables listed in Table 5.5 and an interaction term of age with number of chronic conditions. All covariates, including the main predictor variable, were significantly associated with prescription opioid poisoning ED visit (i.e. *p*-value <0.05). Holding all other variables constant, the odds of having an opioid poisoning ED visit in Kentucky compared to North Carolina is 9% (95% CI= 1% - 16%) less in 2012 compared to 2011. Hence, there is a 9% reduction in likelihood of prescription opioid poisoning ED visit going from 2011 to 2012 in Kentucky, controlling for North Carolina in the model. To recall, prescriber use mandates policy was implemented in Kentucky in July 2012; thus, the reduction in the odds of having an opioid poisoning ED visit may be related to the policy.

The odds of having an opioid poisoning ED visit varied according to other model variables. The odds were significantly higher among 18 to 25 years old, 26 to 34 years, and 35 to 50 years compared to those >50 years old; however, no significant difference in these odds for children 12

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to 17 years old compared to adults >50 years. Males were 1.2 (95% CI= 1.1 - 1.2) more likely to experience an opioid poisoning ED visit compared to females. Black and Hispanic were 69.5% (95% CI= 67.2% – 71.6%) and 54.1% (95% CI= 44.3% - 62.3%) less likely to have an opioid poisoning ED visit compared to white. The odds of an opioid poisoning ED visit were significantly lower among patients with median household income in the second and third quartile compared to those in the first quartile. Medicaid and self-pay patients had 1.1(95% CI= 1.1 - 1.2) and 1.1 (95% CI=1.05 - 1.20) higher odds of an opioid poisoning ED visit compared to Medicare patients. On the other hand, the odds of an opioid poisoning ED visit were 9% (95% CI= 3.1% - 14.4%) less when the primary payer is a private insurance compared to Medicare. Patients not diagnosed with depression or did not have a previous history of drug abuse were 58% (95% CI= 56.0% - 60.0%) and 84% (95% CI= 73.0% - 90.0%) less likely to develop an opioid poisoning ED visit compared to their counterparts. Patients with no chronic conditions were 80% (95% CI= 77% - 83%) less likely to have an opioid poisoning ED visit compared to those with five or more chronic conditions. Similarly, these odds were significantly lower for patients with one to four chronic conditions as compared to those having five or more chronic conditions. The association of the number of chronic conditions with opioid poisoning ED visits varied by age. The odds of an opioid poisoning ED visit for patients with no chronic conditions were not significantly different in patients 35 to 50 years old compared to > 50 years. On the other hand, these odds were significantly lower in other age groups compared to those >50 years old. Among patients with five or more chronic conditions, the odds of an opioid poisoning ED visit were significantly different in adults 18 to 25 years old, 26 to 34 years, and 35 to 50 years compared to > 50 years; however, these odds were not significantly different in children 12 to 17 years compared to adults >50 years. The odds of an opioid poisoning ED visit for patients with

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one to four chronic conditions were significantly different comparing all age groups to > 50 years old.

Table 5. 5: Adjusted logistic regression for prescription opioid poisoning ED visits (KY and NC 2011-2012)

	OR	95% CI Lower limit	Upper limit	Wald Chi-Square (*p*-value)
Year				
2011*	-	-	-	-
2012	0.97	0.92	1.02	1.5355 (0.2153)
State				
KY	1.14	1.08	1.21	19.6692 (<.0001)
NC*	-	-	-	
Mandates*post:				
KY*2012	**0.91**	**0.84**	**0.99**	**4.7572 (0.0292)**
Age (in years)				
12 -17	1.41	0.67	2.97	0.8156 (0.3665)
18 -25	3.47	2.86	4.21	158.6206 (<.0001)
26 -34	2.86	2.50	3.27	230.9870 (<.0001)
35 -50	2.15	1.98	2.33	330.761 (<.0001)
>50*	-	-	-	-
Sex				
Female*	-	-	-	-
Male	1.16	1.11	1.21	50.7203 (<.0001)
Race				
White*	-	-	-	-
Black	0.31	0.28	0.33	1031.9464 (<.0001)
Hispanic	0.46	0.38	0.56	61.1671 (<.0001)
Other	1.04	0.93	1.17	0.4599 (0.4977)
Primary expected payer				
Medicare*	-	-	-	-
Medicaid	1.14	1.07	1.22	15.9351 (<.0001)
Private insurance	0.91	0.86	0.97	8.8403 (0.0029)
Self-pay	1.13	1.05	1.20	12.1622 (0.0005)
Other	1.31	1.19	1.44	30.7756 (<.0001)
Median household income				
Poor*				
Lower average	0.90	0.85	0.95	16.9101 (<.0001)
Higher average	0.94	0.89	0.99	5.4201 (0.0199)
Rich	0.96	0.91	1.02	1.5666 (0.2107)
No. of chronic conditions				
0	0.20	0.17	0.23	469.431 (<.0001)
1	0.30	0.27	0.35	314.1063 (<.0001)

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2	0.42	0.38	0.48	200.2062 (<.0001)
3	0.61	0.55	0.68	82.0078 (<.0001)
4	0.76	0.68	0.85	25.6835 (<.0001)
5*	-	-	-	-
Drug abuse				
No	0.16	0.10	0.27	48.8300 (<.0001)
Yes*	-	-	-	-
Depression				
No	0.42	0.40	0.44	1140.7458 (<.0001)
Yes*	-	-	-	-

Note: OR = odds ratio; CI= confidence interval
* Reference category

Results of the adjusted analysis for the years 2011 and 2013 are summarized in Table 5.6. All covariates were statistically significant (i.e. *p*-value <0.05). Holding all other variables constant, the odds of having an opioid poisoning ED visit in Kentucky compared to North Carolina is 30% (95% CI= 24% - 35%) lower in 2013 compared to 2011. So, these odds were reduced by three-fold compared to the reduction in 2012. The odds of having an opioid poisoning ED visit were significantly higher among all other age groups compared to those >50 years old. Males were 1.14 (95% CI= 1.1 - 1.2) more likely to experience an opioid poisoning ED visit compared to females. Black and Hispanic were 67.5% (95% CI= 65.2% - 69.7%) and 37.4% (95% CI=26.6% - 46.6%) less likely to have an opioid poisoning ED visit compared to white. The odds of an opioid poisoning ED visit were 8.0% (95% CI= 3.0% - 12.0%) lower for patients with median household income in the second quartile compared to those in the first quartile. Medicaid and self-pay patients had 1.2 (95% CI= 1.1 - 1.3) and 1.14 (95% CI= 1.1 - 1.2) higher odds of an opioid poisoning ED visit compared to Medicare patients. On the other hand, the odds of an opioid poisoning ED visit were 8.3% (95% CI=2.4 % - 13.8%) less when the primary payer is a private insurance compared to Medicare. Patients not diagnosed with depression or did not have a previous history of drug abuse were 55.0% (95% CI= 53.0% - 58.0%) and 83.0% (95% CI= 75.0% - 88.0%) less likely to develop an opioid poisoning ED visit compared to their counterparts. Patients with no chronic conditions were 83% (95% CI= 80% - 85%) less likely to

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have an opioid poisoning ED visit compared to those with five or more chronic conditions. Similarly, these odds were significantly lower for patients with one to four chronic conditions as compared to those having more than five chronic conditions.

The association of the number of chronic conditions with opioid poisoning ED visits varied by age. The odds of an opioid poisoning ED visit for patients with no chronic conditions were not significantly different in patients 26 to 34 years old and 35 to 50 years compared to > 50 years. In contrast, these odds were significantly lower among other age groups compared to the reference age group. Among patients with four chronic conditions, the odds of an opioid poisoning ED visit were not significantly different in children 12 to 17 years old compared to adults >50 years; however, these odds were significantly higher in all age groups compared to those >50 years old. Among patients with five or more chronic conditions, the odds of an opioid poisoning ED visit were not significantly different in adults 18 to 25 years old compared to > 50 years; however, these odds were significantly higher in children 12 to 17 years old, adults 26 to 34 years, and 35 to 50 years compared to adults >50 years. The odds of an opioid poisoning ED visit for patients with one to three chronic conditions were significantly higher comparing all age groups to > 50 years old.

Table 5. 6: Adjusted logistic regression for prescription opioid poisoning ED visits (KY and NC 2011-2013)

	OR	**95% CI** **Lower limit**	 **Upper limit**	**Wald Chi-Square (*p*-value)**
Year				
2011*	-	-	-	-
2013	0.97	0.92	1.02	1.6341 (0.2011)
State				
KY	1.15	1.08	1.21	21.8591 (<.0001)
NC*	-	-	-	-
Mandates*post:				

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KY*2013	**0.70**	**0.65**	**0.76**	**69.5745 (<.0001)**
Age (in years)				
12 -17	2.39	1.38	4.13	9.6482 (0.0019)
18 -25	2.66	2.16	3.28	83.6690 (<.0001)
26 -34	2.73	2.39	3.12	222.8204 (<.0001)
35 -50	2.09	1.93	2.26	322.1580 (<.0001)
>50*	-	-	-	-
Sex				
Female*	-	-	-	-
Male	1.14	1.09	1.19	38.4994 (<.0001)
Race				
White*	-	-	-	-
Black	0.33	0.30	0.35	987.9433 (<.0001)
Hispanic	0.63	0.53	0.73	33.3024 (<.0001)
Other	1.00	0.88	1.13	0.0000 (0.9971)
Primary expected payer				
Medicare*	-	-	-	-
Medicaid	1.18	1.10	1.26	24.2162 (<.0001)
Private insurance	0.92	0.86	0.98	7.3700 (0.0066)
Self-pay	1.14	1.06	1.22	14.1759 (0.0002)
Other	1.26	1.14	1.39	19.6974 (<.0001)
Median household income				
Poor*	-	-	-	-
Lower average	0.92	0.88	0.97	8.7359 (0.0031)
Higher average	0.98	0.93	1.04	0.3267 (0.5676)
Rich	1.00	0.94	1.07	0.0013 (0.9716)
No. of chronic conditions				
0	0.17	0.15	0.20	508.7096 (<.0001)
1	0.27	0.24	0.31	356.7509 (<.0001)
2	0.38	0.33	0.43	242.8057 (<.0001)
3	0.54	0.48	0.66	119.5279 (<.0001)
4	0.71	0.64	0.79	39.6031 (<.0001)
5*	-	-	-	-
Drug abuse				
No	0.17	0.12	0.25	86.4097 (<.0001)
Yes*	-	-	-	-
Depression				
No	0.445	0.423	0.469	970.2113 (<.0001)
Yes*	-	-	-	-

Note: OR = odds ratio; CI= confidence interval
* Reference category

The last model compared occurrences of prescription opioid poisoning ED visits in Kentucky and North Carolina for the years 2011 and 2014. Results of the adjusted analysis are summarized in Table 5.7. All covariates were statistically significant (i.e. *p*-value <0.05). Holding all other

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variables constant, the odds of having an opioid poisoning ED visit in Kentucky compared to North Carolina is 29.8% (95% CI= 24.0% - 35.0%) lower in 2014 compared to 2011. Thus, no further reduction in these odds was noticed in 2014 as compared to 2013.The odds of having an opioid poisoning ED visit were significantly higher among all other age groups compared to those >50 years old. Males were 1.15 (95% CI= 1.1 - 1.2) more likely to experience an opioid poisoning ED visit compared to females. Black and Hispanic were 69.5% (95% CI= 67.2% - 71.6%) and 37.5% (95% CI=26.9% - 46.6%) less likely to have an opioid poisoning ED visit compared to white. The odds of an opioid poisoning ED visit were not significantly different among patients with median household income in the third and fourth quartile compared to those in the first quartile. Medicaid and self-pay patients had 1.2 (95% CI= 1.1 - 1.3) and 1.2 (95% CI= 1.1 - 1.3) higher odds of an opioid poisoning ED visit compared to Medicare patients. On the other hand, the odds of an opioid poisoning ED visit were 6.2% (95% CI=0.0% - 11.8%) less when the primary payer is a private insurance compared to Medicare. Patients not diagnosed with depression or did not have a previous history of drug abuse were 56.0% (95% CI= 53.0% - 58.0%) and 73.0% (95% CI= 59.0% - 82.0%) less likely to have an opioid poisoning ED visit compared to none. Patients with no chronic conditions were 81% (95% CI= 78% - 83%) less likely to have an opioid poisoning ED visit compared to those with five or more chronic conditions. Similarly, these odds were significantly lower for patients with one to four chronic conditions as compared to those having five or more chronic conditions. The association of the number of chronic conditions with opioid poisoning ED visits varied by age. The odds of an opioid poisoning ED visit for patients with no chronic conditions were significantly lower in patients 12 to 17 years old, 18 to 25 years, 26 to 34 years, and 35 to 50 years compared to > 50 years. Among patients with one to four chronic conditions, the odds of an opioid poisoning ED

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visit were significantly higher in all age groups compared to adults >50 years. However, for patients with five or more chronic conditions, these odds were not significantly different in all age groups compared to those >50 years old.

Table 5. 7: Adjusted logistic regression for prescription opioid poisoning ED visits (KY and NC 2011-2014)

	OR	95% CI Lower limit	95% CI Upper limit	Wald Chi-Square (*p*-value)
Year				
2011*	-	-	-	-
2014	0.92	0.87	0.97	10.5260 (0.0012)
State				
KY	1.14	1.08	1.21	19.6814 (<.0001)
NC*	-	-	-	-
Mandates*post: KY*2014	**0.70**	**0.65**	**0.76**	**69.4210 (<.0001)**
Age (in years)				
12 -17	1.99	1.17	3.38	6.5185 (0.0107)
18 -25	2.72	2.23	3.31	98.6129 (<.0001)
26 -34	2.48	2.18	2.83	182.7046 (<.0001)
35 -50	1.93	1.78	2.09	259.3394 (<.0001)
>50*	-	-	-	-
Sex				
Female*	-	-	-	-
Male	1.15	1.10	1.20	44.4086 (<.0001)
Race				
White*	-	-	-	-
Black	0.31	0.28	0.33	1074.5333 (<.0001)
Hispanic	0.63	0.53	0.73	34.3520 (<.0001)
Other	0.99	0.88	1.12	0.0223 (0.8813)
Primary expected payer				
Medicare*	-	-	-	-
Medicaid	1.22	1.15	1.30	37.4521 (<.0001)
Private insurance	0.94	0.88	1.00	4.1854 (0.0408)
Self-pay	1.20	1.12	1.29	26.6587 (<.0001)
Other	1.28	1.15	1.43	21.1647 (<.0001)
Median household income				
Poor*	-	-	-	-
Lower average	0.946	0.898	0.997	4.2286 (0.0397)
Higher average	0.962	0.912	1.015	2.0029 (0.1570)
Rich	0.996	0.937	1.059	0.0135 (0.9076)

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No. of chronic conditions				
0	0.19	0.167	0.22	499.3691 (<.0001)
1	0.25	0.22	0.29	389.0633 (<.0001)
2	0.36	0.32	0.41	270.0749 (<.0001)
3	0.51	0.46	0.57	138.9470 (<.0001)
4	0.68	0.61	0.76	51.2393 (<.0001)
5*	-	-	-	-
Drug abuse				
No	0.27	0.18	0.41	37.3729 (<.0001)
Yes*	-	-	-	-
Depression				
No	0.44	0.42	0.47	989.6249 (<.0001)
Yes*	-	-	-	-

Note: OR= odds ratio; CI= confidence interval
*Reference category

Scenario analyses

a. Including ED visits with prescription opioid poisoning listed as the first diagnosis (DX1):

   The adjusted analyses were conducted including only ED visits with prescription opioid poisoning listed as the first diagnosis using the variable DX1. All regression models had better fit compared to the baseline models as indicated by lower value of -2 Log L. This means that the ability to predict the observed outcome is better in these models compared to the base case models. Also, results of the scenario analyses for models that compared years 2013 and 2014 to 2011 indicated significant reduction in prescription opioid poisoning ED visits in Kentucky compared to North Carolina. However, results of the scenario analysis reported no significant difference in the likelihood of prescription opioid poisoning ED visits between years 2011 and 2012 for Kentucky and North Carolina.

b. Considering only unintentional prescription opioid poisoning ED visits:

   The adjusted analyses were conducted considering only ED visits with unintentional prescription opioid poisoning. All models experienced good fit based on Pearson

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Goodness-of-Fit Statistic. Also, the models had better fit compared to the baseline models as indicated by lower value of -2 Log L. Holding all other variables constant, the odds of having an opioid poisoning ED visit was not significantly different in Kentucky than North Carolina comparing the years 2011 and 2012. However, these odds were significantly lower comparing 2013 and 2014 to 2011.

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Chapter 6

Methods and results for specific aim 4:

A. To estimate the direct medical costs associated with prescription opioid poisoning ED visits in Kentucky and North Carolina.

B. To estimate the economic impact of prescriber use mandates in Kentucky.

Section 6.1 Methods

Conceptual framework

Opioid poisoning is a life-threatening condition characterized mainly by respiratory depression; but, it is reversible. Patients who develop an opioid poisoning event need to be transferred to the ED for immediate medical intervention, although some patients may refuse medical help for fear of legal issues or the use of an opioid antagonist available to the community. Most patients transferred to the ED are treated and released. Others may be admitted to the hospital for further medical supervision. In some cases, patients die during the ED visit or the hospital stay.

Figure 6.1 illustrates the conceptual model for patients who develop an opioid poisoning event. Costs are incurred in every step of the model. From a societal perspective, they include direct, indirect, and intangible costs. Direct costs are associated with delivery of care, including all cost that incur while treating patients in the ED or during hospital admission.

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Direct non-medical costs include services that help in the provision of care such as transportation cost. Indirect costs are associated with loss of productivity due to illness (e.g. absenteeism). Intangible costs are hard to measure in monetary value, but include feeling, dissatisfaction, and confusion.

The economic burden of prescription opioid poisoning was assessed from a societal perspective. When a societal perspective is used, three main types of costs are typically considered: direct costs, indirect costs, and intangible costs. However, the current study was interested in output costs resulting from resource utilization associated with prescription opioid poisoning ED visits.

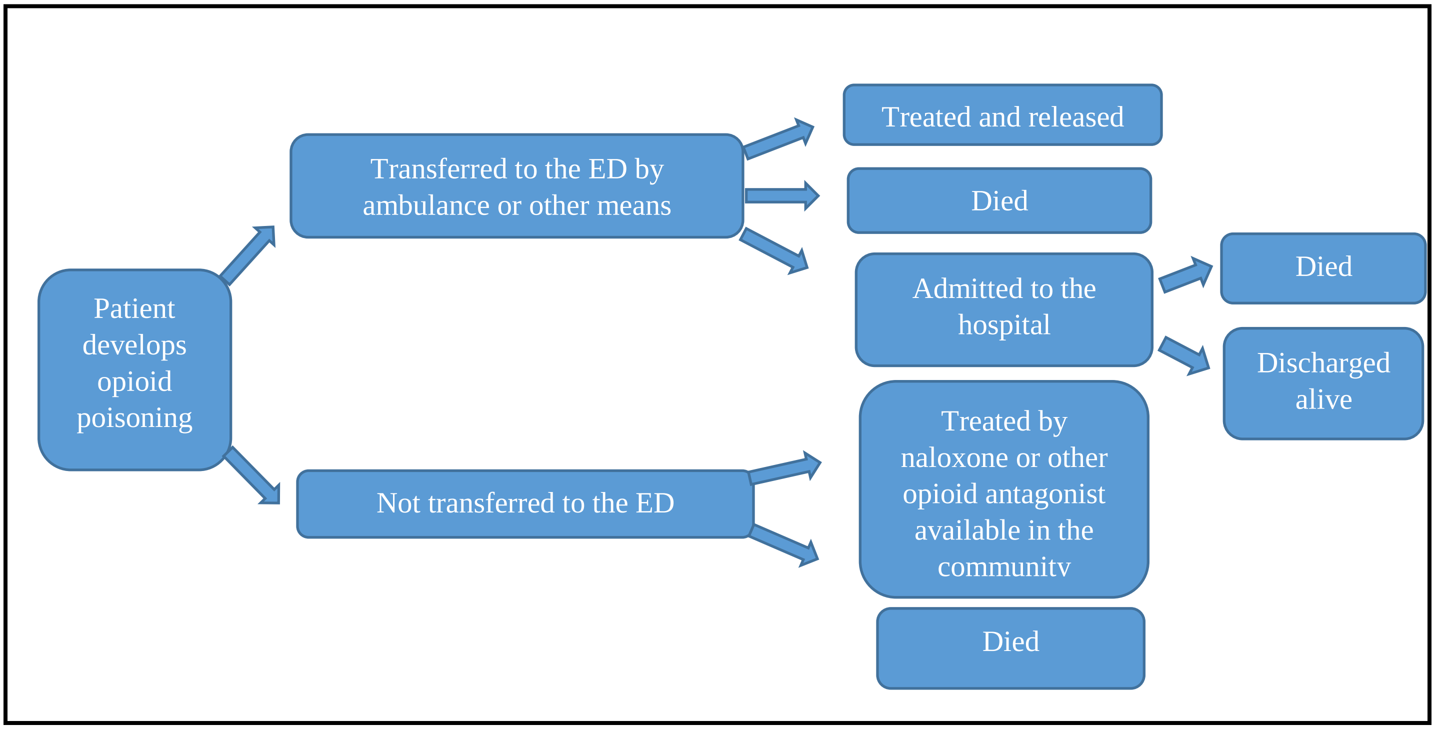

Figure 6. 1: Conceptual model for treating patients who develop opioid poisoning

Study design

Data from current literature was used to develop a cost of illness framework (Figure 6.1). In the model, direct medical costs of prescription opioid poisoning (associated with ED visits) were investigated. Costs associated with inpatients stays, indirect, and intangible costs were not

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considered. Direct medical costs associated with ED visits were estimated over one-year period using a bottom up approach. In this approach, the average unit cost (i.e. costs per ED visit) is multiplied by its prevalence (i.e. number of ED visits). Yearly healthcare inflation rates were used to convert all cost estimates to 2018 monetary values.

Study setting

Prescription opioid poisoning ED visits (including ED visits that resulted in hospital admission) in Kentucky and North Carolina for the years 2011 to 2014.

Data source

The SEDD (treat and release ED visits) and the SID (ED visits that resulted in hospital admission) for Kentucky and North Carolina. See section 4.1.

Sample

Inclusion and exclusion criteria can be found in section 4.1. The final sample size for Kentucky and North Carolina for the years 2011 – 2014 is reported in Table 6.1.

Table 6. 1: Final sample size for specific aim 4

State	Sample size (n)				Total
	2011	2012	2013	2014	
Kentucky	2189	2037	1553	1640	7,419
North Carolina	2949	3101	3292	3256	12,598

Direct medical costs

Direct medical costs considered in this study were costs of utilizing the ED (including treat and release ED visits and ED visits that resulted in hospital stays), physician ED service costs, and ambulance service costs. The current study focuses on ED visits related to prescription opioid

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poisoning and thus, estimated costs associated with ED visits. Costs of inpatient stays is another type of direct medical costs associated with prescription opioid poisoning; however, these costs were not considered in this study. Also, due to data limitation, costs associated with other direct medical costs such as physician office cost, were not considered.

Costs of ED visit

Treat and Release

Total ED visits costs were estimated by multiplying average cost per ED visit by the number of ED visits in Kentucky and North Carolina over four years period. Prescription opioid poisoning ED visits were identified using ICD-9-CM codes listed in Table 4.1. Prescription opioid poisoning ED visits in any listed diagnosis were considered. Costs per ED visit included cost of utilizing the ED and physician fee. Cost of utilizing the ED was obtained using the variable (TOTCHG), which represents total charge per visit. Physician fee costs were estimated by linking CPT-4 procedure codes to the publicly available Medicare Physician Fee Schedule (MPFS). The latter was created by the Centers for Medicare and Medicaid Services (CMS) and contain payment information for services provided by enrolled healthcare professionals. There are up to 25 CPT-4 procedure code recorded for each ED visit in the SEDD. However, only CPT-4 codes that describe physician visit to the ED were considered for the estimation of ED physician costs; these are 99281, 99282, 99283, 99284, and 99285. The latter was used to describe an ED visit for the evaluation and management of a patient, which requires these three key components: a comprehensive history, a comprehensive examination, and Medical decision making of high complexity.[101] These characteristics may describe physician visit to the ED for an opioid poisoning case and thus, the code 99285 was used for the cost analysis. This was applied for all prescription opioid poisoning ED visits and the total physician fee costs were

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calculated. The physician fee cost and the average cost of utilizing the ED were used to estimate total treat and release ED visits related costs.

Costs of ED visits that ended with hospital admissions

This section explains the methods used to estimate costs of ED visits that resulted in hospital admissions; however, costs of hospital admissions were not calculated in this study. ED visits that ended in hospital stays were obtained from the SID databases. To recall, the SID provide information on ED visits that ended with inpatient stays. Information on these ED visits are not available in the SEDD. Inpatient stays with evidence of ED visits related to prescription opioid poisoning were identified using ICD-9-CM codes listed in Table 4.1. Prescription opioid poisoning ED visits in any listed diagnosis were considered. To identify the charge of each ED visit, revenue center codes from the detail charge files were utilized. There are up to ten revenue codes (450 – 459) that can be reported on a discharge record that indicate ED services. Each revenue code has a corresponding charge; multiple revenue codes may be recorded for the same visit. To estimate total charge per ED visit, all revenue codes with their corresponding charges for that ED visit were considered. Unlike the SEDD, the SID do not provide CPT-4 codes. To estimate ED physician fee costs, CPT-4 code (99285) was used. The physician fee cost and the average cost of utilizing the ED were used to estimate total costs of ED visits that resulted in hospital stays.

Ambulance service costs

Ambulance service costs represent direct medical costs that might be incurred in prescription opioid poisoning ED visits. The proportion of ED visits that require ambulance service was assumed to be 38.2% based on a national study of ambulance transport for mental health problems.[102] This proportion was applied to all ED visits (i.e. treat and release ED visits and ED

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visits that resulted in hospital stays) to estimate the number of ED visits that require ambulance assistance. Ambulance service costs were obtained from the Ambulance Fee Schedule (AFS), which was created by the CMS in 2002 and updated annually. AFS provides payment information on state level. HCPCS codes for ambulance services were used to identify payment amount listed in the AFS. HCPCS code considered in this study and its associated payment amount is listed in Table 6.2. Total ambulance service cost was obtained by aggregating cost of ground ambulance services for all ED visits requiring ambulance service. Total ambulance service costs were estimated for Kentucky and North Carolina over a four-year period.

Table 6. 2: HCPCS code for ambulance services and its reimbursement (in 2018 USD)

HCPCS code	**Description**	**Payment amount[a,b] ($)**	
		KY	NC
A0427	Ambulance service, advanced life support, emergency transport, level 1 (ALS 1 – emergency)	375.77	397.54

a. Obtained from the 2018 AFS for the corresponding state.
b. Based on the equation: base rate* Geographic Practice Cost Index (GPCI)* Relative Value Units (RVU). For KY payment amount = 224.74* 0.88* 1.9 = $375.77; NC payment amount = 224.74 * 0.931*1.9 = $397.54

Total direct medical costs of ED visits

The total direct medical costs associated with ED visits were calculated by summing total direct medical costs of treat and release ED visits and ED visits that resulted in hospital admissions.

Cost to Charge Ratio (CCR)

The SEDD and the SID provide total charge of an ED visit or a hospital stay. Also, the SID provide total charge of ED visits that ended with hospital admissions. Charges represent what hospitals bill for services, and they are higher than the actual cost of services or the amount paid for hospitals. The HCUP developed cost to charge ratios (CCRs) for the SID to help converting charge data to cost estimates. The CCR calculation is based on all-payer, inpatient cost and

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charge information from the detailed reports by hospitals to the CMS. Both hospital specific and state average all payer inpatient CCR are provided. Most payers require a bundled bill for patients admitted to the hospital through the emergency department. Thus, the CCRs for the SID were utilized to convert charge of ED visits that ended with hospital admissions to cost estimates. The CCR file for each year was linked to the hospital linkage file using the variable (DSHOSPID); the result was linked to the SID file using hospital identifier variable (HOSPID). Total charge per ED visit that resulted in hospital admission was multiplied by the corresponding CCR (specific to each state/year) to obtain the cost estimate. When available, hospital specific all payer inpatient CCR, APICC was used to estimate total cost per visit. Otherwise, group average all-payer inpatient CCR, GAPICC was used.

The HCUP do not provide CCRs specific to each hospital in the SEDD. However, it conducted a study including eight states and estimated average CCR for treat and release ED visits in these states.[103] The report grouped hospitals based on hospital characteristics such as hospital ownership and location and provided CCR for each group. Also, weighted average CCR for all hospitals was estimated. The latter was used in this study because hospital ownership and hospital region variables are not available in the SEDD.

Method for estimating the economic impact of prescriber use mandates in Kentucky

The economic impact of prescriber use mandates in Kentucky was evaluated in terms of direct medical costs associated with ED visits considered in specific aim 4A. This was accomplished by calculating the odds ratio (OR) of the interaction term (mandates*post). The latter is called difference in difference estimator (DID) and it represents the difference in the change of opioid poisoning ED visits between Kentucky and North Carolina following policy implementation.

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The DID was used to quantify the difference in the number of opioid poisoning ED visits in KY in the pre- and post-mandates periods. This can be explained by the following equation:

Logit (poisoning_indicator=1) = $\beta_0 + \beta_1$ mandates + β_2 post+ β_3 (mandates*post) + $\beta_{(4-n)}\ X_{(4-n)}$

- Mandates is a dummy variable for prescriber mandates (1= Kentucky, 0= North Carolina).

- Post is a dummy variable for post mandates period (1= post mandates (i.e. second half of 2012, 2013 and, 2014), 0= pre-mandates (i.e. 2011 and first half of 2012)).

- (Mandates * post) is an interaction term between the variables mandates and post.

- β_3 is the DID estimator which represents the true effect of mandates:

β_3= (KY post - KY pre) - (NC post - NC pre).

NC pre = β_0

NC post = $\beta_0 + \beta_2$

KY pre = $\beta_0 + \beta_1$

KY post = $\beta_0 + \beta_1 + \beta_2 + \beta_3$

(KY post - KY pre) = $\beta_3 + \beta_0 + \beta_2 - \beta_0 = \beta_2 + \beta_3$ (suppose that $\beta_2 = -0.0333$, $\beta_3 = -0.3556$, post-mandates is 2013, and pre-mandates is 2011)

Thus, (KY post - KY pre) = -0.3889, OR = $e^{-0.3889}$ = 0.68 (i.e. there is a 32% reduction in likelihood of opioid poisoning ED visits going from 2011 to 2013, controlling for NC in the model). Thus, there are (0.32 * number of opioid poisoning ED visits in 2011) fewer ED visits in 2013 as compared to 2011. The economic impact of prescriber use mandates in 2013 was quantified by multiplying the average cost per ED visit by the difference in the number of opioid poisoning ED visits between the years 2011 and 2013 (i.e. 0.32 * number of opioid poisoning ED visits in 2011). The same method was applied to estimate the economic impact of the policy in 2012 and 2014.

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Sensitivity analyses

Sensitivity analyses were performed for Kentucky. Scenario analysis was conducted to test the impact of including ED visits with prescription opioid poisoning listed as the first diagnosis on the estimated total direct medical costs. One way-sensitivity analyses were performed to test the robustness of the base case cost estimates. These analyses included varying values of average CCR used to estimate cost of treat and release ED visits, the proportion of ED visits requiring ambulance run, and cost of ground ambulance run. Also, the estimate of the interaction term for each model was included in the one-way sensitivity analyses. Table 6.3 provides summary of ranges considered for each value.

Table 6. 3: Ranges of values used in one-way sensitivity analysis

Parameter	Value in base case analysis	Values used in one-way sensitivity analysis
CCR	0.514[a]	± 95% CI[b]
Proportion of ED visits requiring ambulance services	38.2%	± 25%
Cost of ground ambulance run	$375.77	$316.43[c]
β_3[d] of the interaction term (mandates*post)	(KY, 2012) = -0.0892 (KY, 2013) = -0.3556 (KY,2014) = -0.3532	±95% CI

a. Weighted average CCR for all hospitals reported in the HCUP study was used because hospital ownership and hospital region variables were not available in the SEDD.
b. Estimated from the mean and standard deviation (SD) using the equation: mean± 1.96*SD.
c. = (224.74* 0.88*1.6) which represents payment amount (in 2018 USD) for HCPCS code: A0429 (ambulance service, basic life support, emergency transport (BLS – emergency)).
d. β_3 for each regression model was used.

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Section 6.2 Results

Aim 4A: To estimate the direct medical costs associated with prescription opioid poisoning in Kentucky and North Carolina.

Kentucky

There were a total of 7,419 prescription opioid poisoning ED visits over the period 2011 – 2014. Treat and release ED visits constituted 46% of total ED visits; the remaining ED visits (54%) resulted in hospital stays. The total (four years) average cost for a treat and release ED visit was estimated at $2,711.61 (see Appendix B for calculations) and the total mean cost for an ED visit that resulted in hospital stay was evaluated at $869.18 (see Appendix B for calculations). The annual average costs of a treat and release ED visit, ED visit that resulted in hospital stay, and physician fee cost are summarized in Table 6.4. The total (four year) ED related costs were estimated at $12.71 million (Table 6.4). About 73.0% of these costs were attributed to treat and release ED visits and 27.0% were related to ED visits that resulted in hospital stays. The total (four year) ambulance service costs of all ED visits were estimated at approximately one million dollars (Table 6.5). The total direct medical costs of prescription opioid poisoning ED visits were evaluated at $13.77 million (Table 6.6).

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Table 6. 4: Prescription opioid poisoning related-ED costs in Kentucky (in 2018 USD)

	Average cost of utilizing the ED per year (SE)[a,b]				Number of ED visits per year (n)				Total average cost per year[c] (in million)				Total (four years) average costs[e] (in million)
	2011	2012	2013	2014	2011	2012	2013	2014	2011	2012	2013	2014	
Treat and release ED visits	2,469.08 (69.33)	2,445.31 (68.14) [d]	2,500.21 (76.32)	2,749.53 (105.29)	970	911	712	835	2.56	2.38	1.90	2.44	
ED visits that resulted in hospital admission	628.50 (20.81)	682.31 (25.88)	699.49 (28.05)	784.09 (33.44)	1,219	1,126	841	805	0.97	0.96	0.73	0.77	
Total average costs of all ED visits per year[f]									3.53	3.34	2.63	3.21	**12.71**

a. The SEDD and the SID do not need to be weighted because it provides a census (not an estimate) of ED visits.
b. Exclude physician fee cost which = $170.58.
c. Total average cost per year= average cost of ED visit per year (i.e. average cost of utilizing the ED in that year+ physician fee cost) * number of ED visits in that year (n).
d. The estimated average cost was missing for one observation.
e. Total (four years) average costs = total average cost of all ED visits in 2011($3.53 million) + total average cost of all ED visits in 2012 ($3.34 million) + total average cost of all ED visits in 2013 ($2.63 million) + total average cost of all ED visits in 2014 ($3.21 million) = $12.71 million.
f. Total average costs of all ED visits per year= total average costs of treat and release ED visits + total average costs of ED visits that resulted in hospital admission in that year.

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Ambulance service costs

Over the four years period, 1,310 treat and release ED visits and 1,517 ED visits that ended with hospital admissions were assumed to have involved ground ambulance transportation. The total (four year) ambulance services costs of all ED visits were estimated at approximately one million dollars (Table 6.5). About 46.2% of these costs were attributed to treat and release ED visits and 53.8% were related to ED visits that resulted in hospital stays. The annual and total costs of ambulance services are summarized in Table 6.5.

Table 6. 5: Annual and total (four years) costs of ground ambulance services in Kentucky (in 2018 USD)

	Number of ED visits requiring ambulance service per year (n)[a]				**Total costs per year[b,c] (in million)**				**Total (four years) costs[d] (in million)**
	2011	**2012**	**2013**	**2014**	**2011**	**2012**	**2013**	**2014**	
Treat and release ED visits	371	348	272	319	0.14	0.13	0.1	0.12	
ED visits that resulted in hospital admission	466	430	322	308	0.17	0.16	0.12	0.12	
Total costs of ambulance services for all ED visits per year					0.31	0.29	0.22	0.24	**1.06**

a. Number of ED visits requiring ambulance service per year = (38.2%) * No. of ED visits in that year.
b. The SEDD and the SID do not need to be weighted because it provides a census (not an estimate) of ED visits.
c. Total average cost per year= cost per ambulance run ($375.77) * number of ED visits requiring ambulance services in a year.
d. Total (four years) costs = total costs of ambulance services for all ED visits in 2011($0.31 million) + total costs of ambulance services for all ED visits in 2012 ($0.29 million) + total costs of ambulance services for all ED visits in 2013 ($0.22 million) + total costs of ambulance services for all ED visits in 2014 ($0.24 million) = $1.06 million.

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Total direct medical costs of ED visits

Total (four year) direct medical costs associated with ED visits were estimated at $13.77 million. About 29.1% of these costs were attributed to ED visits that ended with hospital admissions and 70.9% were related to treat and release ED visits. The annual and total direct medical costs for the period 2011 to 2014 are summarized in Table 6.6.

Table 6. 6: The annual and total direct medical costs of prescription opioid poisoning ED visits in Kentucky (in 2018 USD)

	2011	2012	2013	2014	Total (four year) direct medical costs (in millions)[d]
Total average costs of all ED visits per year[a]	3.53	3.34	2.63	3.21	
Total ambulance service costs for all ED visits per year[b]	0.31	0.29	0.22	0.24	
Total direct medical costs per year[c]	3.84	3.63	2.85	3.45	**13.77**

a. Estimated in Table 6.4.
b. Estimated in Table 6.5.
c. Total direct medical costs per year = total average costs of all ED visits + total ambulance service costs in that year.
d. Total (four year) direct medical costs = total direct medical costs in 2011 ($3.84 million) + total direct medical costs in 2012 ($3.63 million) + total direct medical costs in 2013 ($2.85 million) + total direct medical costs in 2014 ($3.45 million) = $13.77 million.

North Carolina

There were a total of 12,598 opioid poisoning related ED visits over the period 2011 – 2014. Treat and release ED visits constituted 44.8% of total ED visits; the remaining ED visits (55.2%) resulted in hospital stays. Over the four years period, the average cost for a treat and release ED visit was estimated at $ 2,766.67 (see Appendix B for calculations), and the mean cost for an ED visit that resulted in hospital stay was evaluated at $1,011.94 (see Appendix B for calculations). The annual average cost of a treat and release ED visit, ED visit that resulted in hospital stay, and

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physician fee cost are summarized in Table 6.7. The total (four years) ED related costs were estimated at $22.46 million (Table 6.7). About 96.9% of these costs were attributed to treat and release ED visits and 30.1% were related to ED visits that resulted in hospital stays. The total (four year) ambulance service costs of all ED visits were estimated at $1.9 million (Table 6.8). The total direct medical costs of prescription opioid poisoning ED visits were evaluated at $24.37 million (Table 6.9).

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Table 6. 7: Prescription opioid poisoning related- ED costs in North Carolina (in 2018 USD)

	Average cost of utilizing the ED per year (SE)[a,b]				Number of ED visits per year (n)				Total average cost per year[c] (in million)				Total (four years) average costs[d] (in million)
	2011	2012	2013	2014	2011	2012	2013	2014	2011	2012	2013	2014	
Treat and release ED visits	2,251.19[e] (53.90)	2,588.65[f] (84.61)	2,648.11[f] (62.04)	2,896.95[g] (124.87)	1,306	1,361	1,414	1,565	3.16	3.76	3.99	4.80	
ED visits that resulted in hospital admission	765.26 (5.76)	832.34 (11.18)	850.04 (9.85)	918.35(11.60)	1,643	1,740	1,878	1,691	1.54	1.74	1.92	1.55	
Total average costs of all ED visits per year[h]									4.70	5.50	5.91	6.35	**22.46**

a. The SEDD and the SID do not need to be weighted because it provides a census (not an estimate) of ED visits.
b. Exclude physician fee cost which = $170.44.
c. Total average cost per year= average cost of ED visit per year (i.e. average cost of utilizing the ED in that year+ physician fee cost) * number of ED visits in that year (n).
d. Total (four years) average costs = total average cost of all ED visits in 2011($4.70 million) + total average cost of all ED visits in 2012 ($5.50 million) + total average cost of all ED visits in 2013 ($5.90 million) + total average cost of all ED visits in 2014 ($6.35 million) = $22.46 million.
e. The estimated average cost was missing for three observations. f. The estimated average cost was missing for four observations.
g. The estimated average cost was missing for six observations.
h. Total average costs of all ED visits per year= total average costs of treat and release ED visits + total average costs of ED visits that resulted in hospital admission in that year.

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Ambulance service costs

Over the four years period, 2,157 treat and release ED visits and 2,656 ED visits that ended with hospital admissions were assumed to have involved ground ambulance transportation. The total (four years) ambulance services costs of all ED visits were estimated at $1.92 million. About 44.8% of these costs were attributed to treat and release ED visits and 55.2% were related to ED visits that resulted in hospital stays. The annual and total costs of ambulance services are summarized in Table 6.8.

Table 6. 8: Annual and total (four years) costs of ground ambulance services in North Carolina (in 2018 USD)

	Number of ED visits requiring ambulance service per year (n)[a]				**Total costs per year[b,c] (in million)**				**Total (four years) costs[d] (in million)**
	2011	**2012**	**2013**	**2014**	**2011**	**2012**	**2013**	**2014**	
Treat and release ED visits	499	520	540	598	0.20	0.21	0.21	0.24	
ED visits that resulted in hospital admission	628	665	717	646	0.25	0.26	0.29	0.26	
Total costs of ambulance services for all ED visits per year					0.45	0.47	0.50	0.50	**1.92**

a. Number of ED visits requiring ambulance service per year = (38.2%) * No. of ED visits in that year.
b. The SEDD and the SID do not need to be weighted because it provides a census (not an estimate) of ED visits.
c. Total average cost per year= cost per ambulance run ($397.54) * number of ED visits requiring ambulance services in a year.
d. Total (four years) costs = total costs of ambulance services for all ED visits in 2011($0.45 million) + total costs of ambulance services for all ED visits in 2012 ($0.47 million) + total costs of ambulance services for all ED visits in 2013 ($0.50 million) + total costs of ambulance services for all ED visits in 2014 ($0.50 million) = $1.92 million.

Total direct medical costs of ED visits

Total (four years) direct medical costs associated with ED visits were estimated at $24.37 million. About 32.0% of these costs were attributed to ED visits that ended with hospital

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admissions and 68.0% were related to treat and release ED visits. The annual and total direct medical costs for the period 2011 to 2014 are summarized in Table 6.9.

Table 6. 9: The annual and total direct medical costs of prescription opioid poisoning ED visits in North Carolina (in 2018 USD)

	2011	2012	2013	2014	Total (four year) direct medical costs (in millions)[d]
Total average costs of all ED visits per year[a]	4.70	5.50	5.90	6.35	
Total ambulance service costs for all ED visits per year[b]	0.45	0.47	0.50	0.50	
Total direct medical costs per year[c]	5.15	5.97	6.40	6.85	**24.37**

a. Estimated in Table 6.7.
b. Estimated in Table 6.8.
c. Total direct medical costs per year = total average costs of all ED visits + total ambulance service costs in that year.
d. Total (four year) direct medical costs = total direct medical costs in 2011 ($5.15 million) + total direct medical costs in 2012 ($5.97 million) + total direct medical costs in 2013 ($6.40 million) + total direct medical costs in 2014 ($6.85 million) = $24.37 million.

Specific aim 4B: To estimate the economic impact of prescriber use mandates in Kentucky.

From 2011 to 2014, there was a 22.14% reduction in direct medical costs associated with prescription opioid poisoning ED visits. Following prescriber use mandates implementation, the total reduction of direct medical costs associated with ED visits was estimated at about $2.31 million. Table 6.10 summarizes the impact of the policy on the number of opioid poisoning ED visits and the associated direct costs by year.

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Table 6. 10: The impact of prescriber use mandates policy on the number of opioid poisoning ED visits and the associated direct costs (in 2018 USD, millions)

	Pre-mandates	Post-mandates		
	2011	2012	2013	2014
No. of opioid poisoning ED visits[a]	2,189	1,948	1,488	1,423
Total direct medical costs	3.84	3.48[b]	2.74	2.99
Change in total direct medical costs from 2011 to post mandates[c]	-	0.36	1.1	0.85
Percent change in total direct medical costs from 2011 to post mandates	-	- 9.38	- 28.65	- 22.14

a. No. of opioid poisoning ED visits for the years 2012, 2013, and 2014 were estimated based on the DID estimator equation (see Section 5.1 under specific aim 3B) as follow:
$KY_{post} – KY_{pre} = \beta_2 + \beta_3$ (where β_2 is the estimate for the variable post (i.e. post-mandates) and β_3 is the DID estimator). For the year 2012:
$KY_{2012} – KY_{2011}$= - 0.0326 + (- 0.0892)
= -0.1218, OR = $e^{-0.1218}$ = 0.89, then, no. of opioid poisoning ED visits in 2012 = 0.89 * no. of opioid poisoning ED visits in 2011 (2,189)
= 1,948 ED visits in 2012. The same calculations will be applied to estimate no. of opioid poisoning ED visits in 2013 and 2014.

b. Total direct medical costs for 2012 were estimated as follow: no. of opioid poisoning ED visits = 1,948 (treat and release ED visits constituted 44.7% of total ED visits and hospital ED visits that resulted in hospital admission constituted 55.3% of total ED visits (Table 6.4). Thus, there are 871 treat and release ED visits and 1077 ED visits that resulted in hospital admission. Total average costs of treat and release ED visits = (871 * $2,615.89) = $2.28 million, total average costs of ED visits that resulted in hospital admission= (1077 * $852.89) = $0.92 million, total costs of ambulance services for all ED visits = 1,948 * 38.2% = 744; $375.77 * 744 = $0.28 million. Total direct medical costs in 2012= 2.28 + 0.92 + 0.28 = $3.48 million. The same calculations will be applied to estimate total direct medical costs for 2013 and 2014.

c. Change in direct medical costs from 2011 to post mandates = total direct medical costs in 2012 (2013, or 2014) - total direct medical costs in 2011 ($3.84 million).

Sensitivity analyses

Scenario analysis and one-way sensitivity analyses were conducted to test the robustness of the base case cost estimates in KY.

Scenario analysis (including only ED visits with first listed diagnosis of prescription opioid poisoning):

There were 2,322 treat and release ED visits and 2,266 ED visits that resulted in hospital admission, with first listed diagnosis of prescription opioid. Considering these ED visits, the total (four years) direct medical cost of prescription opioid poisoning in KY was estimated at $8.45

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million (compared to $13.77 million in the base case analysis). Results of the scenario analysis are summarized in Table 6.11

One-way sensitivity analyses:

One-way sensitivity analyses were conducted by varying the proportion of average CCR of treat and release ED visits, ED visits requiring ambulance run, cost per ground ambulance run, and the estimate of the interaction term for each regression model. Varying the proportion of CCR over 95% CI range resulted in approximately ± $7.7 million effect on the total (four years) estimated costs. When the proportion of ED visits with ambulance service varied between (28.65% and 47.75%), the total (four years) direct medical costs ranged from $13.5 million to $14 million. Reducing ambulance cost to $316.43 decreased the total direct costs by $70 thousands. When the estimate of the interaction term for all models varied over 95% CI, the total reduction in direct medical costs in post mandates period compared to 2011 ranged from $1.6 million to $3.14 million. Results of the one-way sensitivity analyses are summarized in Table 6.12 and 6.13.

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Table 6. 11: Direct medical costs of ED visits associated with prescription opioid poisoning listed as first diagnosis in Kentucky (in 2018 USD)

	Average cost of utilizing the ED per year (SE)[a,b]				Number of ED visits per year (n)				Total average cost per year[c] (in million)				Total (four years) average costs[d] (in million)
	2011	2012	2013	2014	2011	2012	2013	2014	2011	2012	2013	2014	
Treat and release ED visits	2,283.06 (81.87)	2,236.33[e] (73.34)	2,298.63 (79.03)	2,505.04 (122.92)	633	602	502	584	1.55	1.45	1.24	1.56	
ED visits that resulted in hospital admission	649.92[f] (15.88)	701.72 (15.31)	707.40 (17.66)	791.71[e] (20.12)	686	671	470	436	0.56	0.59	0.41	0.42	
Total ambulance service costs for all ED visits per year[g]									0.19	0.18	0.14	0.15	
Total direct medical costs of all ED visits per year[h]									2.30	2.22	1.79	2.13	**8.44**

a. The SEDD and the SID do not need to be weighted because it provides a census (not an estimate) of ED visits.
b. Exclude physician fee cost which = $170.58.
c. Total average cost per year= average cost of ED visit per year (i.e. average cost of utilizing the ED in that year+ physician fee cost) * number of ED visits in that year (n).
d. Total (four years) average costs = total average cost of all ED visits in 2011($2.30 million) + total average cost of all ED visits in 2012 ($2.22 million) + total average cost of all ED visits in 2013 ($1.79 million) + total average cost of all ED visits in 2014 ($2.13 million) = $8.44 million.
e. The estimated average cost is missing for one observation.

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f. The estimated average cost is missing for two observations.
g. Total ambulance service costs for all ED visits per year = no. of ED visits requiring ambulance service in that year * cost per ambulance run ($375.77).
h. Total average costs of all ED visits per year= total average costs of treat and release ED visits + total average costs of ED visits that resulted in hospital admission in that year.

Table 6. 12: One-way sensitivity analyses on the total estimated direct medical costs in Kentucky (in 2018 USD)

Parameter	Base case value	Base case estimated total direct medical costs (in million)	Value or range tested	Change in estimated total direct medical costs (in million)
CCR	0.514	13.77	95% limit (0.06 - 0.97)	(6.10 - 21.50)
Proportion of ED visits requiring ambulance run	38.2%	13.77	± 25% (28.65%, 47.75%)	(13.52, 14.05)
Cost of ground ambulance[a]	$375.77	13.77	$316.43[b]	13.71

a. Estimated from the mean and SD using the equation: mean± 1.96*SD (0.232)
b. Payment amount (in 2018 USD) for HCPCS code: A0429 (ambulance service, basic life support, emergency transport (BLS – emergency)).

Table 6. 13: One-way sensitivity analysis on the impact of prescriber use mandates (in 2018 USD)

Parameter	Base case value	Range tested	Total direct medical costs in post mandates period (per year)	Change in total direct medical costs from 2011[a]
β_3 associated with the interaction term (mandates * post):				
(KY, 2012)	-0.0892	95% limit (-0.009 - -0.169)	(3.20 - 3.75)	(0.09 - 0.64)
(KY, 2013)	-0.3556	95% limit (- 0.272 - -0.439)	(2.50 - 2.98)	(0.86 - 1.34)
(KY, 2014)	-0.3532	95% limit (-0.270 - -0.436)	(2.71- 3.22)	(0.62- 1.13)

a. Change in total direct medical costs from 2011 = total direct medical costs in 2012 (2013, or 2014) - total direct medical costs in 2011 ($3.84 million).

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Chapter 7

Section 7.1: Discussion

This is the first study to examine the impact of a PDMP prescriber use mandate policy on prescription opioid poisoning ED visits in the United States. The existing literature assessed the effectiveness of PDMPs in terms of their impact on prescribing behavior, opioid consumption, doctor shopping, and opioid-related morbidity (see Chapter 2). The framework used for this research was the **Donabedian** model (Figure 1.2). In addition, this study estimates the direct medical costs associated with prescription opioid poisoning ED visits and the economic impact of prescriber use mandates.

This research focused on the impact of **comprehensive** prescriber use mandates.[90] Difference in difference (DID) framework was used to examine the impact of the policy on prescription opioid poisoning ED visits. The DID model is a well-known statistical methodology used for policy impact evaluation.[77, 86, 99, 100] This study was further strengthened by conducting three comparison models for the years 2012, 2013, and 2014 as compared to 2011.

Prevalence of prescription opioid poisoning ED visits and associated characteristics

This study found that the prevalence rate of prescription opioid poisoning ED visits in 2014 was 43.82 per 100,000 residents for Kentucky and 37.45 per 100,000 residents for North Carolina. In

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the same year, the Agency for Healthcare Research and Quality (AHRQ) estimated the national rate of opioid related ED visits to be 177.7 per 100,000 residents.[104] However, this national estimate included all heroin and non-heroin related ED visits for all age groups. National data from another study was utilized to calculate the rate of non-heroin related ED visits in 2014;[105] the estimated national rate is lower compared to Kentucky and North Carolina (= 25.60 per 100,000 residents).

From 2010 to 2014, the national age adjusted rate of non-heroin related ED visits decreased by 4%.[105] Also, a recent report by the CDC found that the rate of opioid overdose ED visits among those aged 11 years and older decreased by 15% in Kentucky, and increased by 30% in North Carolina from July 2016 to September 2017.[106] Our study estimated 26.1% reduction in the rate of prescription opioid poisoning ED visits in Kentucky and 3.2% increase in North Carolina from 2011 to 2014.

Sociodemographic characteristics of prescription opioid poisoning ED visits described in our study were similar to the existing literature; prescription opioid poisoning ED visits were more prevalent in people aged 35- 50 years old and >50 years compared to other age groups. [105, 107] In addition, our study reported a higher proportion of visits occurring in urban areas, higher rates of opioid related ED visits among females, and white, non-Hispanics had the highest visit rates.[105, 108-110] Medicare was the largest payer for unintentional opioid poisoning; the latter can be caused by poly-pharmacy, which is more common in elderly. This finding is supported by previous studies.[108, 111] Lastly, consistent with Monnat et al.,[112] our study found non-significant relationship between patient location and opioid related ED visits.

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Impact of prescriber use mandates on prescription opioid poisoning ED visits

This study found evidence to support prescriber use mandates and how this differed in Kentucky and North Carolina. Prescriber use mandates implemented in Kentucky in July 2012 were associated with a moderate, but significant reduction in prescription opioid poisoning ED visits in 2012 as compared to 2011, controlling for North Carolina in the model. An even greater reduction in opioid related ED visits was seen in 2013. The impact of the policy has leveled off in 2014, as no further reduction was seen in prescription opioid poisoning ED visits. However, this does not ensure the sustainability of the policy impact; more data points are required to examine a pattern in the observed data.

Results of this study expands the growing body of evidence on PDMP effectiveness. It differs with Maughan et al. who did not find a statistically significant difference in prescription opioid misuse related ED visits between states with and without PDMPs.[83] One explanation for the non-significant results reported by the authors was the low and variable utilization of PDMPs by prescribers at the time of their study.[46-50, 52-62] PDMP use was much greater in Kentucky during the period of our study.

The few studies specific to prescriber use mandates are generally supportive of them. In New York, prescription opioid related ED visits leveled off following prescriber use mandate implementation.[84] New York also saw a significant reduction in opioid prescribing after prescriber use mandates.[85] A national study by Dowell reported significant reduction in prescription opioid related deaths following prescriber use mandates.[86] Only one study found non-significant impact of prescriber use mandates on opioid prescribing.[87]

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Economic impact of prescriber use mandates policy

The current study is the first to estimate the economic impact of prescriber use mandates on non-fatal prescription opioid poisoning ED visits. Existing studies evaluated costs of opioid related ED visits using **national** estimates and included fatal and non-fatal ED visits. To date, four studies have estimated costs of opioid related ED visits utilizing **national** ED visits data. Inocencio et al. assessed direct and indirect costs associated with opioid misuse, abuse, and/or poisoning in the United States. The average estimated cost of a prescription opioid related ED visit was $2,337 in 2017 U.S. dollars.[25] Another study by Yokell et al. estimated average charges of prescription opioid overdose ED visit at $4,454 to $5,043, which would be comparable to Inocencio's cost figures after applying a cost to charge adjustment.[110] Tadros et al. costs were also comparable to Inocencio's.[108] A study using 2007 data found lower average charges for drug poisoning related ED visit of $2,700.[113] To our knowledge, only one study reported **state** level costs of opioid related ED visits and hospital admissions; in Florida, the total estimated costs of ED visits and inpatient stays was $208 million over one-year period (2010 – 2011).[114]

In the current study, the average cost treat- and release ED visits were estimated at $2,500 in Kentucky and $2,600 in North Carolina. These estimated costs are comparable to the average costs reported by Incencio et al.[25] In addition, the average charges per visits estimated in our study were similar to those reported by prior studies.[108, 110] The current study estimated total direct medical costs of prescription opioid poisoning ED visits to be $13.77 and $24.37 million in Kentucky and North Carolina, respectively, over the period 2011 - 2014. Treat and release ED visits contributed to most of costs in both states.

Surprisingly, the average costs of treat- and release ED visits were more than triple compared to the average cost of ED visits that resulted in hospital stays ($2500 vs. $700 for Kentucky and

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$2600 vs. $840 for North Carolina). These findings can be explained through the severity of opioid cases. Patients who were seen in the ED and admitted to the hospital would have more severe cases and thus, require more procedures to be done in the ED. Most payers require bundled payments for patients who were first seen in the ED and then admitted to the hospital. Based on this model, the current study used inpatient CCRs to estimate costs of ED visits that ended in hospital stays. This may explain the low cost of ED visits that resulted in hospital admissions as compared to treat and release ED visits. No other studies have evaluated costs of emergency department services for inpatient stays; therefore, the current findings cannot be supported by any existing evidence. Payments for physician fees used in the current study were the highest documented payment in the MFS for ED services — which may inflate the total estimated direct costs. However, the CPT-4 code selected for use in this study appropriately describes ED services for opioid overdose. Sensitivity analysis was performed to test the robustness of the total estimated costs in Kentucky. Varying the CCR for treat and release ED visits over its 95% CI range had the largest impact on the total cost estimate (± 7 million effect). This was expected due to the large variation in CCR values between hospitals and states estimated in the HCUP report.[103]

The current study evaluated the economic impact of the PDMP policy considering only direct medical costs. Following prescriber use mandates implementation, the reduction of total direct medical costs from 2011 to 2014 was estimated at $2.31 million. The estimated reduction in costs was doubled from 2012 to 2013 and leveled off in 2014 (Figure 7.1). It could be that the policy impact reached its maximum level a year after its implementation (i.e. in 2013) and thus, no further reduction in costs was noted in 2014. This may indicate that the policy need to be updated to increase its effect, or other policies should be implemented to synergize its impact. It

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is worth to note that the estimated reduction in costs following the policy implementation does not reflect savings in cost. Abusers of prescription opioids may shift to heroin and thus, costs associated with abusing heroin and other non-prescription opioids may increase on the other side. A study by Dart et al. on trends on opioid analgesic abuse found a reduction in prescription opioid abuse and a concurrent increase in heroin abuse in the United States from 2010 to 2013.[115] The relationship between prescription opioid abuse and heroin abuse was further supported by Cicero et al.[116]

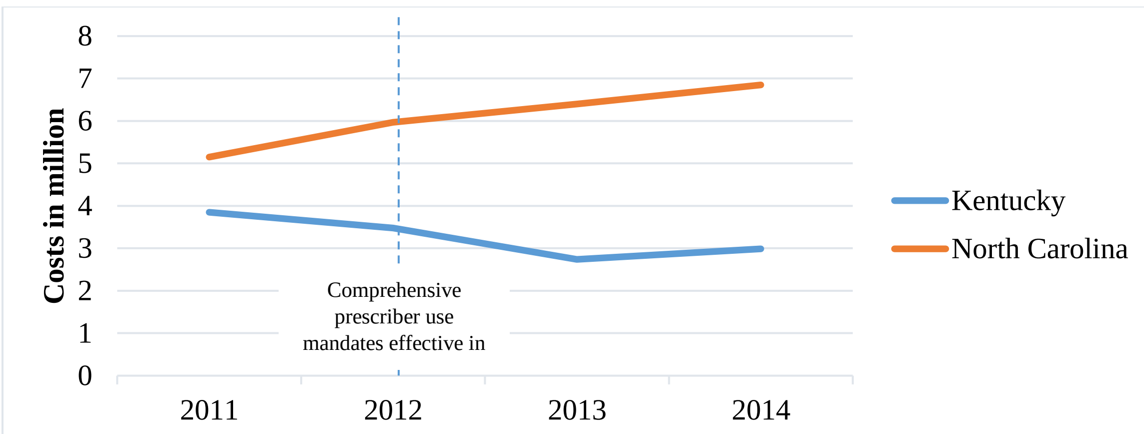

Figure 7. 1: Economic impact of prescriber use mandates on prescription opioid poisoning ED visits in Kentucky (in 2018 USD)

Findings of this study provide information surrounding the effectiveness of comprehensive prescriber use mandates in reducing prescription opioid poisoning ED visits. However, the impact of the policy cannot be isolated from pain clinic regulations, which were part of the House Bill 1 (HB1) legislation implemented in Kentucky in 2012. Also, Kentucky and North Carolina differ in the adoption of other policies, which could impact the assessment of prescriber use mandates (Table 7.1).

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In 2011, North Carolina implemented a state-wide program called Project Lazarus. The program aimed to combat the prescription opioid abuse epidemic and related health outcomes. When first initiated in Wilkes county in 2008, Project Lazarus reduced overdose deaths and opioid abuse related ED visits by 69% and 15%, respectively.[117] Despite the initiative in North Carolina, our study found a significant reduction in prescription opioid poisoning ED visits in Kentucky compared to North Carolina. This finding further supports the effectiveness of prescriber use mandates.

It is important to note that the prescriber use mandate policy does not necessarily ensure prescribers' utilization of PDMPs. Many prescribers oppose the use of PDMPs and, it is not feasible to verify prescriber's use of the system. In addition, as of 2016, only 30 states explicitly provide civil and/or criminal immunity to prescribers and dispensers for accessing, failing to access, or reporting data to PDMPs.[118] As mentioned earlier, there are seven other PDMPs practices proposed to increase PDMPs utilization.[31] Also, other practices that increase PDMPs effectiveness should be considered.[32] These policies and practices should work hand in hand with prescriber use mandates to curb the prescription opioid abuse epidemic.

Table 7. 1: PDMPs practices and other related policies in Kentucky and North Carolina

	KY				NC			
	2011	2012	2013	2014	2011	2012	2013	2014
Proactive reports to prescribers	✗	✗	✗	✗	✗	✗	✗	✗
Delegate access	✓	✓	✓	✓	✗	✗	✗	✓
Naloxone distribution*	✗	✗	✗	✗	✗	✗	✗	✗
Schedules monitored	**II - V**				**II- V**			
Operational PDMP	**1999**				**2007**			
Require prescriber to be trained	✓				✗			

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before using PDMP		
Pain clinic law	**Yes (part of HB1)**	✗
Proactive reports on prescriber (to law enforcement agency)	**Yes (part of HB1)**	✗

Note: ✗ means the policy was not implemented; ✓ means the policy was not implemented
* Effective in 3/2015 in Kentucky; Effective in 6/2016 in North Carolina; HB1= house bill1

Limitations

This study is the first to examine the impact of prescriber use mandates policy on prescription opioid poisoning ED visits using a controlled pre-post study design. However, the study has several limitations.

The intended population were abusers who obtain their prescription opioids from doctors. Unfortunately, the data did not provide information to verify this. Physicians are one leading source of prescription opioids, however, there are other sources from which patients can obtain prescription opioids. According to National Survey on Drug Use and Health (NSDUH), half of non-medical users (50.5%) obtained their opioid from a friend or relative for free, 22.1% got it from one doctor, and 11% bought it from a friend or relative.[119] Improperly stored prescription opioid in households represents another source for abuse that was not captured in the current study. A study by Lewis et al. (2014) reported stockpiling of unused opioids by 65% of patients with only 6.3% dispose unused opioids.[120] Stockpiling opioids was associated with recreational use of these medications in 34% of patients. A similar study by Bates et al. (2011) investigated unused narcotics among discharged patients who underwent surgery.[121] In this study, 67% of patients stockpiled unused narcotics. Therefore, educating patients and providing them with proper drug disposal methods is necessary to reduce the risk of abuse.

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Prescription opioid poisoning is not limited to prescription opioid abusers. Polypharmacy, defined as taking five or more medications, [122] can be a leading cause. Polypharmacy is common in elderly due to having multiple medical conditions. The current study found that more than one third of opioid-related ED visits were attributed to patients >50 years old, however, the possibility of polypharmacy as an underlying cause cannot be determined. Furthermore, this study could not control for patient's living condition (i.e. homelessness), marital status, education, and employment which are potential confounders. Evidence from the existing literature supports the relationship between these variables and opioid abuse; [123, 124] however, no information on these variables were available in the SEDD and the SID for the period of the study. Other data limitations are related to the ICD-9-CM codes; there are no specific codes that identify prescription opioid poisoning and thus, the analyses of this study may overestimate the occurrences of prescription opioid poisoning ED visits.

Other state level unobserved factors may affect the findings of this study. There may be local policies or interventions that were implemented at similar time to prescriber use mandates, which could impact the estimated effect of the policy. These may include other opioid-related prescriber mandates, regulations of naloxone access, and others.

Lastly, findings of the current study may not be generalizable to all states. This is related to two factors, first, differences among the states in conditions under which a prescriber is required to check the state PDMP. This research focused on **comprehensive** prescriber use mandates adopted in Kentucky. To recall, comprehensive prescriber use mandates require all prescribers to consult the PDMP before initial opioid and benzodiazepine prescriptions and at least every three months thereafter.[90] Therefore, it represents the highest level of prescriber use mandates compared to other states. Second, in addition to prescriber use mandates, Kentucky HB1

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legislation included regulations for pain clinics.[125] As a result, the reduction in opioid-related ED visits found in this study may not be attributed to prescriber use mandates only.

Study implications

The current study supports the effectiveness of prescriber use mandates in reducing the number of prescription opioid-related ED visits, also, the economic impact of the policy is considerable. These findings can be of a great importance to policy makers. States without prescriber use mandates policy should consider its adoption. To maximize prescriber use of PDMPs, other policies or practices should also be considered. Prescribers and other intended users of PDMPs should be educated about the importance of using the system and how to use it appropriately. In addition, prescriber should be given the right to authorize other staff, such as nurses to use the PDMP. This will save time for prescribers, hence enhancing PDMPs utilization. Proactive reports is another important practice; sending unsolicited reports to prescribers will notify them about high risk patients, and encourage them to coordinate care with other healthcare providers. Other policies or practices that might synergize the impact of prescriber use mandates are mentioned the NAMSDL report.[31] In addition to these practices, states must adopt laws that specifically provide immunity to prescribers and other intended users for accessing the system and impose sanctions on those who fails to use it.

The current study should guide future research to examine the impact of other prescriber use mandate policies on other opioid related-health outcomes. Findings of the current study are promising; further research is required to support the effectiveness of the policy. Lastly, to curb the prescription opioid abuse epidemic, PDMPs should not be the only area of focus; other plans proposed by the federal government should be considered.[30]

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Section 7.2: Conclusion

The prescriber use mandate policy is effective in reducing prescription opioid poisoning ED visits and their associated costs. However, the impact of the policy cannot be isolated from pain clinic regulations and other regulations included in Kentucky HB1 legislation. PDMP use mandates are one of several policies that can increase prescribers and pharmacists use of the system, thereby support PDMPs effectiveness. Decision makers should consider ways to maximize the implementation of prescriber use mandates, and adopt other policies or practices that enhance the effectiveness of PDMPs.

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Appendix A

Single level CCS	Type of cancer
11	Cancer of head and neck
12	Cancer of esophagus
13	Cancer of stomach
14	Cancer of colon
15	Cancer of rectum and anus
16	Cancer of liver and intrahepatic bile duct
17	Cancer of pancreas
18	Cancer of other GI organs; peritoneum
19	Cancer of bronchus; lung
20	Cancer; other respiratory and intrathoracic
21	Cancer of bone and connective tissue
22	Melanomas of skin
23	Other non-epithelial cancer of skin
24	Cancer of breast
25	Cancer of uterus
26	Cancer of cervix
27	Cancer of ovary
28	Cancer of other female genital organs
29	Cancer of prostate
30	Cancer of testis
31	Cancer of other male genital organs
32	Cancer of bladder
33	Cancer of kidney and renal pelvis
34	Cancer of other urinary organs
35	Cancer of brain and nervous system
36	Cancer of thyroid
37	Hodgkin`s disease
38	Non-Hodgkin`s lymphoma
39	Leukemias

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40	**Multiple myeloma**
41	Cancer; other and unspecified primary
42	Secondary malignancies
43	Malignant neoplasm without specification of site
44	Neoplasms of unspecified nature or uncertain behavior
45	Maintenance chemotherapy; radiotherapy

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Appendix B

Total (four years) average cost of prescription opioid poisoning ED visits (in 2018 USD)

Kentucky:

Treat and release ED visits

Total (four years) average cost = (average cost in 2011 + average cost in 2012 + average cost in 2013+ average cost in 2014) / 4 + physician fee cost.

= ($2,469.08 + $2,445.31 + $2,500.21 + $2,749.53)/ 4 + $170.58

= $2,711.6

ED visits that resulted in hospital admissions

Total (four years) average cost = (average cost in 2011 + average cost in 2012 + average cost in 2013+ average cost in 2014) / 4 + physician fee cost.

= ($628.50 + $682.31 + $699.49 + $784.09) / 4 + $170.58

= $869.18

North Carolina:

Treat and release ED visits

Total (four years) average cost = (average cost in 2011 + average cost in 2012 + average cost in 2013+ average cost in 2014) / 4 + physician fee cost.

= ($2,251.19 + $2,588.65 + 42,648.11 + $2,896.95)/ 4 + $ 170.44

= $12,766.67

ED visits that resulted in hospital admissions

Total (four years) average cost = (average cost in 2011 + average cost in 2012 + average cost in 2013+ average cost in 2014) / 4 + physician fee cost.

= ($765.26 + $832.34 + $850.04 + $918.35)/4 + $170.44= $1,011.94.

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