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Characterizing and Explaining Prevalence and Factors Associated with Non-Fatal Opioid Overdose in Florida

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by

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Table of Contents

List of Tables

List of Figures

Abstract

Many factors contribute to the opioid epidemic in Florida, including, but not limited to, physician over prescribing, opioid manufacturer malfeasance (direct marketing to physicians, hospitals, and universities, as well indirect political contributions, and deliberately obfuscating the impact of the addictive properties of their various drugs), and as the epidemic approaches its 25th year, sociodemographic characteristics. This body of work examines three of these. First, because an opioid naïve persons' typical initial encounter with the drug is through a physician, we sought to shed light on the impact of direct pharmaceutical marketing to physicians. We identified opioid providing physicians from the Medicare Part D and matched them to those in the Sunshine Act (record of payments to individual physicians) using Poisson regression with propensity score matching to help control for confounding. While we failed to find a dose-response relationship between opioid prescribers and marketing efforts, we still noted at the highest frequencies of interactions, a threshold effect, where physicians were much more likely to have higher prescription rates than their opioid prescribing peers. We feel that this sets the stage for more detailed research and that these findings add to the body of work on the unhealthy influence of pharmaceutical marketing.

Second, we set out to look at the area effect of pharmaceutical marketing (defined as the rate of physician encounters per year in each county) on clusters of opioid overdose rates of emergency department (ED) encounters and inpatient (IP) admissions. We used data from Medicare Part D, the Sunshine Act, and Florida Department of Health (FDOH), and, as FDOH reports the data at the county level, aggregated all as such. Then, using techniques from

geographic information systems (GIS) and linear mixed modeling (LMM) we attempted to identify factors that might be associated with clustering of overdose rates between 2016 and 2019. We failed to note any significant relationship between either IP or ED overdose rate clusters and our main outcome of interest, the quantity of opioid marketing, however, we did note that counties with greater Hispanic and non-Hispanic Black individuals were more likely to be found in a cluster, and that treatment resources saw an inverse association between the IP and ED clustering. We feel this study opens the doors to using more robust GIS informed modeling techniques.

Last, we sought to examine the effect of the opioid epidemic on IP admissions and ED encounters over time, relative to the changeover of the International Classification of Diseases versions nine (ICD-9) to ten (ICD-10) in the last quarter of 2015. We obtained quarterly Florida hospital discharge data from the Agency for Healthcare Administration (AHCA), parsed according to IP versus ED and whether opioids were related to the presenting problem as well as co-morbid conditions. We used interrupted time series modeling to examine both the immediate effect, and any change in trends occurring post ICD changeover. We noted large immediate level changes in all groups and increase in ED encounters overall with a decrease in overall IP admissions, as well as increases in non-White ED encounters, and increases in the number of co-morbid conditions. We feel this shows that opioid trend data should be analyzed with care and that ICD-9 and ICD-10 data related to opioids should be examined separately. Additionally, our findings on the co-morbid conditions can be used to inform researchers interested in designing interventions. Overall, this dissertation adds to the body of work and sets the stage for future efforts aimed at understanding the opioid epidemic.

Chapter 1:

Introduction

Background

By virtually all accounts, deaths rates for drug overdoses, most notably opioids, have increased sharply in the United States (U.S.) over the past 20 years. In the United States, the 1999 rate of age-adjusted overdose deaths (OD) was approximately 5 per 100,000 persons, but then increased steadily to 21.7 in 2017, dropping slightly to 20.7 in 2018 [1]. Opioid-specific age-adjusted OD death has also risen steadily since 2000, spiking sharply in 2013-2014 and steadying out to around 14.9 per 100,000 in 2017. By 2017 opioid overdoses made up about 69% of all drug overdose deaths [1].

In terms of geographic variation, by 2005, there were 16 states with an overdose death rate higher than 11.6 per 100,000 persons with 5 states clustered around New Mexico in the Southwestern region of the United States. The rest were geographically dispersed across the country from Florida to Maine, including some in the Southeastern region of the U.S. known as the "Bible Belt." Moving forward to 2014, the US rate increased to 14.7 per 100,000 persons, again with substantial variability across the states. For example, the rate in West Virginia was more than triple the national rate (46 per 100,000). New Mexico, Ohio, Kentucky, New Hampshire, and Rhode Island all had a rate above 24 per 100,000 persons, and 37 other states had rates above 11 per 100,000 persons [2, 3]. As the national rate continued to increase, distinct

regional patterns began to appear [2, 3]. Specifically, Appalachia and New England regions struggled with rates far above the rest of the country, a pattern that persisted even as the national rate dropped slightly to 20.7 per 100,000 in 2018 [2, 3].

Statement of the Problem

Nationwide

Between 1999 and 2016, more than 350,000 people died from opioid-related injuries in the United States. Twice as many men died compared to women, and the mean age at death was 40 years [4, 5]. During this time, more than half of the country (28 states) had age-adjusted drug overdose mortality rates that effectively doubled within short intervals (such as within 2 years), and Washington DC tripled each year between 2013 and 2016 [4, 5]. Of the 28 states with substantial increases between 1999 and 2016, 14 along with the District of Columbia had lower age-adjusted overdose rates between 2017 and 2018: Alaska,, Florida, Georgia, Indiana, Iowa, Kentucky, Maine, Minnesota, New York, North Carolina, Ohio, Pennsylvania, West Virginia, and Wisconsin [4]. Five states experienced rate increases from 2017 to 2018: California, Delaware, Missouri, New Jersey, and South Carolina [4]. The states with the highest age-adjusted rate per 100,000 persons were West Virginia (51.5), Delaware (43.8), Maryland (37.2), Pennsylvania (36.1), Ohio (35.9), and New Hampshire (35.8) [4]. The states with the lowest age-adjusted rates were Texas (10.4), North Dakota (10.2), Iowa (9.6), Nebraska (7.4), and South Dakota (6.9) [4]. By 2018, four of the five states that experienced notable increases in age-adjusted rates per 100,000 were already significant geographic hot spots. New Hampshire increased (30.2 to 35.8), Maryland more than doubled (17.7 to 37.2) Pennsylvania tripled (10.9 to 36.1), and Ohio increased by 70% (21.1 to 35.9) [1, 4, 5].

Florida

The State of Florida Department of Health (FDOH) reported for 1999 an age-adjusted overdose (OD) death rate of approximately 5.3 per 100,000 persons, which doubled by 2001 and nearly tripled by 2010 to 14.3 per 100,000 [1, 4]. Then, between 2010 and 2014, the rate decreased to 10 per 100,000 persons, only to increase in subsequent years, peaking at 25.1 per 100,000 persons by 2017 (Figure 1) [1]. By 2018, the rate had decreased nominally to 22.3 per 100,000 persons, and Florida was ranked 20th highest in the United States. However, given Florida's large population, it experienced an absolute number of overdose deaths (4,693) that ranked second only to California (5,348) [1]. According to medical examiner reports, the four most frequently occurring drugs involved in overdose deaths in Florida between 2014 and 2019 were opioids, cocaine, benzodiazepines, and alcohol [6]. Among opioid-related deaths, nearly all persons had varying amounts of either heroin, fentanyl (synthetic opioids), and morphine in their systems at the time of death [6].

Figure 1: Age-adjusted Rate of Overdose Deaths in Florida from 1999 to 2017

Specific Drugs Leading to Overdose Deaths in Florida

The Florida 2000 age-adjusted death rate was under 2 per 100,000 persons for all individual substances. By 2001, natural opioids (morphine, codeine) started to rise to 2.5 per 100,000 persons. Cocaine death rates increased slightly to around 2 per 100,000, whereas by 2011, non-synthetic opioid death rates rose to approximately 7 per 100,000 [7]. In 2011-2012, there was a notable dip in all substance use deaths by about 2 per 100,000 persons except for heroin and psychostimulants (methamphetamine, amphetamine, PCP) which started to increase slightly [1, 4]. The year 2015 marked the beginning of another increase in substance use deaths for all substances except for heroin which stayed steady at 3.6 per 100,000 persons. The death rate from psychostimulants which had been steady at 0.4 per 100,000 persons jumped to 2.2 per 100,000 persons and cocaine use deaths doubled from 3.0 to 6.7 per 100,000 persons. Death rates from natural opioids started to return to pre-2010 numbers back to 5.4 per 100,000 persons and the rate for synthetic opioids more than tripled from about 3 to 11 per 100,000 [1, 4].

Regional Variation in Opioid-Related Overdose Deaths in Florida

County-level data in Florida for age-adjusted all-cause drug overdose deaths were not consistently available prior to 2014, and it appears that routine tracking and dissemination of data at this geographic granularity are coincident to the advent of the Prescription Drug Monitoring Program (PDMP) in 2012. By 2014, the Florida semi-annual report of Drugs Identified in Deceased Persons had been made available online by Florida medical examiners to help track burgeoning interest, including improved data granularity down to the county level [6]. This granularity of data was able to quantify high opioid-related overdose death rates per 100,00 persons selected counties in 2017 including Dixie (31), Manatee (33), Okeechobee (24), Pasco (23), and Brevard (23) [3]. By 2019, the death rate in Manatee County increased to 41 per

100,000 persons (leading the state for several years), and there were 9 Florida counties with death rate above 30 per 100,000 persons.

Opioids and Other Drugs Regional Variation 2014-2018

Currently, the state of Florida provides the Drugs Identified in Deceased Persons semi-annual report which has been available online since 2014 (Figure 2) [6]. In addition, the Annual State Epidemiological Outcomes Workgroup (SEOW) has produced reports on Florida Overdose Deaths by subtype and year (Figure 3).

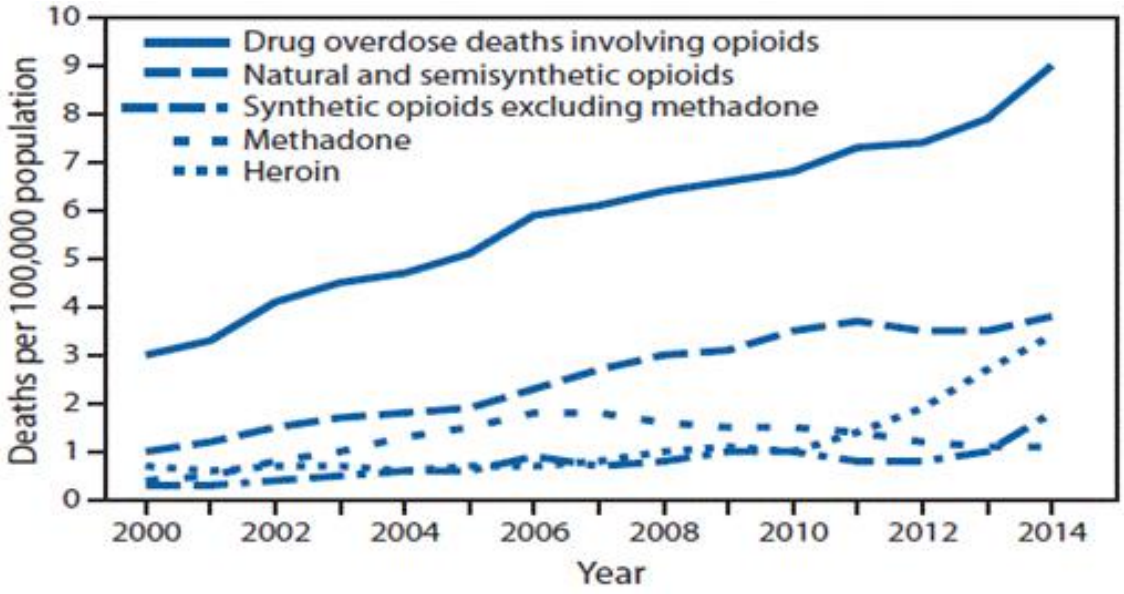


Figure 2: Death Rates in Florida Per 100,000 Persons for Individual Substances (Drugs Identified in Deceased Persons Semi-Annual Report)

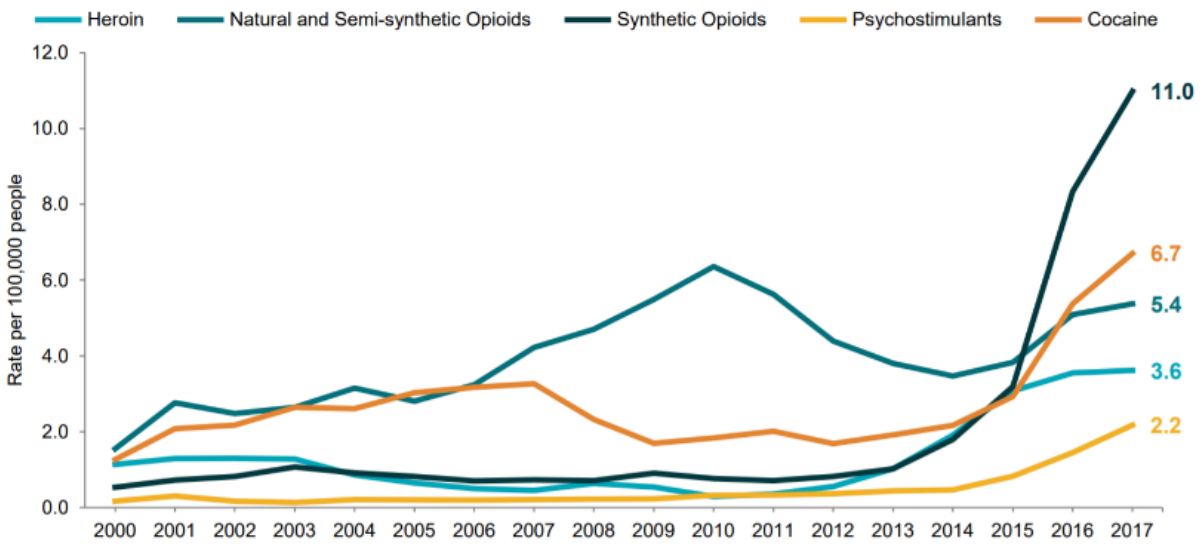


Figure 3: Death Rates in Florida Per 100,000 Persons for Individual Substances (Florida Annual State Epidemiological Outcomes Workgroup (SEOW) Report

There are some possible examples of geospatial clusters of overdose deaths by year. By 2014, opioid overdose deaths (both natural and synthetic) were occurring most often in central and North Florida, while cocaine was primarily impacting the southeast coast (Miami-Dade), and benzodiazepines were widespread on both coasts [3, 6, 7]. In 2015, Dixie County had the highest rates for Xanax (<25) Oxycodone (<25) cocaine (>25) and Vicodin (<15). Manatee County began to see a secular increase in opioid overdose deaths with both morphine (<25) and fentanyl (<25), while Monroe County had issues with cocaine (>25) and Oxycodone (>25) [3, 6, 7]. Benzodiazepines and cocaine overdose deaths decreased in 2015 while their respective areas of influence both shifted towards the west coast of Florida. In 2016, Dixie, Charlotte, and Marion counties had high rates per 100,000 persons of morphine overdose death (<25), whereas Duval, Palm Beach, and Monroe counties had high rates of cocaine related deaths (>25), and Manatee and Duval counties had high rates of fentanyl related deaths (<25) [3, 6, 7].

The impact of cocaine overdose shifted slightly west, while areas that were already struggling with various opioids, like Manatee and Duval counties, started to see encounters with fentanyl as well. By 2017, only Palm Beach and Manatee counties were >25 per 100,000 persons with opioid deaths of any kind (fentanyl and analogues), although, there were concentrated areas of opioid overdose deaths in the Big Bend, northeast, and central west coast [3, 6, 7]. Opioid use continued to be widespread in 2017-2018, but most counties were below 15 opioid overdose deaths per 100,000 persons [3, 6, 7]. The four exceptions were Holmes, Seminole, Liberty, and Lafayette counties with rate greater than 20 per 100,000 persons. However, fentanyl-related deaths spread throughout the majority of Florida with rates of more than 15 per 100,000 persons [3, 6, 7]. Cocaine and fentanyl deaths were mostly concentrated around Seminole county (>25), and the surrounding 5 counties (excluding Lake) were all >15 [3, 6, 7].

Theories Associated with Opioid Overdose Increases

There are many different theories associated with the increase in fatal and non-fatal opioid overdose in the United States since the late 1990s [1, 4]. These range from neurobiological theories, comparing genetic traits of those diagnosed with substance abuse disorders, to examining how the social determinants of health (including the built environment) can mediate an exposure to opioids [1, 4]. Others have suggested that the differing pharmacological properties of new synthetic opioids may mediate drug overdose deaths [5].

Some theories postulate that there was a change in opioid prescribing patterns of physicians including patterns influenced by marketing efforts of opioid producing big pharma [4]. Still, other researchers postulate that public health policy changes related to the treatment of pain in the early 21st century have been associated with increased prescribing of opioids by physicians (leading to addiction), including the American Pain Society's efforts throughout the

1990s [4]. As a third potential explanation, the rise of opioid related drug overdose in Florida may have been influenced by the rise and fall of the so called “pill mills” leading increased opioid use and abuse in Florida and across the southern United States [1, 4]. Finally, concerns have been identified in the evaluation of hospital level opioid overdose data over time due to the changeover from classification schemes at the end of 2015 [8]

Purpose of the Work

The purpose of this dissertation was to investigate the prevalence and factors associated with fatal and non-fatal opioid overdose in Florida. This work utilized data from several disparate sources including the Florida Agency for Health Care Administration (AHCA) inpatient and emergency room discharge data from 2009-2020, the Florida Sunshine Act physician records of payment by medical manufacturers 2010 to 2020, and the Centers for Medicare and Medicaid Services: open payments and Medicare part D 2010-2020. Using these sources, three related areas of research were examined in separate manuscripts. The aims for the three research studies were to: (i) explore the relationship between pharmaceutical marketing of transfers of value to individual Florida physicians their subsequent rate of opioid prescriptions; (ii) perform a sociodemographic analysis of geospatial clustering in non-fatal opioid overdose in Florida; and (iii) examine the impact of the International Classification of Diseases transition from the Ninth Edition (ICD-9-CM) to the Tenth Edition (ICD-10-CM) which occurred on October 1, 2015 for diagnoses made during inpatient and emergency department encounters. For this analysis, the focus was on examining how the transition from ICD-9-CM to ICD-10-CM was related to prevalence and trends of SUD-related hospital encounters and documentation of related physiological co-morbidities in discharge data.

Research Questions

1. What is the relationship between pharmaceutical opioid marketing of transfers of values to Florida physicians and the number of opioid prescriptions written per patient? (Chapter #2)
2. To what extent are geospatial clusters of sociodemographic characteristics associated with rates of fatal and non-fatal opioid overdose in Florida? (Chapter #3)
3. To what extent has the transition from ICD-9 to ICD-10 had on annual rates of opioid use disorders (as primary and secondary diagnosis) on emergency department and in-patient hospital admissions in Florida? (Chapter #4)
4. To what extent has the ICD-9 to ICD-10 transition resulted in changes in documented physiological comorbidities documented among patients with of opioid use disorders? (Chapter #4)

Hypotheses

1. Opioid-focused pharmaceutical marketing of transfers of values to Florida physicians (such as meals, breakfast/lunch/dinner presentations in office, consulting fees, speaking engagements or appearance fees associated with payment) will be positively associated physicians' rates of opioid prescriptions. (Chapter #2)
2. The postulated relationship between pharmaceutical marketing and physician opioid prescribing rates will occur for multiple definitions of physician receipt of transfers of value including (i) any receipt of transfer; (ii) frequency of transfers of received; and (iii) dollar value of transfers received. (Chapter #2)

3. Sociodemographic indicators of disadvantaged neighborhoods (e.g., low median household income, high crime rates) in Florida will be associated with geospatial autocorrelation of county-level fatal and non-fatal opioid overdose. (Chapter #3)
4. The postulated association between disadvantaged neighborhood status and county-level fatal and non-fatal opioid overdose will be independent of race and ethnicity representation across geographic areas, as well as secular changes in racial and ethnic geographic makeup. (Chapter #3)
5. Physiological comorbidity profiles secondary to opioid-related diagnoses in Florida have become more complex and severe over a 10-year period due to availability of more diagnosis code fields in the data and/or a new code system (10th edition vs. 9th edition) (1998-2018). (Chapter #4)
6. Independent of secular changes in the occurrence of opioid dependence in Florida, formal modifications to the DSM and ICD classification systems will be associated with an immediate increase in rates of fatal and non-fatal opioid overdose death. (Chapter #4)

Significance of the Work

For Chapter #2, it is plausible that pharmaceutical companies have influenced provider prescribing in a way that has fueled/exacerbated the opioid crisis [9-12]. There are gaps in the opioid literature with regards to understanding the role that pharmaceutical companies played in the ongoing opioid epidemic that is plaguing the United States. This is especially germane to Florida where rates of opioid use disorders have been high as compared to the national average and opioid “pill mills” have existed suggesting that Florida has played a central role in the opioid

crisis [13]. Therefore, it is of public health importance that this topic be better understood so that effective mitigation policies can be put into place.

For Chapter #3, areas where some or all social determinants of health (such as employment, housing, education, food scarcity, healthcare access) are lower than necessary for basic subsistence have been shown to be associated with higher levels of opioid use disorders [14, 15]. The social disadvantage(s) found in these areas often takes the form of increased fatal opioid overdoses, and studies have found that a greater percentage of the opioid mortality can be found in poor counties/regions where there are comparatively lower levels of educational attainment, employment, and family health insurance [16, 17]. However, a gap also exists in understanding the diverse geographic, temporal, and sociodemographic patterns of fatal and non-fatal opioid overdose in Florida. Florida is a large state filled with big cities and large rural areas. While no area has been immune to the opioid epidemic, some areas have fared worse than others. Thus, it is important to understand this variation so that policy makers can be informed, ultimately driving better decision making.

For Chapter #4, another noteworthy gap in the substance abuse literature is examination as to how diagnostic changes related to opioids from the transition from ICD-9 to ICD-10 have impacted annual emergency department and in-hospital rates of opioid use disorders (primary and secondary) Policy makers, health care providers, public health experts, and researchers continue to rely on these discharge data to investigate trends and outbreaks, identify causes and risk factors, and plan for services, referrals, and interventions among vulnerable populations. Therefore, it is important to help administrators and researchers better understand the caveats in this data source related to such an important transition.

Chapter 2:
A Multi-Method Approach to Quantifying the Association between Opioid Marketing and Physician Prescribing Behavior in Florida

Abstract

Background

Multiple factors have contributed to the opioid epidemic in Florida including but not limited to overall poor understanding of the addictive properties of opioids, lack of pharmaceutical regulations, and prescribing behaviors of physicians. Because a person's first encounter with opioids is often from a prescription, it is important to examine the relationship between pharmaceutical marketing efforts and opioid prescribing by physicians.

Methods

We used data from the Sunshine Act, a Florida public record of all marketing efforts an individual physician receives each year since 2013, and Medicare part D physician payments which includes individual physician records of opioid-specific billing and prescribing rates each year. These data were merged to create a database of physicians linked to their acceptance of transfers of value related to opioid marketing efforts. Unmatched multivariable and propensity score matched Poisson regression models were fit to examine the relationship between pharmaceutical transfers of values to physicians and their corresponding prescribing rates of opioids per 100 patients. We evaluated three definitions of physician exposure to pharmaceutical marketing: (i) receipt of transfer(s) of any value; (ii) number of transfers of value received; and (iii) dollar amount of transfers received.

Results

The sample included 29,992 physicians in Florida, of whom, 3,918 (13.1%) accepted transfers of value from opioid manufacturers over the years 2013 to 2017. We found mixed evidence for a relationship between pharmaceutical marketing efforts and the likelihood for physicians who received transfers of value to prescribe opioids. First, in both the unmatched and matched analysis, the binary definition of exposure (receipt of any transfer of value) was not associated with physician prescribing rate of opioids per 100 patients. In the unmatched analysis, physicians who received the highest annual number of transfers (11.5 or more) had a higher prescribing rate of opioids compared to physicians who did not receive transfers (adjusted relative risk (RR) = 1.49, 95% confidence interval (CI): 1.45 – 1.53, $p < 0.0001$). Results were generally similar when evaluating annual dollar value of transfers received (exposure definition iii). In contrast, in the unmatched analysis, physicians who received either 1 or 1 to 3 transfers had a non-significantly lower rate of opioid prescriptions per 100 patients (adjusted RRs of 0.82 and 0.94, respectively) compared to physicians who did not receive transfers. Similar results were observed in the matched analysis.

Conclusions

This analysis did not find evidence of a dose response relationship between extent of pharmaceutical marketing and physician rate of opioid prescriptions per 100 patients. Although the analysis indicated that pharmaceutical marketing to physicians at the highest level, particularly the number of transfers of value provided to physicians, was associated with higher rates of opioid prescriptions, it also indicates the need for more research, especially in terms of optimal classification as to manner that pharmaceutical marketing to physicians is quantified. Such improvement in physician exposure classification will almost certainly improve our

understanding as to how pharmaceutical marketing to physicians influences prescribing behavior. This may lead to new and improved public health policy interventions in Florida directed towards limiting or mitigating negative influences of pharmaceutical marketing to physicians.

Introduction

Research has shown that the rise in overdose-related deaths is due to a combination of factors, including but not limited to social determinants of health, poor understanding of the addictive properties of pharmaceutical opioids, poor health policy (lack of pharmaceutical regulations), and physicians' prescribing behavior [4, 18, 19]. Changes in physician prescribing behavior at the start of the opioid epidemic may have contributed to the sharp rise in opioid overdoses [18].

In Florida, opioid-prescribing rates have been consistently higher than the rest of the United States (U.S.) [4, 19]. According to the Centers for Disease Control and Prevention (CDC), compared to a 2006 U.S. rate of 72.4 opioid prescriptions per 100 persons, the corresponding prescription rate in Florida was higher at 79.7 per 100 persons, and the Florida rate increased to 87.3 per 100 persons in just 3 years. The high prescribing rate in Florida remained until about 2014 which is when the prescription drug monitoring act was passed [4, 19]. Following this passage, in 2018 Florida's prescription rate was lower at 60.9 per 100 persons [4], however, this lower rate still remained above the national average of 51.4 per 100 persons.

Factors that impact physicians' opioid prescribing behavior is an important, active field of research [19-24]. Some studies in this area have reported an association between pharmaceutical marketing of opioids and subsequent changes in prescriber behavior, as reflected

by increases in opioid dispensing rates following increased marketing activities [21, 22, 24]. Analysis of prescribing practice is important because a person's initial encounter with opioids usually emanates from a physician's prescription [4].

Multiple publications support the postulate that pharmaceutical marketing to physicians influences subsequent prescribing behavior. A cross-sectional study of United States counties involving 65,000 physicians reported increased prescribing rates in counties where marketing occurred [21]. Similarly, the "Follow the Money" study from New York in 2018 found that 1 in 10 physicians had received money or gifts (median value of about $3,500) from opioid manufacturers, and such gifts were associated with substantive increases in prescriptions being written [24]. Another observational study analyzed 2013-2015 data from a cohort of about 6,400 physicians from around the United States and found that receipt of marketing-related items of value was associated with higher prescribing levels [25]. This study is methodologically noteworthy (e.g., potentially less biased) because it matched on different prescribing characteristics and used a difference-in-difference analysis to control for potential confounders.

The empirical evidence suggesting an association between pharmaceutical marketing and physician prescribing behavior is consistent with a recent lawsuit and criminal complaint filed by the state of Florida against several of the major opioid manufacturers Purdue, Endo, Cephalon, Jansen, Teva, and Allergan. This complaint alleges the following:

"Defendants cooperated to sell and ship ever-increasing quantities of opioids into Florida. To create newfound demand for opioids, Defendants used unfair and misleading marketing – including the use of front groups, paid "opinion leaders," and Continuing Medical Education courses ("CMEs") – to convince both doctors and patients that opioids could safely be prescribed for common ailments that cause chronic pain [26]."

The allegations from this lawsuit provide a scientific (and legal) rationale to examine the effects of opioid marketing on prescriber behavior specifically in Florida [26]. Moreover, given the role that Florida played in the opioid crisis – such as the pill mills that fostered the spread of illegally diverted opioids across the eastern United States – an increased understanding of root causes within the state could be beneficial to prevent future problems of a similar nature [13, 26-29].

Notwithstanding the literature reviewed above, gaps exist in the current body of research, in large part due to methodological limitations including but not limited to use of cross-sectional designs and relatively small sample sizes [18, 20-24], as well as county-level assessments rather than the more preferred assessment of individual providers, inadequate time periods of assessment, and suboptimal control of confounding when estimating the influence of pharmaceutical marketing on physician prescribing patterns. Therefore, this study aimed to improve understanding of the association between pharmaceutical marketing and opioid prescribing patterns of physicians in Florida. This included analyzing individual provider prescribing patterns over a 5-year period (2013-2017) which is postulated to represent a sufficiently long timeframe for analysis [21, 22, 24]. By design, this study also used multivariable regression and propensity score methodology [30-32] with the goal of achieving better control for confounding (less bias) as compared to previous studies. For this analysis, we hypothesized that increased pharmaceutical opioid focused marketing efforts to individual physicians in Florida, as quantified by frequency of marketing contacts and US dollar value, would be associated with higher rates of opioid prescriptions written.

Methods

Medicare Part D Utilization and Payment Data

This dataset permitted identification of Florida physicians who prescribe opioids during their practice. Organized individually by year, downloadable text files contain information on physician-level opioid prescribing data by name, practice, and prescribing rate per 100 persons, as well as billing information that includes the number of patients seen per year. The dataset includes an average patient "risk score" based on the CMS Hierarchical Condition Categories (CMS-HCC) to better characterize the severity of their patient panel [33]. The HCC has been implemented since 2003 as a risk adjustment model that calculates scoring for Medicare beneficiaries (both disabled and aged) and represents the expected medical cost to Medicare in the upcoming year. The risk score for each person is calculated using the *Demographics + Diagnosis/Diagnoses = Risk Adjustment Factor (RAF) Score. Demographics* include age, gender, and whether a patient is in a community/nursing home or a current enrollee of Medicare/aid; *Diagnoses* constitutes a list of all medical conditions listed hierarchically based on the International Classification of Diseases, Tenth Edition (ICD-10). The resultant RAF values are assigned HCCs, where sicker patients have a higher RAF. The RAF values are additive and the base level RAF is always less than 1 [33].

The Physician Payments Sunshine Act Database

This is a publicly searchable database (available at https://openpaymentsdata.cms.gov/) that began in 2013 from which physician level data files for Florida during the years 2013-2017 were downloaded. These files contain detailed information on physician's name, practice type, location, itemized payments accepted, who paid them, the nature of the payment (dinner out,

office lunches, speaking), the drug or device being discussed, the frequency of contact, and the US dollar value of any transfers received (i.e., the primary study exposure).

Study Sample

From the Medicare Part D database, we identified 40,500 providers of opioid medications, each who had an opioid prescribing rate of at least 1 per 100 patients. We excluded 5,978 providers who did not have an opioid prescribing rate of at least 1 per 100 patients because it reflected insufficient variability to examine the relationship between pharmaceutical opioid marketing and opioid prescribing rate. Incorporation of data from the Sunshine Act dataset required identifying opioid-related transfers of value to qualifying physicians, which included marketing for opioid analgesics and specific drugs associated with the use of opioid interventions, such as specialized laxatives and pumps for liquid opioids. We included payment of all types including speaking engagements, teaching, travel, conferences, lunches, pens, pads of paper, etc. There were 5,217 physicians who had documentation of accepting at least one qualifying payment. Following the work of Hadland (2018) and Schieber (2019), we excluded research- and equity-related payments that may include intellectual property and dividends because they are less likely to be direct targeted marketing efforts designed to produce an increase in opioid related prescribing behavior [21, 22, 24].

We merged the Medicare D set with Sunshine Act Payments to ascertain detailed payment information for providers in the study; those without a record in the Sunshine Act database were assumed to have no opioid-related transfers of value. An initial challenge was absence of a common identification number or identifying factor that would allow for a simple direct merge of provider information between the two data sources. Therefore, using a stepwise hierarchical data linkage algorithm that used various exact and fuzzy linkages based on a

combination of physician's surname, first name, practice type, and zip code of practice, we left merged providers from the Sunshine Act data set (n=5,217) to the Medicare provider data (n=40,500). Using this approach, we were able to match 4,528 physicians. Using additional information obtained through the linkage, we then removed all non-physicians (n=5,989). Of the 29,992 opioid prescribing physicians in Florida, we linked 3,918 to a payment record in the Sunshine Act Database (Figure 4). All data linkage and cleaning were performed with SAS 9.4 software.

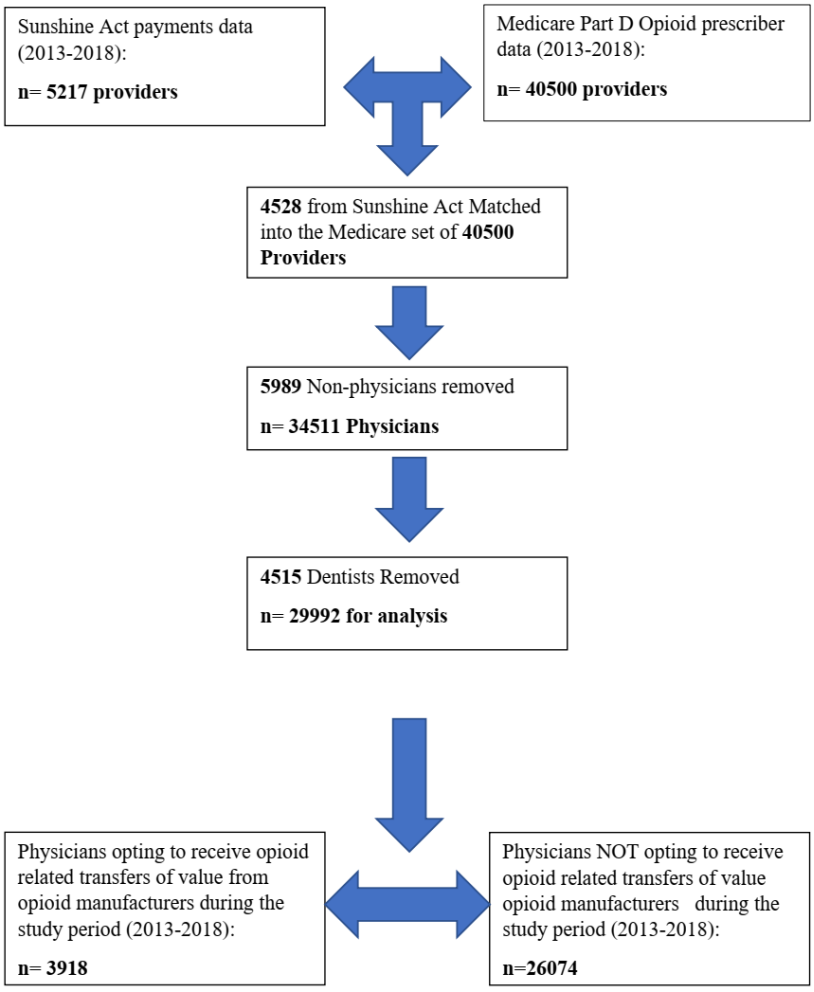


Figure 4: Variable Selection Procedure

Outcome and Exposure

The primary outcome of interest was the physician opioid prescribing rate, expressed as the number of opioid prescriptions per 100 patients. The primary exposure was physician acceptance of transfers of value directly related to opioid marketing efforts. While different definitions of "marketing" exist, for this study "marketing" included transfers of value directly related to opioid marketing efforts, including meals, breakfast/lunch/dinner presentations in office, consulting fees, speaking engagements or appearance fees associated with payment (e.g., honoraria). The exposure was operationalized in three different ways. First, for each provider and for each year, we explored whether any acceptance of a transfer of value (a binary indicator) might impact prescribing behavior, regardless of the number of transfers or the total cash value. For this definition, 3,918 of the total 29,992 providers (13.1%) were classified as exposed.

We next considered an exposure measure based on the frequency of transfers of value received by the provider. Most providers received 0 (n=26,074, 86.9%) 1 (n=1974, 6.5%), or >1 to 3 (n=1,282, 4.3%) transfers. Therefore, these levels were defined as separate groups with 0 transfers serving as the referent group. For the remaining distribution of providers with more than 3 transfers, we identified the number of transfers at the 75% percentile to define a potential "threshold" value. This corresponded to 11.5 or more transfers (n=282, 0.9%) received. The remaining portion of the distribution (from >3 to < 11.5 transfers) was 642 physicians (2.1%)

For the third exposure measure based on annual dollar value of transfers received, again, physicians who did not receive a transfer served as the referent group. The remaining portion of the distribution was split by quartiles to include the categories < $16 (n=1,131, 3.8%), $16 to < $30 (n=1,007, 3.4%), $30 to < $76 (n=1,023, 3.4%), and more than $76 (n=1,019, 3.4%).

Model Covariates

Other independent variables for analysis were limited to those included in the Medicare and the Sunshine Act data sets. Although data on physician received payments were available on an annual basis, we collapsed all 5 years that a physician received payments into an average annual amount per year. With this approach, physicians did not have to be in the study for all five years. The other provider-level variables in the dataset included the annual number of Medicare beneficiaries provided opioids at least once, gender of the physician, the HCC risk score, the annual total number of opioid pills supplied, the annual number of claims submitted to Medicare, the location of the practice, and the physician's specialty which was grouped into four practice groups due to the large variation in specialties (n=78). The 4 groups included general practice, chronic pain treatment, surgeons, and other practice.

Analysis

We used descriptive statistics to initially compare characteristics of physicians who did and did not accept at least one marketing transfer of value from an opioid manufacturer. For both continuous and categorical variables, we calculated the standardized mean difference (SMD) with a value of .10 or higher considered to represent a meaningful difference between the two groups (potential confounding variable).

To control for confounding, we used two approaches. First, we fit a covariate-adjusted physician practice-group nested Poisson model using random intercepts with compound symmetry correlation matrix to account for the correlation between practice subtypes of the physicians. The model was fit by regressing the continuous variable of annual physician prescription rate with the three different exposure definitions (defined above) evaluated in

separate models, while adjusting for HCC risk score, the quantity and dollar value of claims billed to Medicare, number of opioid pills prescribed, physician gender, and physician specialty.

In the second approach, we used matched propensity score methodology [30-32], Specifically, we fit a logistic regression model with receipt of opioid related payments (yes/no) as the outcome variable and variables available in the Medicare Part D database as predictor variables. From this model, propensity scores [30-32] of the estimated probability of receiving one or more transfer of value were calculated. We then used 1:1 propensity score matching (PSM) with a maximum propensity score probability difference of 0.01 to construct matched groups of physicians who did or did not receive opioid related payments. Theoretically, this propensity score method aimed to achieve a balanced distribution of confounders across the comparison groups, and thereby more closely emulate the properties of a randomized clinical trial [30-32]. After use of the matching algorithm, there were 6,776 physicians evenly balanced into two groups each of 3,388 physicians consisting of those providers who opted to accept opioid related transfers of value and those who did not. As described above, SMDs were calculated to examine the balance of covariates before and after matching of physicians who did and did not receive transfers of value. These analyses were completed using SAS version 9.4.

Results

The unadjusted analysis included 29,992 physicians, of whom, 3,918 (13.1%) accepted transfers of value from opioid manufacturers (Table 1). Physicians who accepted transfers of value had a higher median number of Medicare claims (median = 219, IQR: 71, 655) compared to physicians who did not receive transfers of value (median = 42, IQR: 20, 104 (SMD = 0.62). Similarly, the median number of opioid related expenses billed to Medicare was also higher among physicians who accepted transfers of value compared to those that did not ($6,300 versus

$490 (SMD = 0.42), as was the median number of treated patients using opioids (75 versus 32), (SMD = 0.61). Physician gender was similar between the two groups whereas physicians who accepted transfers of value were more likely to be pain specialists (12.1% versus 1.1%). Male physicians had higher median prescription rates than female physicians (13.6 versus 7.4). Of the specialty groups, pain specialists had the highest percentage of physicians choosing to receive transfers (61.3%) compared to surgeons (13.6%), general practice physicians (12.8%), and those in other specialties (9.3%). After propensity score matching, physicians who did and did not receive transfers of value were similar on all characteristics (SMD < .10).

Unmatched Analysis

In the unmatched multivariable Poisson regression analysis, there was no association between physician receipt of transfers of value (yes/no) and the rate of opioid prescriptions per 100 patients (rate ratio (RR) = 0.97, 95% confidence interval (CI): 0.77-1.24, p=0.84) (Table 2, exposure definition #1). The number of claims billed to Medicare, the number of pills prescribed, and pain and surgery specialties were associated with a higher rate of opioid prescriptions.

When evaluating the annual frequency of transfers of value (exposure definition #2) with no transfers received as the referent group, physicians who received either 1 or 1 to 3 transfers had a non-significantly lower rate of opioid prescriptions per 100 patients (adjusted RRs of 0.82 and 0.94, respectively (Table 2). In contrast, physicians who received more than 3 and less than 11.5 transfers had a significantly higher rate of opioid prescriptions per 100 patients (RR = 1.32, 95% CI: 1.13 – 1.55, p = 0.0005), as did physicians who received 11.5 or more transfers of value (RR = 1.49, 95% CI: 1.45 – 1.53, p < 0.0001). Results were generally similar when evaluating annual dollar value of transfers received (exposure definition #3). In this analysis, physicians who received more than $76 per transfer (highest exposure category) were 1.35 times more

likely (95% CI: 1.16 – 1.57) to have a higher rate of opioid prescriptions compared to physicians who did not receive transfers of value.

Table 1. Comparison of Covariates Before and After Propensity Score Matching by Exposure History

Variable	Unmatched			Matched		
	Exposed (n=3918)	**Unexposed (n=26074)**	**SMD**	**Exposed (n=3388)**	**Unexposed (n=3388)**	**SMD**
Number of Medicare Claims, Median (Q1, Q3)*	219.3 (70.8, 654.8)	42.4 (20.3, 103.6)	0.61	196 (71, 472)	185 (49, 470)	0.05
Amount Opioid-Related Billed (USD), Median (Q1, Q3)**	6299.7 (1395.9, 30435.3)	490.4 (198.2, 1686.6)	0.42	5359 (1363, 17120)	3512 (416, 13260)	0.07
Medicare Patients Treated, Median (Q1, Q3)***	74.7 (34.6, 153.6)	31.7 (18, 62)	0.59	65 (30, 116)	72 (30, 131)	0.01
Number of Opioid Pills Supplied, Median (Q1, Q3)****	5041 (1184.6, 17158.4)	400 (148, 1598)	0.60	4406 (1188, 11349)	3770 (433, 10881)	0.06
HCC Risk Score, Median (Q1, Q3)	1.49 (1.2, 1.7)	1.64 (1.2, 1.8)	-.26	1.47 (1.20, 1.64)	1.44 (1.17, 1.62)	0.09
Physician Specialty (%)						
General	1895 (48.3)	12847 (49.2)	0.01	1813 (53.5)	1813 (53.5)	0.0
Other	969 (24.7)	11049 (42.3)	0.26	768 (22.6)	768 (22.6)	0.0
Pain	477 (12.1)	302 (1.1)	-0.45	204 (6.0)	204 (6.0)	0.0
Surgery	710 (18.1)	5393 (20.6)	0.02	603 (17.7)	603 (17.7)	0.0
Female Provider	772 (19.7)	7435 (28.5)	-0.07	682 (20.1)	622 (18.3)	0.05

SMD: Standardized Mean Difference. *Annual yearly claims processed through Medicare. **Annual opioid related billing processed through Medicare. ***Annual number of Medicare patients treated with opioids. ****Annual number of opioid pills supplied to Medicare patients.

Table 2. Unmatched Poisson Regression of Association Between Physician Receipt of Transfers of Value and Rate of Opioid Prescriptions per 100 Patients (N=29,847)

Parameter	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**P-value**
Exposure definition #1: Any receipt of transfer (vs. none)	0.97	0.77	1.24	0.84
Covariates				
HCC risk score (per 10 units)	0.87	0.12	6.23	0.89
Number of claims billed to Medicare (per 100 patients)	4.12	3.26	5.22	<.00001
Dollar amount of claims billed to Medicare (per $1,000)	1.11	0.74	1.82	<.00001
Number of opioid pills prescribed (per 10 pills)	0.64	0.60	0.68	<0.0001
Female physician	0.86	0.71	1.03	0.09
Physician specialty (vs. General)				
Pain	3.50	3.06	4.01	<0.0001
Surgery	2.97	2.89	3.06	<0.0001
Other	1.85	1.76	1.95	<0.0001
Exposure definition #2: Annual frequency of transfers of value (versus none)				
1	0.82	0.64	1.04	0.10
>1 to 3	0.94	0.72	1.23	0.66
>3 to <11.5	1.32	1.13	1.55	0.0005
11.5 or more	1.49	1.45	1.53	<0.0001
Exposure definition #3: Annual dollar value of transfers received (versus none)				
< $16	0.83	0.61	1.13	0.24
$16 to < $30	0.74	0.53	1.05	0.09
$30 to < $76	1.01	0.85	1.20	0.93
More than $76	1.35	1.16	1.57	0.0001

Matched Analysis

In the propensity score matched analysis, physician receipt of any transfer of value (exposure definition #1) was not statistically associated with the rate of opioid prescriptions per 100 patients (RR = 0.91, 95% CI: 0.81 – 1.01, p = 0.08) (Table 3). For exposure definition #2, annual receipt of one transfer of value was associated with a significantly lower rate of opioid prescriptions (RR = 0.82, 95% CI: 0.73 – 0.92, p = 0.0009), whereas physician receipt of 11.5 or

more transfers of value was associated with a significantly higher rate of opioid prescriptions (RR = 1.53, 95% CI: 1.24 – 1.87, p < 0.0001). For exposure definition number three, and as compared to no receipt of transfers of value, physicians who received less than $76 per transfer had a lower rate of opioid prescriptions whereas only the highest exposure category of transfers more than $76 were associated with a nominally higher rate of opioid prescriptions per 100 patients (RR = 1.20, 95% CI: 1.04 – 1.39, p = 0.01).

Table 3. Matched Poisson Regression of Association Between Physician Receipt of Transfers of Value and Rate of Opioid Prescriptions per 100 Patients (N= 6776)

Parameter	**Estimate**	**Lower 95% CI**	**Upper 95% CI**	**P-value**
Exposure definition #1: Any receipt of transfer (vs. none)	0.91	0.81	1.01	0.08
Exposure definition #2: Annual frequency of transfers of value (versus none)				
1	0.82	0.73	0.92	0.0009
>1 to 3	0.86	0.74	1.00	0.06
>3 to <11.5	1.12	0.97	1.29	0.12
11.5 or more	1.53	1.24	1.87	<0.0001
Exposure definition #3: Annual dollar value of transfers received (versus none)				
< $16	0.81	0.70	0.94	0.006
$16 to < $30	0.77	0.65	0.91	0.002
$30 to < $76	0.90	0.82	1.00	0.05
More than $76	1.20	1.04	1.39	0.01

Discussion

Using a statewide cohort of physicians whose practices included Medicare patients from the state of Florida, we found mixed evidence for a relationship between pharmaceutical marketing efforts and the likelihood for physicians who received transfers of value to prescribe opioids. In the larger unmatched analysis, nearly 4,000 physicians made the choice to receive at least one transfer of value from opioid manufacturers during the five years of the study period,

which could take the form of salary from speaking engagements and other honoraria, offices lunches, dinners out, travel and lodging, etc. Using different definitions of exposure there was a general indication that physicians who received a high frequency and high dollar amount of transfers had higher rates of opioid prescriptions per 100 patients. However, as compared to physicians who did not receive transfers of value, there was also a suggestion that low marketing exposure (i.e., few transfers received, and lower dollar amounts of transfers) was associated with lower rates of opioid prescriptions per 100 patients. Thus, at the broadest level, this analysis did not find evidence of a dose response relationship between extent of pharmaceutical marketing and physician rate of opioid prescriptions per 100 patients.

In terms of the highest level of exposure (receipt of transfers of value), our analysis suggests that the number of transfers of value received may have more impact on the rate in which physicians prescribe opioids, as compared to the dollar value of transfers received. While our results are tentative, this suggestion was slightly unexpected as it was initially expected that the amount of money received by physicians would be most strongly associated with opioid prescribing rates. If our results are true, they lend credence to other theories that suggest that there is a psychological component to the sheer number of manufacturer contacts that potentially drives physician behavior [9, 28]. This is consistent with the finding that the higher the level of pharmacy sales representatives' interaction with physicians and residents is associated with lower prescription rates for generic drugs along with higher costs of prescribing and non-rational prescribing and speedy adoption of prescribing new drugs [9, 11].

In this regard, Van Zee points out that during the early years of the opioid epidemic, the larger drug companies like Purdue funded thousands of pain-related educational programs throughout the US, using methods like grants and sponsorships to blur the lines between

marketing and education, making it even harder for physicians to get reliable prescribing information [9, 11]. Our indication of the highest levels of pharmaceutical marketing being associated with higher prescribing rates of opioids is consistent with the research by Hadland (2018) and Zezza (2018) who reported that opioid manufacturers who used their sales force were able to influence the prescribing behaviors of the physicians [11, 21, 24].

The lack of evidence for a dose response relationship in our analysis is puzzling and difficult to explain, and a likely reason for which the crudest definition of exposure (any transfer of value versus none) was not associated with physician rate of opioid prescriptions in both the unmatched and matched analysis. While entirely speculative, it is possible that physicians who elected to receive small amounts of transfers of value later questioned the motivation and integrity for which the transfers were provided by the pharmaceutical industry, thereby predisposing to an overall reluctance of the receiving physician to prescribe opioids. Alternatively, the lack of dose response relationship may simply be the result of residual confounding and/or overall poor exposure measurement and classification. At a minimum, our analysis indicates the need in future research for more granular and balanced exposure group classification of physician exposure history as well as possible need to separately examine individual types of transfers of values received rather than using a "catch-all" approach for all transfers of value.

Strengths and Limitations

Strengths of this study include assessment of physician exposure to pharmaceutical marketing and rate of opioid prescribing at the individual (physician) level, large sample size, multi-years of evaluation, and multiple methods used to control confounding. This study also has limitations. First, our data permitted statistical adjustment for only a limited number of measured

factors. Almost certainly, there are many factors not included in our analysis that are strongly associated with physician prescribing behavior and may also be associated with the likelihood for physicians to be receptive to accepting transfers of value. Second, our analysis relied solely on physicians from Florida who service Medicare patients and thus captures only a small fraction of the total patient population who are prescribed opioids. Third, there may have been errors in our matching process as we did not have a common identifier and thus used provider name, practice type and zip code to match physicians between the Medicare D and the Sunshine Act data. The expected net effect of errors in the matching process would be bias towards the null hypothesis of no association. Fourth, the approach to quantifying the amount of contact a sales representative had with a physician was linked only to the receipt of transfers of value and thus did not consider the amount of sales representative contact with the physician that did not result in transfers of value. Again, this circumstance provides a future rationale for more granular quantification of pharmaceutical marketing exposure to physicians. Similarly, in terms of the rationale for more granular exposure classification, we were not able to split payments received by subtype (such as dinners, honoraria, etc.) due to record quality (e.g., missing, or unmatched descriptions of payment types).

Conclusions

Our analysis provides mixed evidence that pharmaceutical marketing to physicians at the highest level, particularly the number of transfers of value provided to physicians, is associated with higher rates of opioid prescriptions. This postulate adds to the growing public health concern that "big pharma" has too much influence over physicians' prescribing behaviors. Our analysis also indicates the need for more research, especially in terms of optimal classification as to manner that pharmaceutical marketing to physicians is quantified. Such improvement in

physician exposure classification will almost certainly improve our understanding as to how pharmaceutical marketing to physicians influences prescribing behavior. This may lead to new and improved public health policy interventions in Florida directed towards limiting or mitigating negative influences of pharmaceutical marketing to physicians. Still, given the magnitude of marketing by pharmaceutical companies (e.g., financial expenditures) in the US, even markedly improved understanding of how pharmaceutical marketing to physicians influences prescribing behavior may not necessarily lead to needed regulatory changes.

To date, opioid laws in Florida related to easing the burden of the opioid epidemic have been focused on morbidity and mortality, such as treatment programs and expanded Naloxone access. There has been only a mild push towards helping physicians learn about opioid use disorders, and by having them voluntarily examine their prescribing behaviors. These attempts have met with limited success, and more research is needed into other outside factors that may be inappropriately influencing prescriber behavior. This may lead to crafting of legislation that moves toward the mitigation of overprescribing of opioids.

Chapter 3:

The Geospatial Distribution of Pharmaceutical Opioid Marketing Clusters of Non-Fatal Opioid Overdose Data in Florida

Abstract

Background

Identifying geographic areas with high concentrations of drug overdose is important for developing and implementing targeted public health interventions. This ecological study makes use of generalized and specific measures of "hot spots" or clusters of georeferenced variables associated with clusters of non-fatal opioid overdoses in Florida, over a 5-year period. The analysis was conducted in relation to county level socio-demographic characteristics including the geospatial distribution of intentional marketing of opioids to local physicians, and access to treatment availability on measures of opioid non-fatal overdoses.

Methods

We utilized data from the Florida Agency for Healthcare Administration (AHCA), 2010 U.S. Census, Medicare Part-D prescribing rates, Sunshine Act, and the Substance Abuse and Mental Health Services Administration (SAMHSA). Data sets were merged by Florida county and year and first analyzed to detect the presence of spatial autocorrelation of opioid overdoses. We tested for clustering using a generalized Moran's I to test for spatial autocorrelation, eigenvector spatial filtering (ESF) and subsequent Moran's I based ESF (MESF) regression was utilized to assess geospatial autocorrelation. Gettis-Ord (Gi*) analysis was utilized to map the

candidate eigenvectors from each MESF, producing maps for positive spatial autocorrelation. The resulting standardized statistics (z-scores) for both dependent variables were regressed, using linear mixed models (LMM) to control for multiple observations over time.

Results

We identified several significant clusters of opioid overdose hospital admissions during the 4-year study period. Regression analysis showed significant clusters occurring in areas where there were higher proportions of non-whites, opioid prescribers, and treatment for opioid abuse (e.g., naloxone availability).

Conclusions

Features associated with county level clustering of overdose hospitalizations in Florida based on GIS mapping are multifactorial in nature and include, but are not limited to, the race and ethnic makeup of the county, and the availability of opioid treatment resources. County level analysis of opioid overdoses has marginal utility, as it is hampered by variability of demographics in local geography, however, this study does open the door to using more diverse and granular spatial statistics-based techniques.

Background

The geospatial distribution of opioid and other substance-related overdose deaths tracked by surveillance systems have focused primarily on simple choropleth maps with few comparative statistics, despite the effectiveness of geographic information systems (GIS) in conveying more rich information regarding where and why overdose deaths occur. More sophisticated and insightful GIS methodologies are seldom employed by local, state, and federal agencies [1, 3, 4, 34]. Moreover, GIS methods commonly employed rarely assess or account for latent spatial dependence, which can lead to inaccurate inferences [3]. Insufficient considerations of these

methodological issues may miss the importance of the influence of geography on an outcome of interest, and this is extremely important when designing effective, targeted interventions. Therefore, this paper aimed to utilize modern GIS methods to investigate the occurrence and emergence of latent positive and negative geospatial autocorrelation (e.g., “hot spots”) with opioid related overdose hospital admissions in Florida from 2016 to 2019.

At its simplest level, GIS-focused opioid research on certain opioid-related health outcomes, such as counts and rates of overdose and overdose death is done using GIS software to create simple maps called choropleths [35]. These maps utilize changes in shading, colors, or symbols within specifically defined geographic areas to show changes in rates, counts, or averages of an outcome [5, 22, 35-37]. Such maps are simple and easy for laypersons to understand and interpret, however they could potentially miss key insights that could be derived from geographic data, specifically the presence of clustering (residual geo-spatiotemporal autocorrelation) [38]. Clusters occur when neighboring areas have effects on each other causing the outcome of interest (e.g., opioid overdose rates) to increase or decrease due to some inherent factor [36]. There is a moderate amount of opioid-focused research dealing with clustering and other more advanced GIS topics at this time, and localized geographies within certain cities have started to make use of clustering analysis and simple simulations (Austin, Texas; Cincinnati, Ohio) [39, 40]. More advanced analysis of spatial clustering can be utilized to more accurately identify locations with shared determinants of adverse outcomes, which is likely to improve the design and effectiveness of targeted interventions by policy makers [36, 38].

This county-level, 4-year ecological study used advanced techniques of GIS modeling to investigate the occurrence of geospatial autocorrelation amongst Florida counties experiencing non-fatal opioid overdoses in relation to their respective socio-demographic characteristics and

opioid marketing exposure. Geospatial autocorrelation refers to the degree to which one location (e.g., census tract, zip code, county) has a frequency or rate that is similar to nearby locations [36]. We postulated that indicators of disadvantaged counties in Florida would be associated with latent positive autocorrelation of higher rates of opioid overdose admissions (inpatient and emergency department). Additionally, we hypothesized that opioid marketing, prescriber behavior, low county percent insured, high social deprivation index (SDI) a composite of factors indicating area disadvantage, and treatment availability would be associated with clustering of higher rates of opioid overdose admissions (inpatient and emergency department). Furthermore, this association between SDI and positive autocorrelation for non-fatal opioid overdose, and opioid use disorder (OUD) would be independent of race and ethnicity representation across geographic areas, as well as secular changes in racial and ethnic geographic makeup from 2016 to 2019.

Methods

State of Florida Department of Health Substance Use Dashboard

County-level estimates of non-fatal opioid overdose counts were obtained from the above listed dashboard. Age-adjusted non-fatal overdose rates per 100,000 persons were calculated by year for the four years, separately for inpatient (IP) and emergency department (ED) admissions of the study using county level population estimates from Florida Health Charts website [35].

"Population Dashboard" of FLHealthCHARTS

Data from the Florida Department of Health contains county-level sociodemographic information (race, age, ethnicity) and population estimates. Race is listed in three categories by percent, white, black, and other, whereas ethnicity is grouped by percent Hispanic. Also

available are social measures such as percent uninsured, and rates of violent crime per 100,000 persons. Data for racial, ethnic, and social measures were downloaded, by county, for the study years 2016-2019 and presented in the study as percent non-white and percent non-Hispanic [37].

Medicare Part D Utilization and Payment Data

This data set permitted the identification of Florida physicians prescribing opioids during their practice. Organized individually by year, downloadable text files contained information on physician-level opioid prescribing data, by name, practice, and prescribing rate per 100 persons, as well as billing information that included the number of patients seen per year.

Sunshine Act Open Payments

This is a publicly searchable database (available at https://openpaymentsdata.cms.gov/) that began in 2013, from which we downloaded physician level data files for Florida during the years 2013-2017. These files contain detailed information on physician's name, practice type, location, itemized payments accepted, who paid them, the nature of the payment (dinner out, office lunches, speaking), the drug or device being discussed, the frequency of contact and the U.S. dollar value of any transfers received (i.e., the primary study exposure). The data were extracted at the physician level, then aggregated to the year and county level, taking the median frequency of transfers per 1000 opioid prescribers made within the county.

Centers for Disease Control and Prevention U.S. Opioid Dispensing Rate Maps

The data upon which the maps are based represent the rate of opioid prescriptions per 100 persons per year from 2006 to 2019. Data are available for download at both the county and state level. Data for Florida were extracted by county for the years of this study 2016-2019 [41].

Social deprivation index (SDI)

This is composite measure of characteristics based primarily on data collected as part of the American Community Survey to be reflective of the social determinants of health, including: percent living impoverished, percent unemployed, percent without a high school diploma, percent single parent home, percent rent-not-owned, percent overcrowded housing, percent without automobile, and percent below age 65 [42]. Historically, areas that have a high score in any of these areas tend to be less cohesive and transient with little social and financial investment in their communities or neighborhoods, allowing for only very limited social capital, which has also been shown to be associated with opioid overdose death [43]. SDI was assumed to be a measure of poverty and resource availability in communities. SDI was only available for 2015, however, due to the short time frame of the study (5 years) we assumed minimal meaningful secular change within counties.

Analysis

All datasets were aggregated and then merged at the level of the county. Bivariate associations using Pearson's correlation coefficient were examined between non-fatal opioid overdoses treated via emergency department and inpatient hospital admissions (analyzed separately), percent unemployed, violent crime rate per 100,000 persons, percent uninsured, SDI, opioid marketing exposure rate of opioid providers per 1000 opioid prescribers, the county percent non-white, percent non-Hispanic, and the number of methadone clinics and Naloxone providers [44]. Analysis was performed using R 4.2.1.

Using the complete georeferenced, merged data set, raster-map layers were added for each county-level variable of interest to produce a single shapefile: non-fatal opioid overdoses

treated via emergency department and inpatient hospital admissions, percent unemployed, violent crime rate per 100,000, percent uninsured, SDI, opioid marketing exposure rate, the opioid prescription rate per 100,000 persons, the county percent non-white, percent non-Hispanic, and the number of methadone clinics and Naloxone providers. Georeferencing was performed using ArcGis ArcMap 10.7.1.

We extracted the shapefile to R and for all variables in the georeferenced data set we used Moran's test as a measure of spatial autocorrelation (clustering between counties) [36, 45, 46]. Our assumption was that Moran's I would indicate if there was a geographic pattern in non-fatal opioid overdose separated by ED and IP revealing any geographic patterns [46]. Moran's test computes a generalized (between all counties) geographic correlation and an accompanying z-score and p-value where greater than approximately two standard deviations in any direction indicates the possibility of geographic clusters [36, 45, 46]. This test was used to assess the null hypothesis that non-fatal opioid overdose admissions (IP and ED analyzed separately) are randomly distributed[36]. All calculations were performed using open software R 4.2.1 and spdep package.

To control for spatial dependency with respect to the model predictors, Moran eigenvector spatial filtering (MESF) and was utilized [45, 46]. First a spatial weights matrix was created and specified using the georeferenced Florida data set, specified with queens' connectivity where any county with touching borders is characterized as a neighbor [36, 45, 47, 48]. In a process very similar to principal components analysis, this matrix was decomposed into component eigenvectors and the highest values, which represented spatial dependency [36, 45, 47, 48]. The selected eigenvectors were also used to map clusters, using the Gettis-Ord GI* algorithm, that were present in our georeferenced data for our two dependent variables IP and

ED non-fatal opioid overdose admissions [36, 45]. The Gettis-Ord GI* process creates ranked (99%, 95%, 90% confidence of clustering) county-level z-scores which we then mapped [36]. The resulting county level, geospatially normalized z-scores from the selected eigenvectors were included as the outcome variable in a linear mixed model including all variables of interest as coefficients. As a test of sensitivity we modeled our regression using a varying intercept by county and an autoregressive (AR1) covariance matrix to adjust for multiple observations over time per county without controlling for any latent spatial dependency [47, 49]. Matrix calculations were performed using R version 4.01, and Moran eigenvector spatial filtering and regressions were performed using R and the "spmoran" package which provides functions for estimating spatial varying coefficient models, mixed models, and other spatial regression models.

Results

There were 67 Florida counties evaluated over a 4-year period in this ecological study. Most counties (n=44, 66%) experienced a decrease in rates of IP or ED non-fatal overdoses in 2016 and 2017. ED visits exhibited modest but significant positive association (Table 4) with median income ($r= .34$, $p<.001$), number of methadone clinics ($r= .46$, $p<.001$), and naloxone providers ($r =.30$, $p< .001$), whereas there were significant but smaller associations with SDI score ($r = -.24$, $p<.001$) and percent non-Hispanic ($r= -.12$, $p= .04$). IP admissions showed a modest positive association with opioid prescription rate ($r= .30$, $p<.001$) and a small positive association with percent non-Hispanic ($r= .14$, $p=.02$), and naloxone providers ($r= .14$, $p=.01$). There were modest, negative associations with percent non-white ($r= -.28$, $p< .001$) percent poor ($r= -.25$, $p<.001$) and SDI score ($r = -.19$, $p =.002$).

Table 4: Correlation with Non-Fatal Opioid Overdose

Variable		*Pearson's r*	*p-value*
Prescription Rate			
	Emergency Dept	0.06	0.37
	Inpatient Admission	0.30	<.0001
Percent Uninsured			
	Emergency Dept	-0.01	0.87
	Inpatient Admission	0.05	0.45
Violent Crime Rate			
	Emergency Dept	0.09	0.14
	Inpatient Admission	-0.01	0.84
Median Income			
	Emergency Dept	0.34	<.0001
	Inpatient Admission	0.06	0.3
Percent non-Hispanic			
	Emergency Dept	-0.12	0.04
	Inpatient Admission	0.14	0.02
Percent Non-white			
	Emergency Dept	0.03	0.62
	Inpatient Admission	-0.28	<.0001
Percent Poor			
	Emergency Dept	-0.35	<.0001
	Inpatient Admission	-0.25	<.0001
Naloxone Providers Per 100,000			
	Emergency Dept	0.30	<.0001
	Inpatient Admission	0.14	0.02
Methadone Clinics			
	Emergency Dept	0.47	<.0001
	Inpatient Admission	0.11	0.08
SDI score			
	Emergency Dept	-0.23	0.0001
	Inpatient Admission	-0.19	0.001
Opioid Marketing			
	Emergency Dept	-0.05	0.39
	Inpatient Admission	0.04	0.50

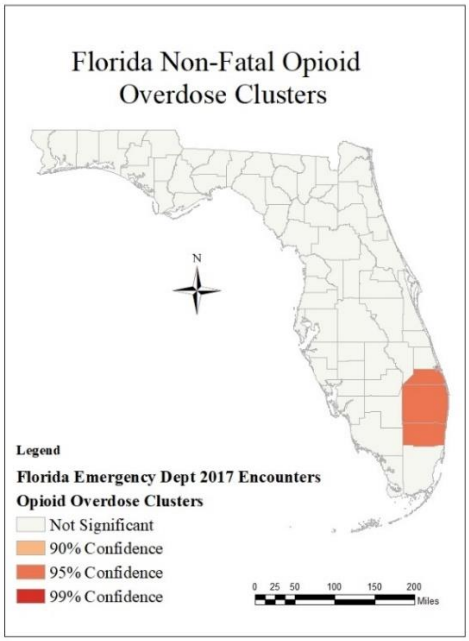
Emergency Department Encounters

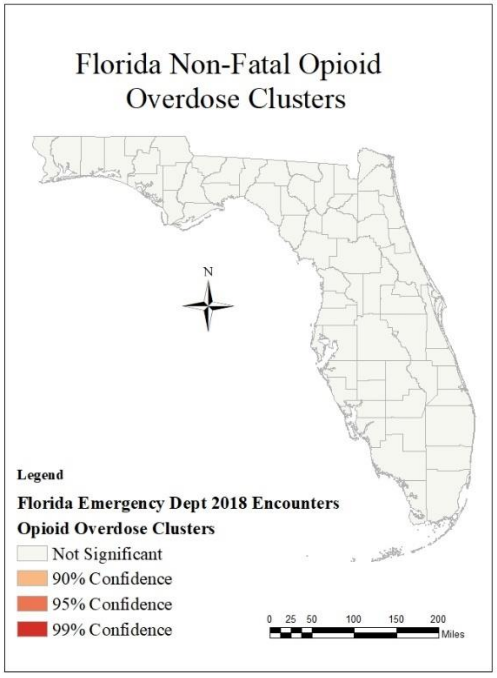
Non-fatal opioid overdose ED visit rates exhibited significant geospatial clustering (Figure 5). In 2016, at the highest confidence was Manatee (99 percent) (166 per 100,000 persons) and surrounding counties of Sarasota (53 per 100,000 persons), Hillsborough (47 per 100,000 persons), and Desoto (22 per 100,000 persons), while two counties surrounding Palm Beach (111 per 100,000 persons), Broward (78 per 100,000 persons), and Martin (66 per 100,000 persons) were at 90 percent significance. Again in 2017, Palm Beach (111 per 100,000 persons), Broward (70 per 100,000 persons), and Martin (6 per 100,000 persons) were at the 90 percent significance. Between 2018-2019, Manatee averaged 341 per 100,000 persons and neighbors Sarasota, Hillsborough, and Desoto averaged 103, 40, 30 per 100,000 persons, respectively.

Spatially adjusted linear mixed model regression (Table 5), revealed that for every methadone clinic added to a county, the corresponding significant clusters or "hot spots" z score increased by .36 standard deviations (CI .17, .54, $p<.001$). For every Naloxone prescriber added to a county, the z-score increased by .097 standard deviations (CI .04, .15, $p<.001$), while for every one percent increase in non-Hispanic residents, the county level z-score dropped by -.22 standard deviations (CI -.47, .04, $p<.097$) although this number was not statistically significant.

Table 5: Linear Mixed Model Regression of Significant Clusters of ED Encounters

	Estimate	Lower CI	Upper CI	p
County Opioid Prescription Rate (per 100,000)	0.005	-0.001	0.010	0.076
County Percent Uninsured	-0.015	-0.053	0.023	0.437
County Violent Crime (per 100,000)	-0.002	-0.003	-0.001	0.002
County Median Income	0.000	0.000	0.000	0.580
County Percent Non-Hispanic**	-0.220	-0.479	0.040	0.097
County Percent Non-White**	0.024	-0.186	0.235	0.821
Naloxone Prescribers	0.097	0.042	0.151	0.001
Number of Methadone Clinics	0.362	0.179	0.545	<0.0001
SDI	-0.002	-0.015	0.011	0.739
Opioid Marketing Rate (per 1000 physicians)				
Less than 50	-0.065	-0.395	0.265	0.699
Greater than 50 less than 275	0.204	-0.212	0.621	0.337
Greater than 275	0.237	-0.172	0.647	0.256
*CI- 95% confidence interval ** Rounded to nearest whole number				





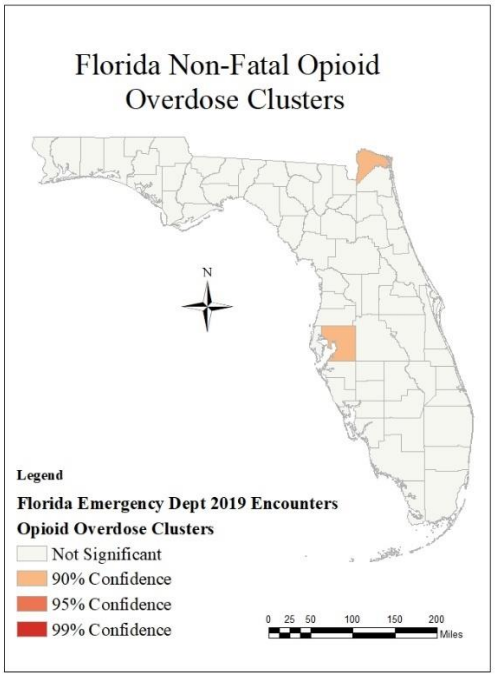


Figure 5 continued: Clusters of Non-Fatal Emergency Department Opioid Overdose Rates

Inpatient Admissions

Non-fatal opioid overdose IP admission rates exhibited significant geospatial clustering at the highest confidence (99 percent) in Bradford (45 per 100,000) and surrounding counties of Nassau (52 per 100,000), while Baker (56 per 100,000), and Duval (53 per 100,000), were significant at 90 percent during 2016 (Figure 6). In 2017 Bradford (53 per 100,000) and Nassau (48 per 100,000) were 90 percent significant, while Hillsborough (48 per 100,000) and Pinellas (65 per 100,000) were 95 percent significant, even as neighbors Pasco (63 per 100,000), and Sumter (26 per 100,000) were 90 percent significant. In 2018 the clustering moved primarily to the "Big Bend" counties just before the Florida panhandle area where counties in the 99th percentile included Dixie (47 per 100,000) and Levy (41 per 100,000) while neighboring counties Gilchrist (63 per 100,000) and Lafayette (46 per 100,000) were in the 95th percentile. During 2019 we again saw Nassau (58 per 100,000), Bradford (29 per 100,000), and Baker (96 per 100,000) in the 95th percentile, and once more Hillsborough (32 per 100,000) and Pinellas (63 per 100,000), Pasco (62 per 100,000), and Sumter (32 per 100,000) were all 95 percent significant.

Spatially adjusted linear mixed model regression, (Table 6), revealed that for every methadone clinic added to a county, the corresponding clusters or "hot spots" z score increased non-significantly by .06 standard deviations (CI -.04, .16, p= .256). For every Naloxone prescriber added to a county the z-score decreased non-significantly by -.06 standard deviations (CI -.16, .03, p= .203), We also observed was also noted that for every one percent increase in non-Hispanic residents, the county level z-score dropped -.03 standard deviations (CI -.05, .003, p=.08) and one percent increases in county level non-white residents, the rate decreased -.04 standard deviations (CI -.07, -.01, p = .01).

Table 6: Linear Mixed Model Regression of Significant Clusters of IP Admissions

	Estimate	Lower CI	Upper CI	p
County Opioid Prescription Rate (per 100,000)	0.003	-0.001	0.006	0.098
County Percent Uninsured	0.000	-0.001	0.001	0.405
County Violent Crime (per 100,000)	-0.025	-0.049	0.000	0.050
County Median Income	0.000	0.000	0.000	0.319
County Percent Non-Hispanic**	-0.025	-0.053	0.003	0.082
County Percent Non-White**	-0.040	-0.071	-0.009	0.012
Naloxone Prescribers	-0.063	-0.160	0.034	0.203
Number of Methadone Clinics	0.059	-0.043	0.162	0.256
SDI	0.223	-0.043	0.489	0.101
Opioid Marketing Rate (per 1000 physicians)	0.006	-0.013	0.026	0.516
Less than 50	0.183	-0.108	0.474	0.218
Greater than 50 less than 275	0.015	-0.303	0.333	0.925
Greater than 275	0.253	-0.115	0.620	0.178
*CI- 95% confidence interval ** Rounded to nearest whole number				

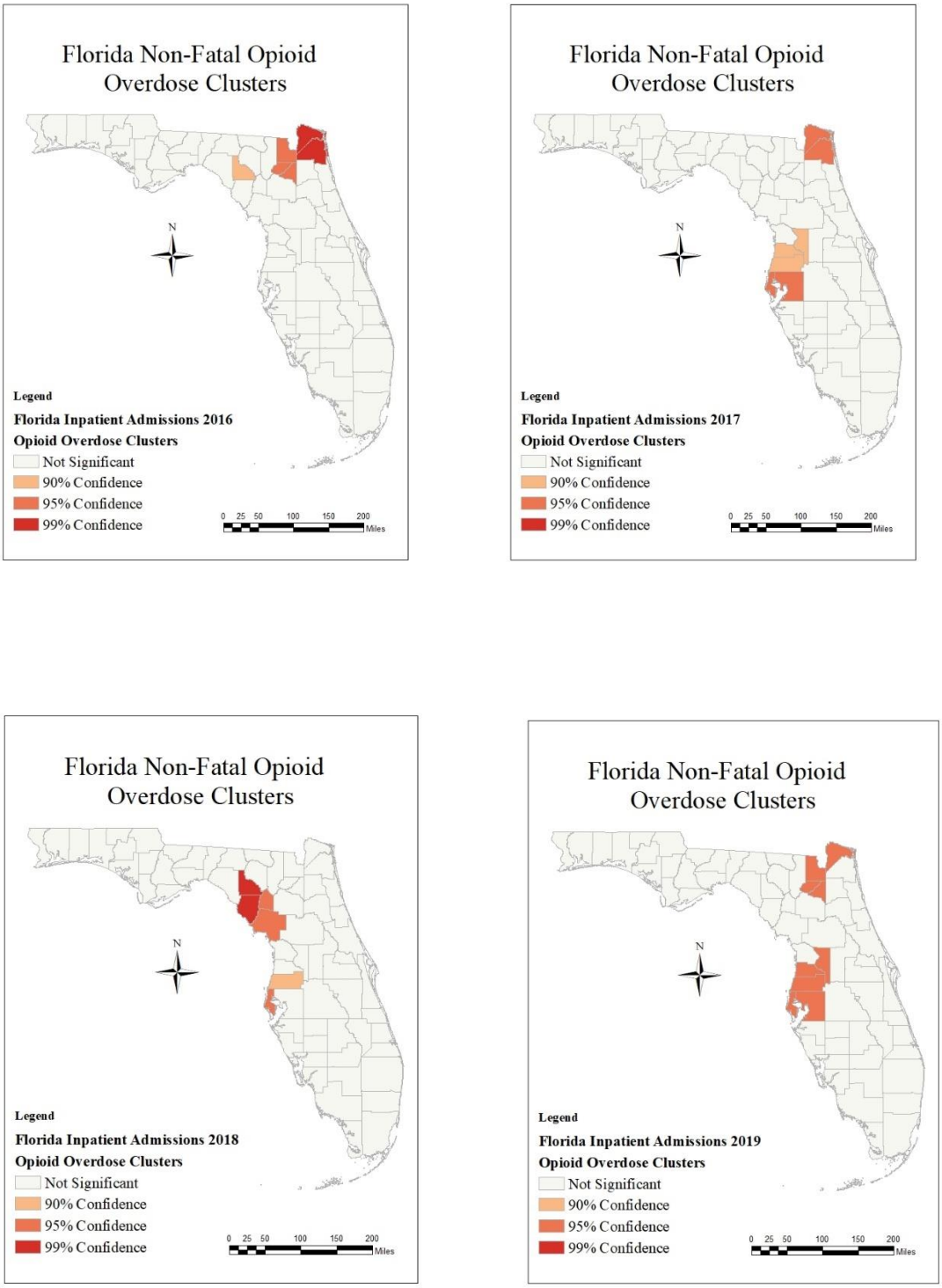


Figure 6: Clusters of Non-Fatal Inpatient Opioid Overdose Rates

Discussion

During the 4 years of this study, we found several clusters (hot spots) that appeared consistently present in more than one year. First, within the ED encounters data we observed similar clusters ("hot spots") occurring around Manatee and Palm Beach counties in 2016 and 2017. As hypothesized, regression analysis revealed that the availability of treatment resources (defined as methadone clinics and Naloxone providers) and non-white race and Hispanic ethnicity were positively associated with ED visits of opioid overdose clusters. In contrast, SDI and opioid marketing at all levels were not associated with ED visits of opioid overdose clusters.

Within IP admissions we observed clusters of between two and five counties (depending on year) occurring around Pinellas and Bradford counties from 2017 through 2019. As hypothesized, regression analysis revealed that counties that were higher percent non-white and non-Hispanic were still less likely to have clusters of opioid overdose admissions. Unexpectedly, opioid marketing was not related to clusters of non-fatal opioid overdose admissions, and the same lack of association was observed for SDI and the availability of opioid treatment resources. Also unexpectedly, and counter to our results from the ED analysis, both methadone clinics and Naloxone providers were associated with modest drops in standard deviation of "hot spots."

Interpretation of Results

It is challenging to explain the unexpected results in ED visits and IP admissions and disadvantaged counties, given that studies exist supporting the association of social disadvantage (in the form of social capital) with non-fatal overdoses [43]. With regards to seeing higher non-fatal overdoses in counties that identify as higher percent non-white and non-Hispanic, there is a small body of research documenting that the opioid epidemic has spread to the African

American and Hispanic communities [14]. The failure to note any association between opioid marketing rates and clusters of overdoses could be from a threshold effect whereby the potential adverse influence of opioid marketing only becomes evident at very high levels. Additionally, the lack of association could be from a loss of variation in the data from the necessity of aggregating up from the zip code level due to non-fatal opioid overdose (the outcome of interest) data only being available at the county level. Alternatively, this may be the result of residual confounding and/or overall poor exposure measurement and classification. Other explanations could include opioid prescription diversion, where medications are being sold across county lines, masking an effect (if any), and in the case of ED visits, could be that the improved availability of Naloxone has allowed at home treatment, preventing the overdoses from being recorded.

Also unexpectedly, and counter to our results from the ED analysis, both methadone clinics and Naloxone providers were associated with modest drops in standard deviation of "hot spots" in IP admissions. While unexpected, this is not unheard of. Naloxone has been available since the 1960's, and when administered appropriately, its effectiveness on treating opioid overdose and preventing death is well documented [50]. Additionally, methadone clinics exist to treat opioid use disorder (OUD), who are the highest risk group for overdose, and in Florida, have Naloxone providers on staff [51]. We feel that the combination of greater availability of treatment resources brings with it a higher concentration of persons with OUD, which brings an inherent increased risk of overdose. Furthermore, the presence of Naloxone, and its subsequent use as an intervention has been shown in small studies to reduce the severity of symptoms, allowing for treatment in the ED without necessitating further admission, which could be the cause of the difference between IP and ED [52]. Another possible cause is that some counties

only have Eds and must transfer more complicated patients out of county to receive treatment, potentially masking this effect.

This study aimed to produce a sociodemographic geospatial analysis of the opioid epidemic combining several publicly available datasets in Florida from 2014 to 2019. The aim was to examine the changing landscape of the epidemic, looking at what factors continue to be associated with Florida's struggle with the opioid crisis, with a principal aim of examining the impact of pharmaceutical opioid marketing on clusters of emergency department and inpatient admissions for non-fatal opioid overdose. We did not observe statistically significant associations between county-level clusters of non-fatal and fatal opioid overdose rates and high frequency pharmaceutical opioid marketing. This is inconsistent with other bodies of work in the United States that have linked associations of opioid-related pharmaceutical marketing payments to increased physician prescribing and subsequent opioid related overdose [20, 53].

Despite the lack of association with our primary outcome of interest, this research still adds to the body of knowledge by providing geographic context to a complicated issue. We believe this approach can be helpful in two ways. First, it allows the opportunity for Florida county health administrators to learn from the counties that have clusters of opioid overdose admissions, allowing for both targeted mitigation strategies of fatal and non-fatal overdoses in counties that could be impacting their immediate neighbors, and the opportunity to identify and study areas where this outcome is much lower. Additionally, these techniques build on existing GIS frameworks by reducing inherent error in some of the older techniques such as Gi*. They are replicable in open license (free to use) software such as R and Python, allowing public health professionals with limited budgets to utilize robust packages that were previously limited to expensive licensed products [14].

Limitations

This study has several limitations. First, the opioid marketing data relies solely on physicians who could be matched through the Medicare D reporting and thus may not accurately reflect all marketing activity in any one county. Second, this study uses county-level data and relies on the SDI composite score to reflect their socio-demographic characteristics, and more granular geospatial units (e.g., census tract/block) were not consistently available across databases used in this study. The expected net effect for this lack of granularity would be bias toward the null of no association. Third, we believe there is difficulty tracking occurrences of non-fatal overdoses due to the widespread availability of prescription and non-prescription naloxone [54]. This could result in many overdoses not being reported due to the ability to treat opioid overdose in the community without physician intervention. Fourth, it was difficult to quantify the direct impact that pharmacy marketing has on an area due to potentially high levels of prescription diversion, resulting in opioids leaving their county of origin. Finally, an area of possible bias is that county-level associations cannot be extrapolated to the individual level (potential ecological fallacy). This includes the SDI, which is typically a neighborhood measure. Since there are areas of poverty in wealthy counties we could have missed important associations that might have appeared evident at a more granular level.

Conclusion and Future Work

The U.S. is facing a resurgence of the opioid crisis. Thus, there is need for less expensive, more effective evidence-based strategies than can be quickly implemented and used to expedite policies that will help save lives while retaining fiscal resources. At a minimum, our analysis indicates the need for future research that makes use of more granular-level data to more precisely identify areas in need of interventions and/or additional resources. Methodologically,

this study may motivate the use of other spatial statistics-based techniques. More specifically, network autocorrelation can be used to visualize and understand the flow of prescribed opioids that are sold to drug dealers (diversion), and Bayesian based species distribution modeling can be used in predicting changes of outcomes related to the opioid epidemic.

Chapter 4:

Using Interrupted Time Series to Evaluate Secular Changes in Rates of Opioid Abuse and Comorbidities in Hospital Admissions Relative to the Administrative Change from ICD-9 to ICD-10 in Florida from 2009-2020

Abstract

Background

Hospital admission and discharge data are often crucial in helping public health entities and decision makers understand the burden of a particular health condition, assisting them in making conscientious health policy decisions. In Florida, the Agency for Healthcare Administration (AHCA) mandates the use of the ICD coding system. This system was expected to show changes in rates of clinical diagnostics starting in the third quarter of 2015 due to a formal classification modification from ICD-9 to ICD-10. This paper examined the effect of the formal modification from the ICD-9 to the ICD-10 on primary and non-primary opioid emergency department and in-hospital admission rates and their associated co-morbidities.

Methods

We used AHCA admission data from all covered hospitals throughout Florida between the first quarter 2009 and the first quarter 2020 (12 years). We then estimated quarterly prevalence rates for all emergency department and in-hospital admissions where opioids where either the primary or non-primary diagnoses, examining the ICD-9 and ICD-10 data separately to

facilitate comparison. We used interrupted time series with segmented regression to estimate both the immediate impact of the formal modifications as well as change in trend across years.

Results

Between 2009 and 2019 there were more than one million opioid related admissions (emergency department and hospital inpatient) in Florida. For emergency department admission records where the primary diagnosis was opioid related, every demographic subgroup (except persons under age 18) saw an approximate 500% to 700% level increase in the case rates per 100,000 admissions immediately after the switch to the ICD-10. For in-hospital admissions, corresponding increases ranged from approximately no change to 200% and were highest among persons older than 64 years of age and those with more comorbidities. Results for in-hospital admission rates were generally similar where opioid diagnosis was secondary, whereas for emergency department visits, the increase in rates were less profound for secondary diagnosis compared to primary opioid diagnosis. After the switch to ICD-10, and large initial increase in admission rates, there was a general decrease in rates of opioid admissions over time, yet not returning to rates observed with ICD-9, and consistent with stringent opioid distribution and use laws passed in 2014 by Florida state legislature. The patterns of change in admission rates post ICD-10 varied among subgroups with some showing modest reductions or leveling off over time and others showing continued increases over time.

Conclusions

As hypothesized, after the transition to ICD-10 we observed immediate substantial increase in rates of emergency department and in-hospital opioid admissions, including both as primary and secondary diagnoses. However, some of the observed changes in trend across years after the switch to ICD-10 were unexpected, including the significant, consistent increase in non-

white, opioid primary diagnosis, emergency department admissions. These findings may help investigators focused on combating the resurgence of the opioid epidemic to develop more inclusive policies.

Background

Individuals diagnosed with opioid use disorder (OUD) are frequently admitted for treatment at hospital inpatient (IP) and emergency departments (ED) and often have other co-morbid conditions related to the continuing use and abuse of these drugs, which commonly include chronic pain, smoking, heart disease, and misuse of other substances [55-57]. The National Institute on Drug Abuse (NIDA) reports that patients with long-term opioid abuse often exhibit chronic, co-morbid physical and behavioral health conditions which have been associated with low-level functioning, shorter life-expectancy, a much lower quality of life, and higher healthcare costs [56].

An important part of modern medical treatment is the electronic medical records (EMR), hospital discharge data, and Medicare and Medicaid treatment and discharge database, maintained by private and government healthcare organizations for the purposes of billing and continuity of care. These large administrative databases have been increasingly used to estimate the prevalence, trends, and other outcomes for a myriad of conditions, including mental health and substance use disorders. Since 1948, healthcare providers have relied upon guidance from the World Health Organization's (WHO) standardized diagnostic manual, the International Classification of Diseases (ICD) to document medical treatment and conditions. On October 15, 2015, the most major revision was to transition from ICD-9 to ICD-10, which added more than 50,000 new coding categories. With regards to opioids, the number of available diagnostic codes increased from 25 to more than 100.

Due to such a large increase in available diagnostic codes and the potential for substantive differences in code assignment, it is important to assess the comparability of hospital discharge data pre and post changeover as it has the potential to impact studies that may seek to make use of these data. Opioid use accounts for a large amount of the global problem of disease, and in the United States it was estimated that by 2019 the amount of use would exceed 10 million persons [41]. The overall population is aging, and with it those that continue to use opioids. Some studies have shown that as they age, opioid users can have more severe disease profiles [55, 58]. This continued use, coupled with the burden of aging has been shown in other countries to increase admission frequency and length of stay making this an increasingly more costly and burdensome public health concern [55, 58].

Additionally, comorbidity profiles among hospitalizations where the primary diagnosis is opioid related tend to have a more severe, and greater number of secondary diagnoses [55]. This is in part due to improved opioid overdose interventions which are allowing greater numbers of opioid users to survive into long term use, increasing stress on an overburdened system as they progressively deteriorate, requiring a greater number of admissions and resources to treat [55, 56]. The impact of this burden is little understood due to previous issues with high mortality and long-term opioid use and to some extent, interest on the part of researchers [55, 59]. Furthermore, other research has noted increasing levels of co-morbid severity in older opioid users, especially those with a reported history of long term use [59]. Therefore, increasing our understanding of this burden will add to the body of research devoted to the treatment of individuals impacted by opioid use. To be thorough, we should also examine the impact that the switch from the ICD-9 to the ICD-10 had on opioid rates to better ensure comparability between admissions occurring during each period.

Very little research has been done to examine changes in opioid admissions relative to the administrative change from ICD-9 to ICD-10. One analysis in October 2015 was performed by the Agency for Healthcare Research and Quality (AHRQ) using data from the Healthcare Cost Utilization Project (H-CUP). This was a small case study, utilizing inpatient data, stratified by age groups from three states: Colorado (population 5 million), Kentucky (population 4.75 million), and Minnesota (population, 5.7 million) [8]. Compared to Florida, these were smaller states with smaller representative opioid admissions and the studies were purely descriptive, making it difficult to assess the extent to which the reported impacts might vary across states with different underlying populations and rates of OUD [8]. Early in 2021, AHRQ repeated a similar analysis using more current data from 2016-2018, observing increases in the number of opioid-related stays pre and post ICD-9 to ICD-10 which they believed to be a one-time shift, and not indicative of any secular trend after adoption of ICD-10 [60]. However, this work was also largely descriptive and did not implement statistical approaches best capable of detecting the impact of these coding changes. Both the lack of other research and the limitations of the one study leave substantive knowledge gaps that could have broader implications in organizational and public health policy, given the WHO's announcement of ICD-11 set to launch in early 2022 [8, 57].

To address the gaps in knowledge, we sought to implement an interrupted time series analysis and leverage 12 years (2009-2020) of statewide hospital discharge data to investigate the extent to which the ICD-9 to ICD-10 transition resulted in either an immediate or longer-term change in OUD and its related comorbidities. We postulated that, in Florida, comorbidity profiles among hospitalizations with a primary diagnosis that is opioid related have become more complex, indicated by an increase in conditions over an 11-year period (2009-2019). We also

expected that, independent of secular changes in opioid related encounters and admissions in Florida, over an 11-year period, formal modifications to the ICD classification system would be associated with an immediate increase in opioid related ED presentations and inpatient admissions. Finally, we postulated that secular changes in comorbidity profiles secondary to opioid dependence would occur independent of the ICD modifications.

Methods

Data

The primary data were acquired from the Agency for Health Care Administration (AHCA). AHCA is a Florida agency created by statute that is responsible for FL Medicaid and statewide licensing of healthcare care facilities and hospitals. It gathers data from all facilities, sharing through the Florida Center for Health Information and Analysis (FCHIA). De-identified encounter level data for each quarter within each year were acquired on both IP and ED admissions from 2009-2020. Each record contained sociodemographic data, procedure codes, and the emergency department information contained space for nine other diagnostic codes in addition to the primary reason for admission. The inpatient record contained 30 additional data elements for other diagnoses in the form of ICD-9 or ICD-10 codes, that contributed to the care the patient received. In addition, there were three data elements that captured diagnosis codes related to external cause of injury.

For both ED visits and IP admissions, the data were parsed into the primary diagnosis code (opioid code in the first diagnostic element) and non-primary (opioid code(s) present in any other diagnostic code field). All opioid codes were combined to produce a composite opioid identifier (see appendix B for codes included). Since patients seen in the ED who were ultimately admitted would be captured in both the inpatient and ED datasets, we excluded from the ED

dataset those patients who were subsequently hospitalized to avoid double-counting. Co-morbid conditions were chosen based on a report from the National Institute on Drug Abuse (NIDA) and additional work by Medved and Clausen on somatic disease burdens and co-morbidities of those diagnosed with opioid use disorder [55, 56]. All data manipulation and cleaning were performed using the SAS system, version 9.4.

Analysis

For inpatient and emergency department encounters, we calculated descriptive statistics (frequency, percentages) by opioid status, number of comorbid conditions by year, and gender to better describe the data from both the emergency department and inpatient admissions. Admission rates were calculated for all admissions and by age groups, number of co-morbid conditions and specified co-morbidities.

To examine the impact of the change on the rates related to opioid hospital encounters and their co-morbidities between the ICD-9 and ICD-10, we used segmented regression within an interrupted time series structure (ITS) [61-63]. The ITS methodology is most often used to estimate the impact of policy changes or interventions at a clearly differentiable point in time. Its simplicity, interpretability, and ability to measure both the immediate change and the effect over time makes ITS particularly appropriate for a project of this nature [61-63]. Because observations over time are correlated with one another (autocorrelation) and often contain cyclical, seasonal correlation as well, we needed an appropriate regression model. Thus, we used a Durbin Watson test statistic to assess for autocorrelation [61-63].

Our model was the following:

for every rate at time t: $\mathbf{Rate_t = \beta_0 + \beta_1 * time_t + \beta_2 * ICD\ Flag_t + \beta_3 * Post\ Change_t + e_t}$

Variables were created to count the number of admissions among non-white, white, Hispanic, non-Hispanic, and age groups classified as 18 and under, 19-36, 37-56, 56-64, and +64 [59, 64, 65]. Using these counts, we calculated the rate (per 100,000) of opioid related admissions at each level for each group, and the following secondary diagnoses: psychiatric disorders, chronic pain, diabetes, chronic obstructive pulmonary disorder (COPD), tobacco use, obesity, other substance use disorder, hypertension [61]. The full data set was then aggregated to each quarter of each year, leaving counts for each variable at each time point (4 per year x 11 years = 44 levels of observation). An indicator variable (0 or 1) representing the inception of ICD-10 was used to assess immediate change in rates, and a time variable that started at the beginning of ICD-10 (1-17) was used to measure change in trend [61]. To make the direct implications easier to interpret, following previous work by Salemi et al., we expressed the immediate impact as a percent change in average prevalence rates relative to each period, ICD-9 versus ICD-10, and the difference in slope coefficients as change in direction or no change [62, 63]. All statistical analysis were performed using the SAS system, version 9.4 and R version 4.0.3, Coda 0.9-.4, R-beta 1.0.

Results

In the present analysis, there were 130,097 ED encounters that had a diagnosis code where the patient received a primary diagnosis related to opioid use, abuse, or dependence. With the alternate definition of non-primary opioid diagnosis, there were 297,463 ED visits. For in-hospital admissions, there were 92,764 and 618,555 opioid primary and non-primary diagnoses, respectively. The tables and figures that follow compare rates of opioid diagnoses based on ICD-9 versus ICD-10 coding (mandatory starting on October 15, 2015), and within patient subgroups.

Emergency Department Data – Impact of Switch from ICD-9 to ICD-10

Primary Opioid Diagnosis. In emergency department visit records where the primary diagnosis was opioid related, we observed that every demographic subgroup other than age 18 years and younger, along with the number of comorbidities groups exhibited an approximate four-to-seven-fold increase in the case rates per 100,000 persons immediately after the switch to the ICD-10. The age group 18 and under saw a smaller 200% increase (Table 7).

Table 7: Rates of Emergency Department Opioid Diagnoses (Primary)

Group	N	ICD-9 Rate per 100k persons	N	ICD-10 Rate per 100k persons	% Change in the Rate
Overall	25,675	19.9	104,422	116.7	593%
Men	14,126	24.2	64,139	147.2	613%
Women	11,549	16.2	40,283	87.8	517%
White	22,040	22.3	89,306	122.6	541%
Non-White	3,643	12.17	15,116	76.1	605%
Age:					
18 and under	1,745	6.6	2,525	13.5	205%
19-36	13,207	50.6	58,468	332.0	657%
37-56	7,737	23.7	31,919	172.7	728%
57-64	1,518	8.74	6,221	62.3	712%
Over 64	1,331	5.21	4,700	31.3	602%
Comorbid Conditions:					
None	4,499	41.7	19,234	259.1	621%
One	5,639	44.4	27,506	262.0	591%
Two	4,804	44.4	19,443	262.0	591%
Three	3,393	31.4	12,367	166.5	531%
Four	2,423	22.4	7,972	107.3	479%
Five	1,540	14.3	5,234	70.5	495%
Six	1,017	9.4	3,542	47.7	507%
Seven	682	6.3	2,365	31.8	505%
Eight	739	6.8	2,758	37.1	545%
Nine	938	8.6	4,001	53.8	623%

**Comorbid Conditions are one or more additional physical or mental health conditions.*

Overall, after the switch to ICD-10, opioid primary diagnoses increased substantially and consistently for about 6 quarters (Figure 7). This was followed by a modest decline and then a leveling off, however, ICD-10 rates continued to be much higher than previous ICD-9 rates and in subgroup analyses, stratification by patient gender showed a similar pattern of sharp increase in rates following the transition to ICD-10 followed by a gradual decline that remained at levels above ICD-9 (Figure 8). This pattern was observed for Whites (Figure 8), whereas non-whites showed an immediate substantial increase in the rate of ED encounters which continued to accelerate over time. All adult age groups other than ages 19-37 showed a large increase in the rate of ED encounters after the transition to ICD-10 which continued to accelerate over time. This pattern was also observed among persons with nine comorbidities.

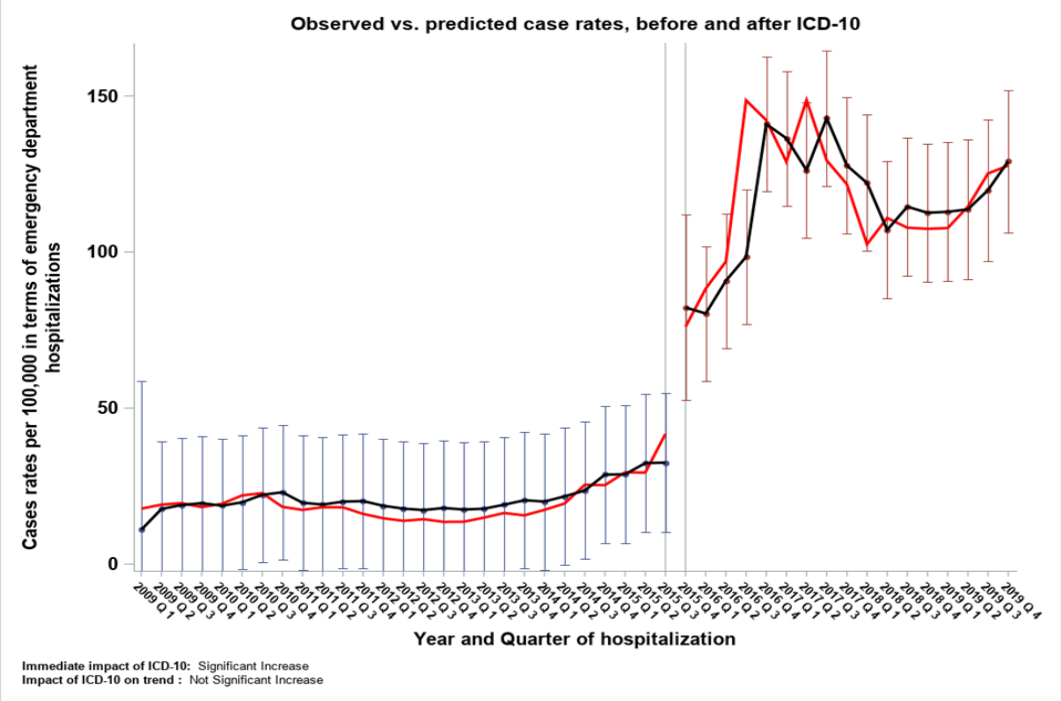
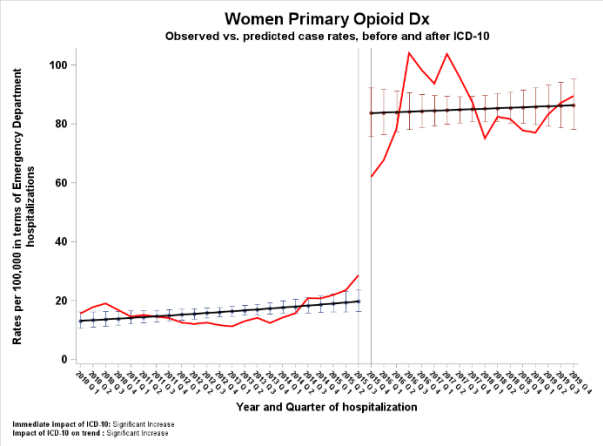
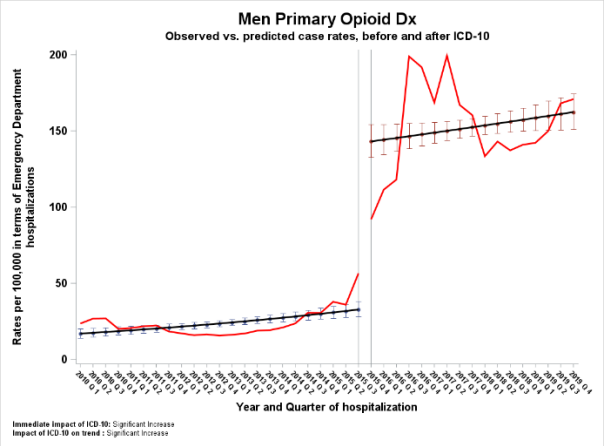
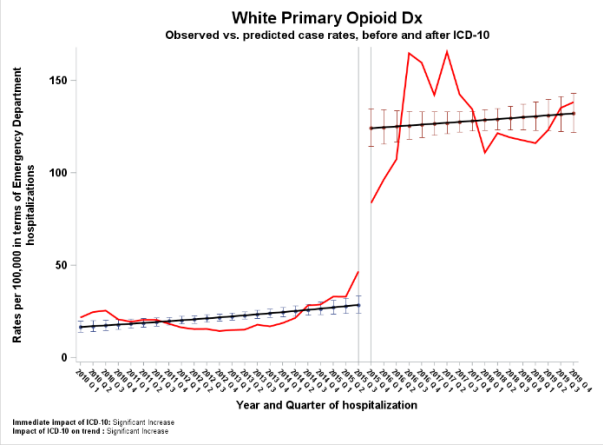


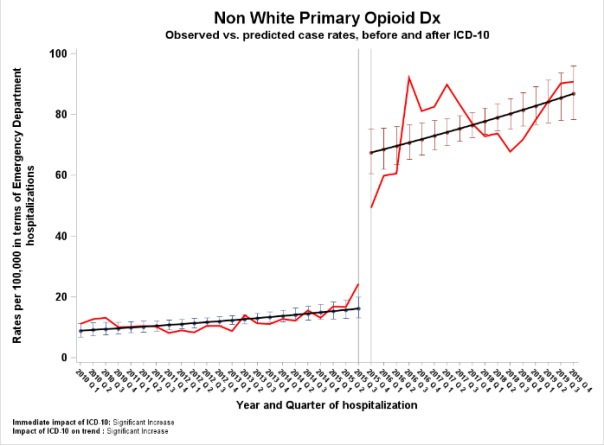
Figure 7. Emergency Department Visits Over Time- Opioids as Primary Diagnosis

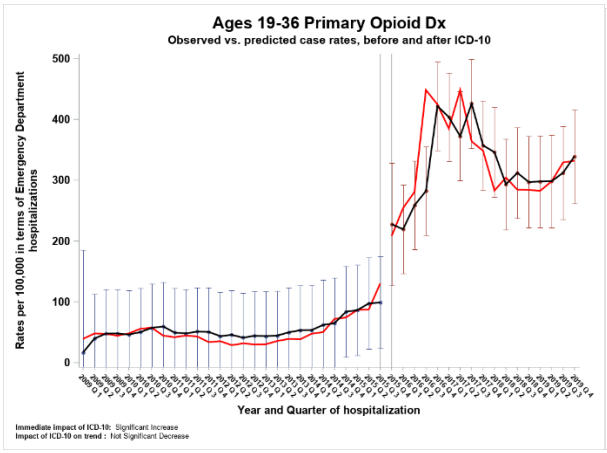
Quarterly hospital prevalence estimates for all emergency department visits where an opioid code was the primary diagnosis. The reference lines delineate when the change from the ICD-9 to the ICD-10 occurred. The red line markers and estimates represent observed quarterly rates during both time periods. The black line represents the predicted regression models with 95% confidence intervals.

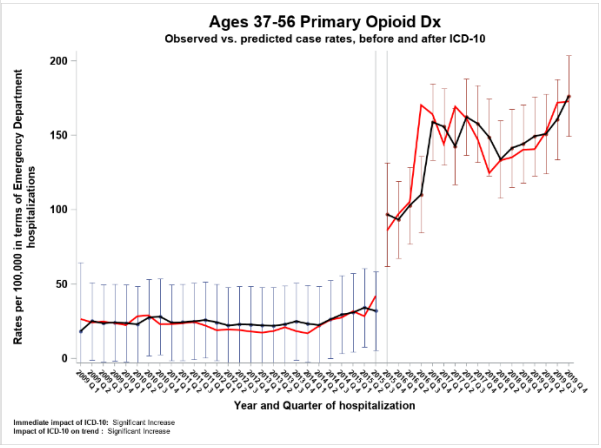


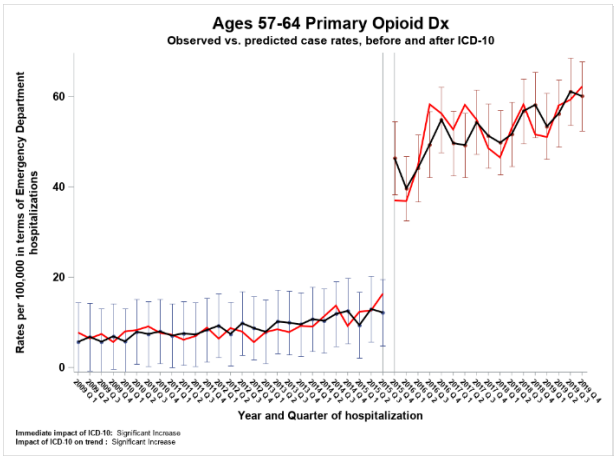


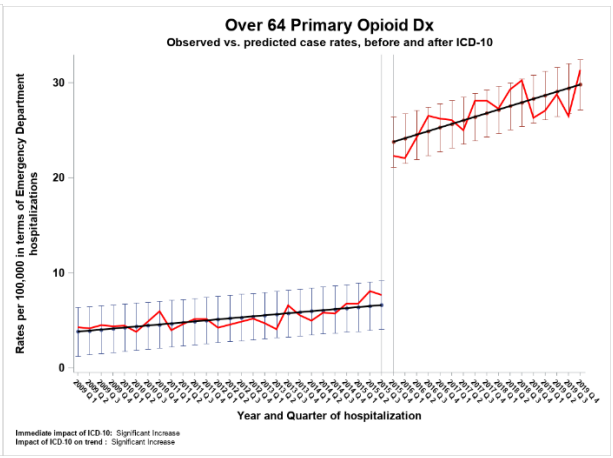


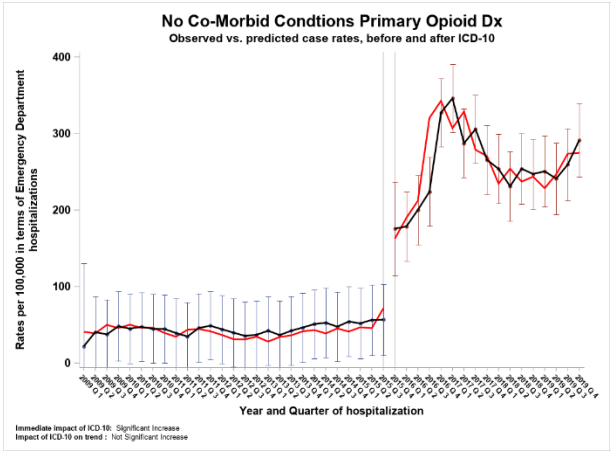












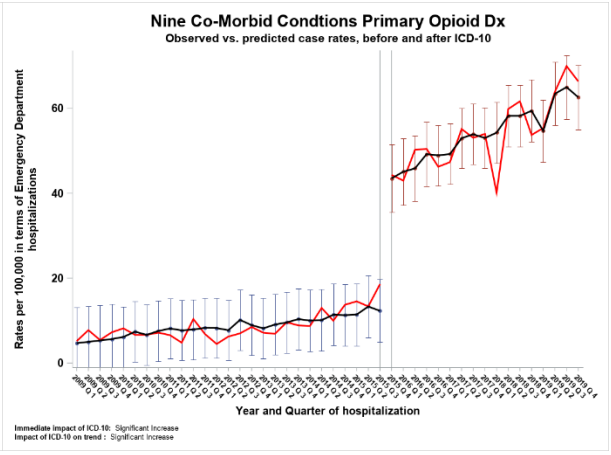


Figure 8. Emergency Department Visits-Subgroups Over Time Primary Diagnosis Opioids Quarterly hospital prevalence estimates for segments where emergency department visits where an opioid code was the primary diagnosis. The reference lines delineate when the change from the ICD-9 to the ICD-10 occurred. The red line markers and estimates represent observed

quarterly rates during both time periods. The black line represents the predicted regression models with 95% confidence intervals.

Non-Primary Opioid Diagnosis. In emergency department visit records with non-primary opioid diagnoses, we observed an approximate 3.5-fold increase in case rates per 100,000 persons in nearly all population groups relative to the switch to ICD-10 (Table 8). For patients with at least one mental health comorbidity, the rate of having a non-primary opioid diagnosis increased markedly from 267 per 100,000 persons based on ICD-9 compared to 1,087 per 100,000 persons with ICD-10.

Table 8: Rates of Emergency Department Opioid Diagnoses (Non-Primary)

Group	N	ICD-9 Rate per 100k persons	N	ICD-10 Rate per 100k persons	% Change
Overall	91,697	70.4	205,766	230.1	327%
Men	44,545	70.3	113,406	260.3	371%
Women	47,152	70.6	92,360	201.3	285%
White	78,068	76.9	172,431	247.2	322%
Non-White	13,629	45.5	33,336	161.9	356%
Age					
18 and under	3,165	12.1	4,018	22.0	183%
19-36	40,453	156.9	100,249	560.9	357%
37-56	34,295	100.3	68,220	303.7	303%
57-64	6,993	40.4	16,258	136.5	338%
Over 64	8,591	33.6	17,022	96.9	288%
Comorbid Conditions					
Chronic Pain	20,439	73.3	31,511	164.7	225%
Obesity	1,402	3.5	3,537	14.3	409%
Hypertension	15,397	37.8	71,247	124.9	330%
Tobacco Use	24,302	88.7	72,399	408.9	461%
COPD	7,431	50.4	29,371	194.1	385%
Mental Health	21,767	267.1	154,633	1087.2	407%
SUDS	68,511	633.5	189,769	1778.8	281%

**Comorbid Conditions are one or more additional physical or mental health conditions.*

The pattern of increase of non-primary opioid diagnoses following ICD-10 was generally similar to that of primary opioid diagnoses, that is, substantial consistent increases for about 6 quarters followed by a modest decline and then a leveling off that left ICD-10 rates still much higher than previous ICD-9 rates (Figure 9). In subgroup analyses, two patterns of change in rates of non-primary opioid ED encounters were observed after the transition to ICD-10. In both women and men and among whites, rates of non-primary opioid diagnoses were highest from three to six quarters after the shift to ICD-10 (Figure 10), and then showed modest declines thereafter. In contrast, in non-whites, older age groups, and those with selected comorbidities (mental health issues, obesity, COPD) the initial increase in rates of non-primary opioid ED encounters after the transition to ICD-10 was followed by consistent gradual increases over time.

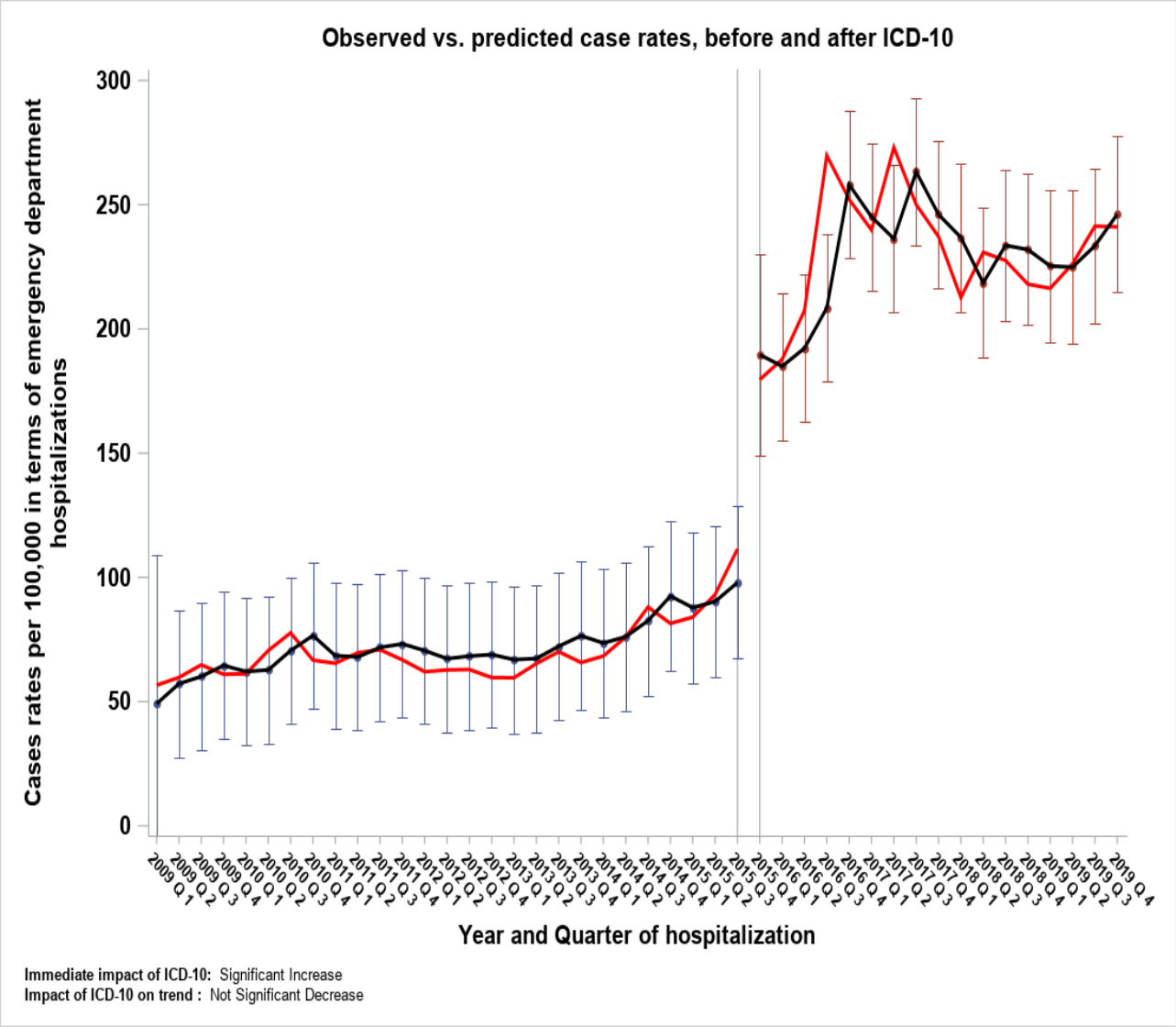
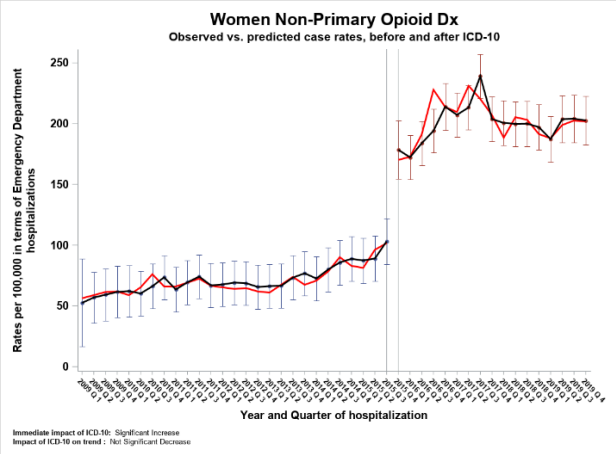
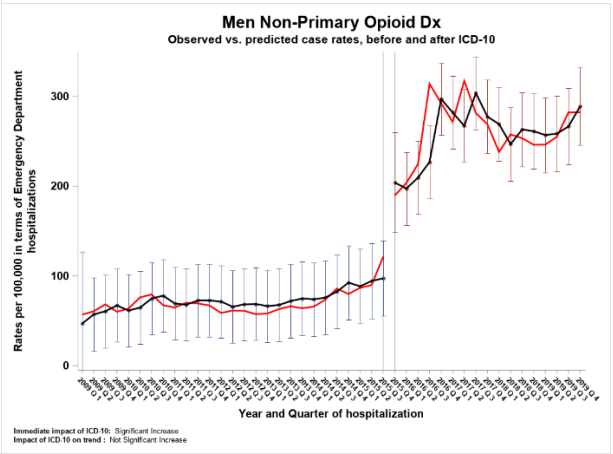
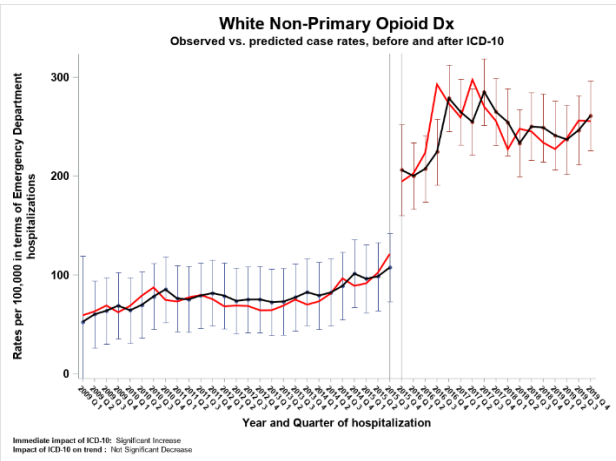
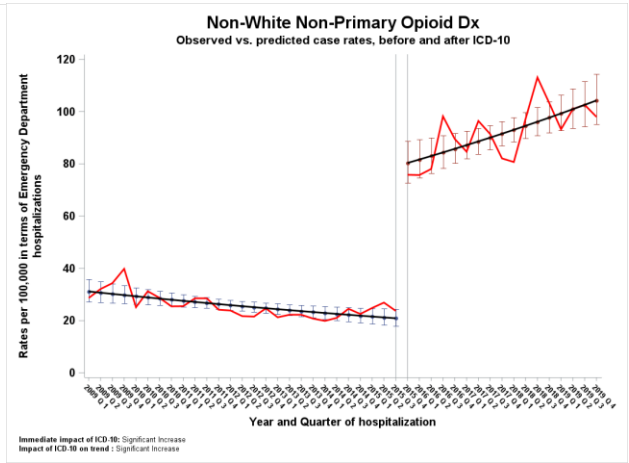


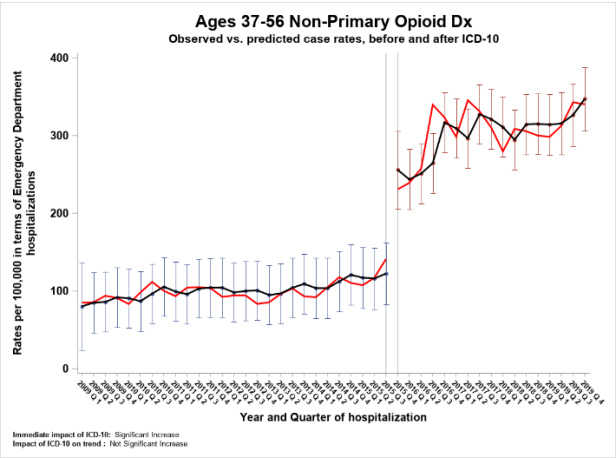
Figure 9. Emergency Department Visits Over Time - Non-Primary Diagnosis of Opioids
Quarterly hospital prevalence estimates for all emergency department admissions where an opioid code was present. The reference lines delineate when the change from the ICD-9 to the ICD-10 occurred. The red line markers and estimates represent observed quarterly rates during both time periods. The black line represents the predicted regression models with 95% confidence intervals.

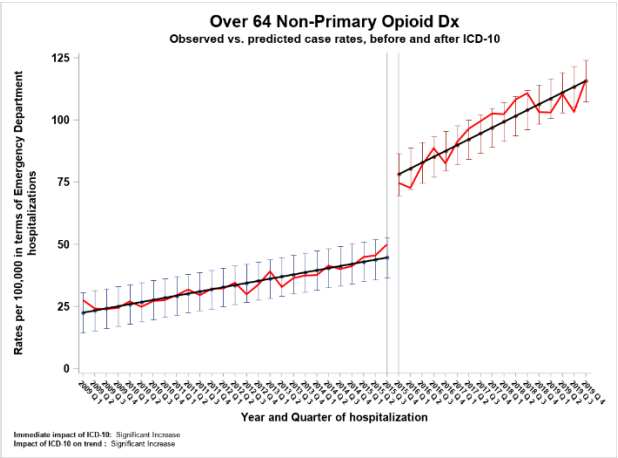

Women Non-Primary Opioid Dx
Observed vs. predicted case rates, before and after ICD-10
Rates per 100,000 in terms of Emergency Department hospitalizations
Year and Quarter of hospitalization
Immediate impact of ICD-10: Significant Increase
Impact of ICD-10 on trend : Not Significant Decrease


Men Non-Primary Opioid Dx
Observed vs. predicted case rates, before and after ICD-10
Rates per 100,000 in terms of Emergency Department hospitalizations
Year and Quarter of hospitalization
Immediate impact of ICD-10: Significant Increase
Impact of ICD-10 on trend : Not Significant Increase


White Non-Primary Opioid Dx
Observed vs. predicted case rates, before and after ICD-10
Rates per 100,000 in terms of Emergency Department hospitalizations
Year and Quarter of hospitalization
Immediate impact of ICD-10: Significant Increase
Impact of ICD-10 on trend : Not Significant Decrease


Non-White Non-Primary Opioid Dx
Observed vs. predicted case rates, before and after ICD-10
Rates per 100,000 in terms of Emergency Department hospitalizations
Year and Quarter of hospitalization
Immediate impact of ICD-10: Significant Increase
Impact of ICD-10 on trend : Significant Increase


Ages 37-56 Non-Primary Opioid Dx
Observed vs. predicted case rates, before and after ICD-10
Rates per 100,000 in terms of Emergency Department hospitalizations
Year and Quarter of hospitalization
Immediate impact of ICD-10: Significant Increase
Impact of ICD-10 on trend : Not Significant Increase


Over 64 Non-Primary Opioid Dx
Observed vs. predicted case rates, before and after ICD-10
Rates per 100,000 in terms of Emergency Department hospitalizations
Year and Quarter of hospitalization
Immediate impact of ICD-10: Significant Increase
Impact of ICD-10 on trend : Significant Increase

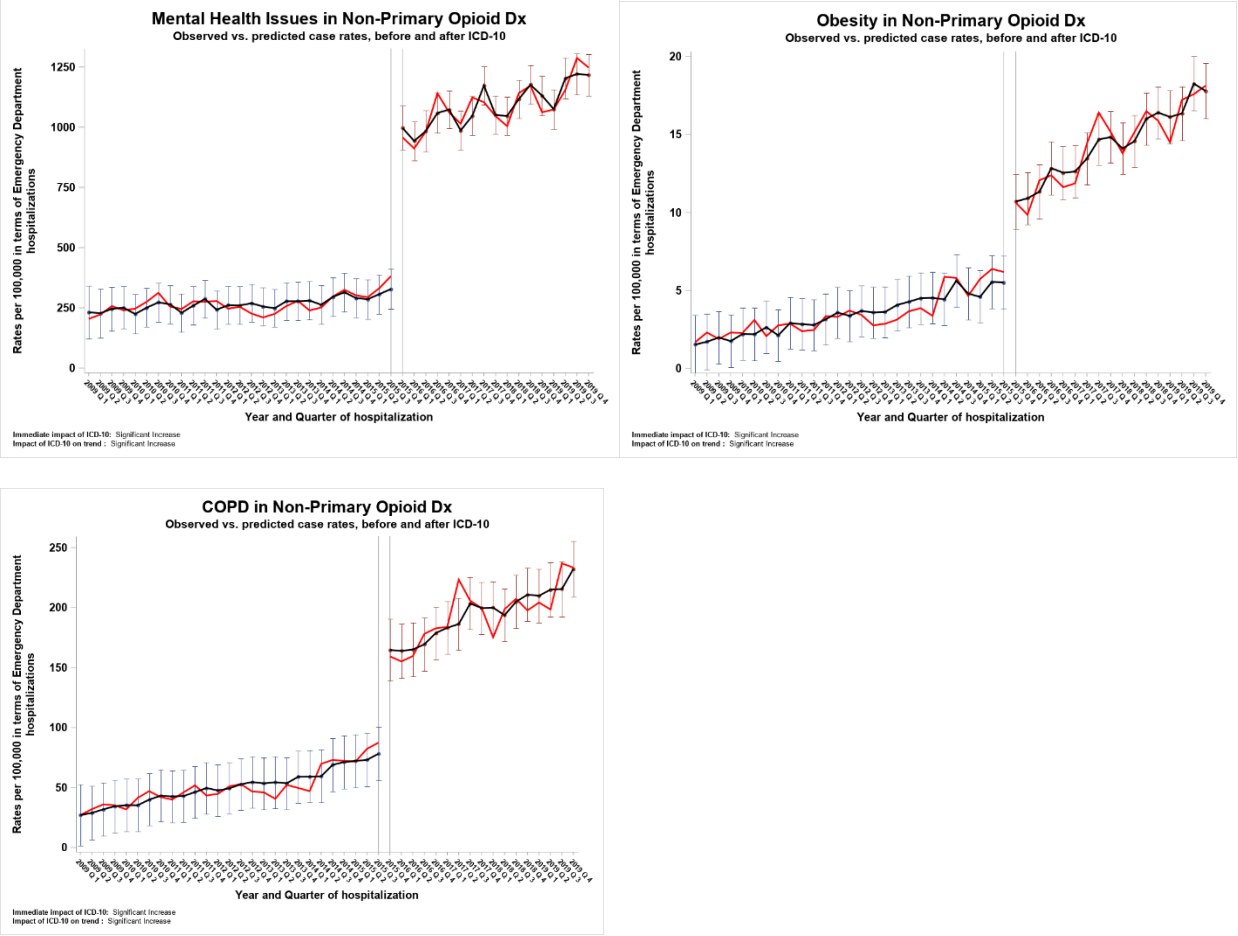


Figure 10. Emergency Department Visits - Subgroups Over Time Non-Primary Diagnosis of Opioids.

Quarterly hospital prevalence estimates for segments where emergency department visits where an opioid code was the not the primary diagnosis but was still present. The reference lines delineate when the change from the ICD-9 to the ICD-10 occurred. The red line markers and estimates represent observed quarterly rates during both time periods. The black line represents the predicted regression models with 95% confidence intervals.

Inpatient Admissions Data - Impact of Switch from ICD-9 to ICD-10

Primary Opioid Diagnosis. Among in-patient hospital admissions where the primary diagnosis was indicative of opioid dependence, abuse, or use, the magnitude of change in rates per 100,000 persons before and after implementation of ICD-10 ranged from approximately no change to 200% (**Table 9**). The largest percentages increase in rates per 100,000 persons occurred among persons ages 64 and older (204%) and persons with nine or more comorbidities (204%). The percentage increase in rates per 100,000 persons increased steadily as the number of comorbidities increased.

Table 9: Rates of Hospital In-Patient Opioid Diagnoses (Primary)

Group	**N**	**ICD-9 Rate per 100k persons**	**N**	**ICD-10 Rate per 100k persons**	**% Change**
Overall	43,711	39.7	49,053	73.1	163%
Men	23,205	48.8	26,932	79.0	168%
Women	20,506	30.8	22,121	70.4	157%
White	39,550	69.4	43,082	119.5	171%
Non-White	4,161	30.7	5,971	62.4	164%
Age					
18 and under	978	3.7	493	2.7	-27%
19-36	16,259	62.9	18,593	104.4	166%
37-56	16,347	50.3	16,433	73.4	146%
57-64	4,946	28.6	15,616	52.8	184%
Over 64	4,696	18.4	16,699	37.4	204%
Comorbid Conditions					
None	2,911	27.3	1,707	23.1	-15%
One	1,911	23.1	1,735	30.7	33%
Two	2,477	23.2	2,264	30.7	32%
Three	2,853	26.6	2,654	35.9	35%
Four	3,566	33.2	2,918	39.5	19%
Five	3,075	28.7	3,097	41.9	146%
Six	2,944	27.5	3,186	43.1	157%
Seven	2,800	26.1	3,153	42.6	163%
Eight	2,739	25.5	2,999	40.6	159%
Nine	2,387	22.2	2,904	39.2	177%
More than nine	16,051	148.7	22,436	302.6	204%

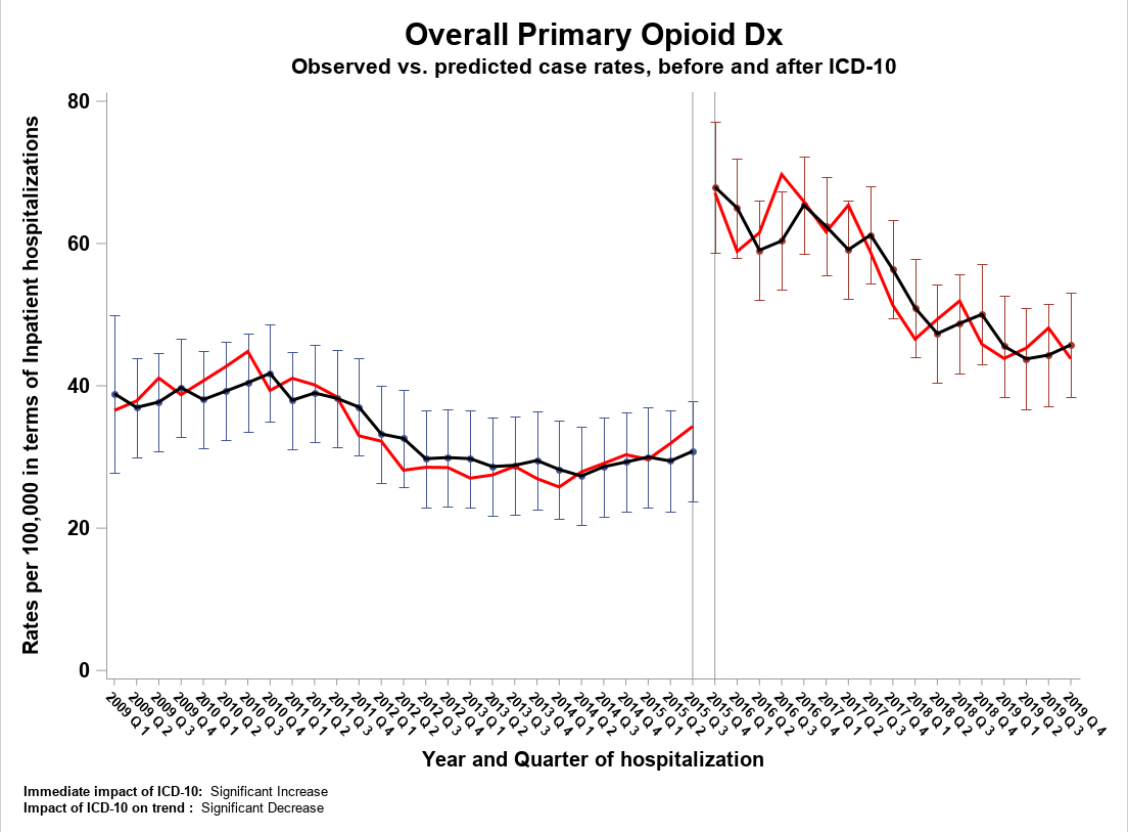
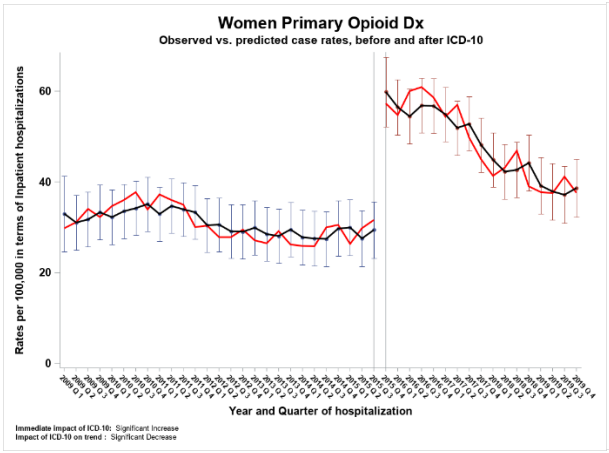


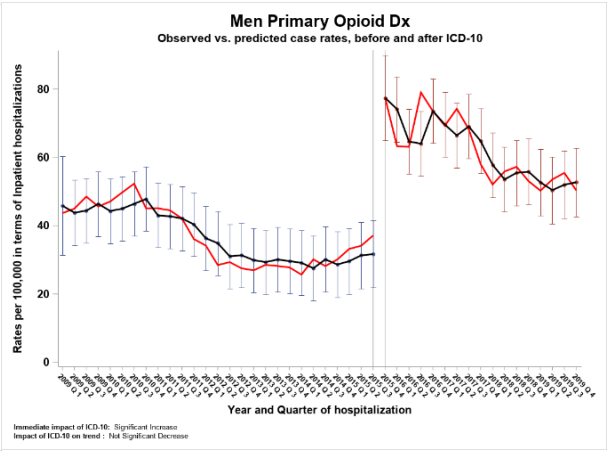
Figure 11. In-Patient Admissions Over Time - Opioids as Primary Diagnosis
Quarterly hospital prevalence estimates for all inpatient admissions where an opioid code was the primary diagnosis. The reference lines delineate when the change from the ICD-9 to the ICD-10 occurred. The red line markers and estimates represent observed quarterly rates during both time periods. The black line represents the predicted regression models with 95% confidence intervals.

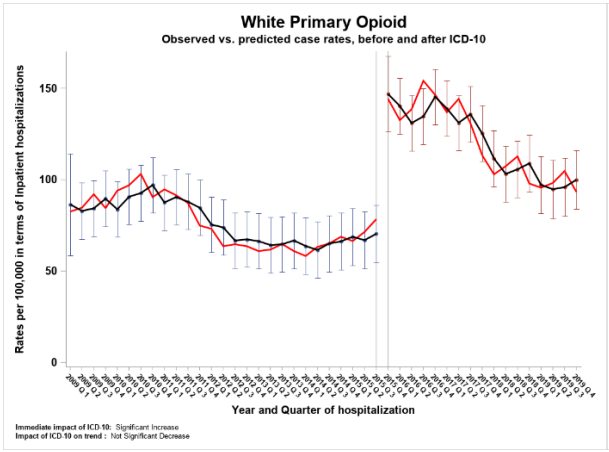
Immediately following the shift to ICD-10, there was a very substantial increase in the in-hospital rate of a primary diagnosis indicative of opioid dependence, abuse, or use (Figure 11). This was followed by a consistent reduction over time, yet rates of primary opioid diagnoses remained higher at all time periods after the switch to ICD-10.

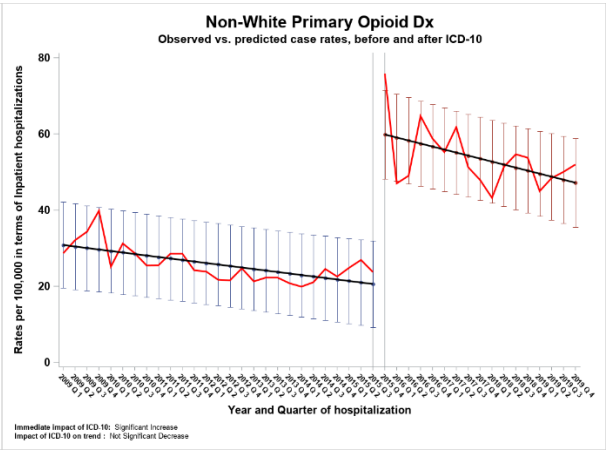
Among nearly all subgroups, the pattern of change in the rate of in-patient admissions following the switch to ICD-10 was an immediate large increase followed by gradual reduction

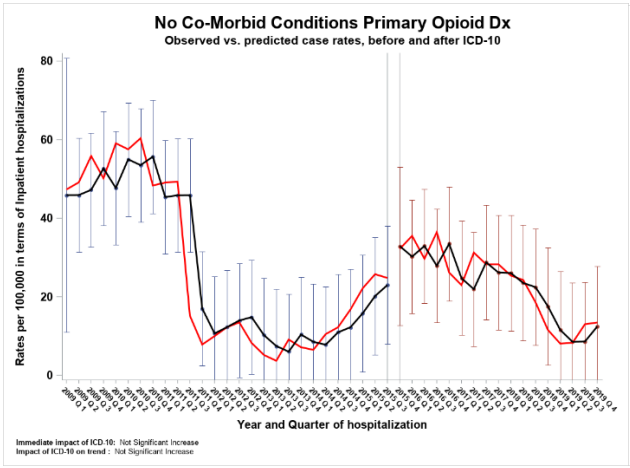
over time (Figure 12). Rates of in-patient admissions with a diagnosis indicative of opioid dependence, abuse, or use remained higher after the switch to ICD-10.











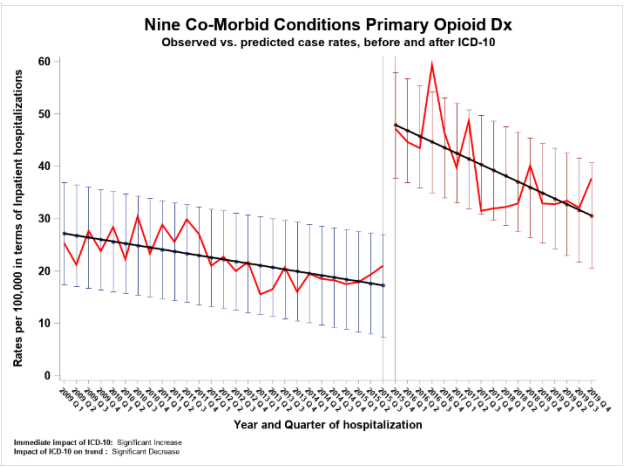


Figure 12. In-Patient Admissions: Subgroups Over Time - Primary Diagnosis Opioids

Quarterly hospital prevalence estimates for segments where inpatient admissions had an opioid code as the primary diagnosis. The reference lines delineate when the change from the ICD-9 to the ICD-10 occurred. The red line markers and estimates represent observed quarterly rates during both time periods. The black line represents the predicted regression models with 95% confidence intervals.

Non-Primary Opioid Diagnosis. Among in-patient hospital admissions where opioid indications of dependence, abuse, or use were a non-primary diagnosis, the magnitude of change in rates per 100,000 admissions before and after implementation of ICD-10 ranged from an increase of 125% to 273% (Table 10). The largest percentages increase in rates per 100,000 in-patient admissions occurred among non-whites (246%) and persons ages 57 and older (235% to 247% increase).

Table 10: Rates of Hospital In-Patient Opioid Diagnoses (Non-Primary)

Group	N	ICD-9 Rate per 100k persons	N	ICD-10 Rate per 100k persons	% Change
Overall	261,106	153.3	357,449	399.8	199%
Men	122,507	163.4	171,160	393.1	203%
Women	137,995	146.6	186,229	406.2	196%
White	226,804	172.5	299,504	429.5	273%
Non-White	34,305	104.5	57,945	281.6	246%
Age:					
18 and under	4,084	15.5	3,888	21.4	138%
19-36	76,582	293.4	94,287	528.1	180%
37-56	98,054	300.5	122,552	546.3	182%
57-64	31,189	179.8	52,768	443.3	247%
Over 64	48,612	203.1	83,954	478.3	235%
Comorbid Conditions:					
Chronic Pain	113,864	408.2	97,431	509.3	125%
Obesity	27,215	67.9	26,773	97.4	143%
Hypertension	86,889	150.4	100,528	360.8	240%
Tobacco Use	3,473	295.3	88,763	472.6	160%
COPD	80,832	548.4	120,844	1195.2	218%
Mental Health	118,912	2284.1	161,848	4526.3	198%
SUDS	205,130	1989.8	258,447	3482.0	184%

Immediately following the shift to ICD-10, there was a substantial increase in the in-hospital rate of non-primary opioid diagnoses that remained consistent over time (Figure 13). After the switch to ICD-10, rates of in-hospital admissions with non-primary opioid diagnoses were approximately 2-fold higher than rates when ICD-9 was in use.

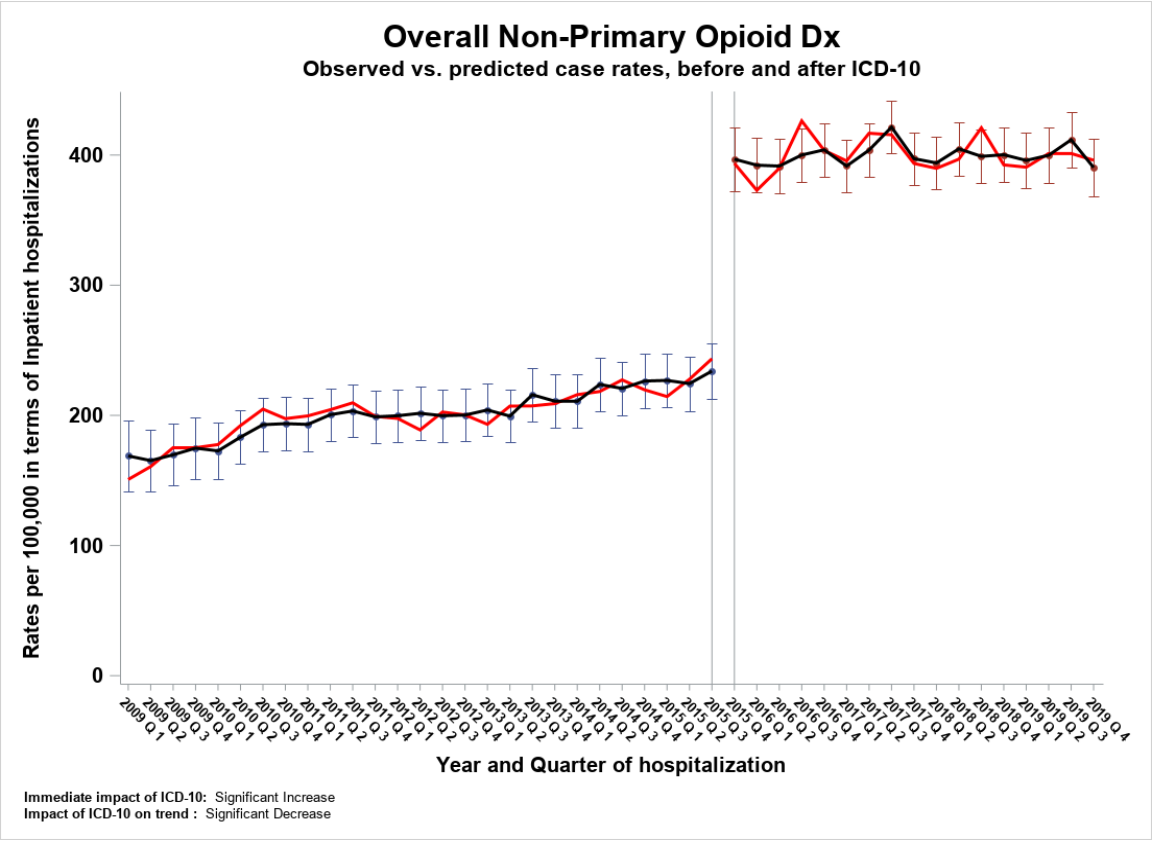
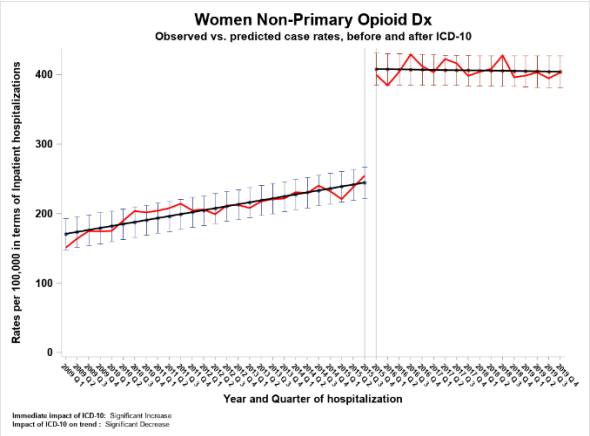
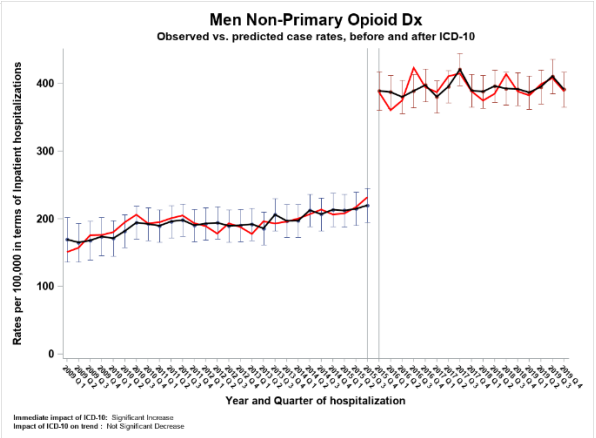


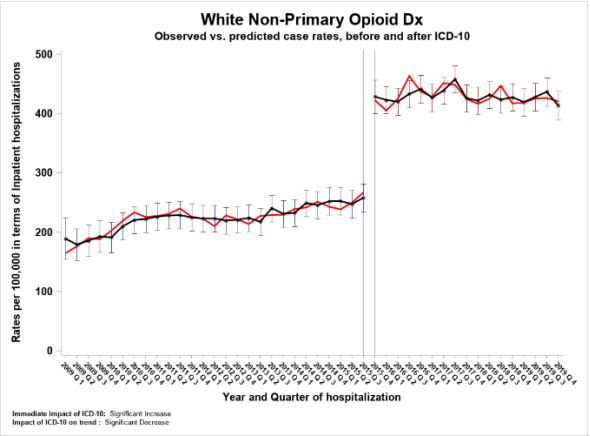
Figure 13. In-Patient Admissions Over Time - Non-Primary Diagnosis of Opioids. Quarterly hospital prevalence estimates for all inpatient admissions where an opioid code was present. The reference lines delineate when the change from the ICD-9 to the ICD-10 occurred. The red line markers and estimates represent observed quarterly rates during both time periods. The black line represents the predicted regression models with 95% confidence intervals.

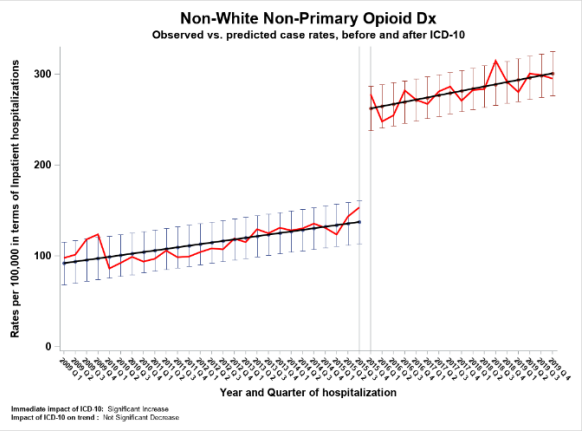
Finally, among subgroups, the large increase in rates of non-primary opioid diagnoses was consistent and similar over time in men and women and among whites (Figure 14). In non-whites and older age subgroups (ages 57 and older) the large increase in the rate of non-primary

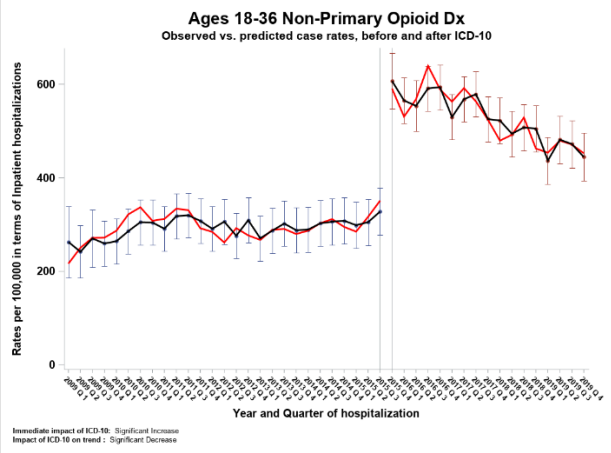
opioid diagnosis after the transition to ICD-10 continued to rise steadily over time. In contrast, persons ages 18 to 36 saw a consistent decline in the rate of non-primary opioid diagnosis after the abrupt increase that occurred after the transition to ICD-10.

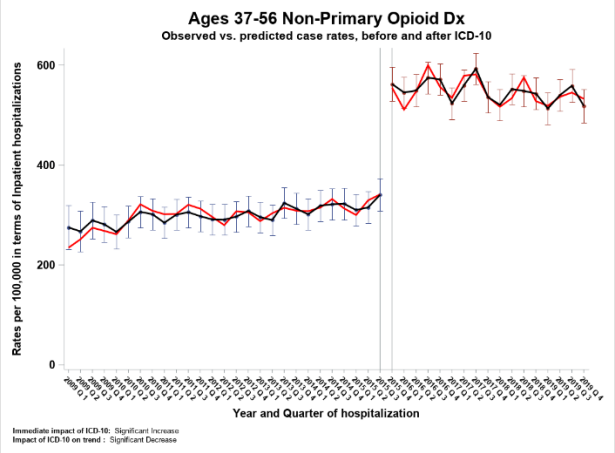












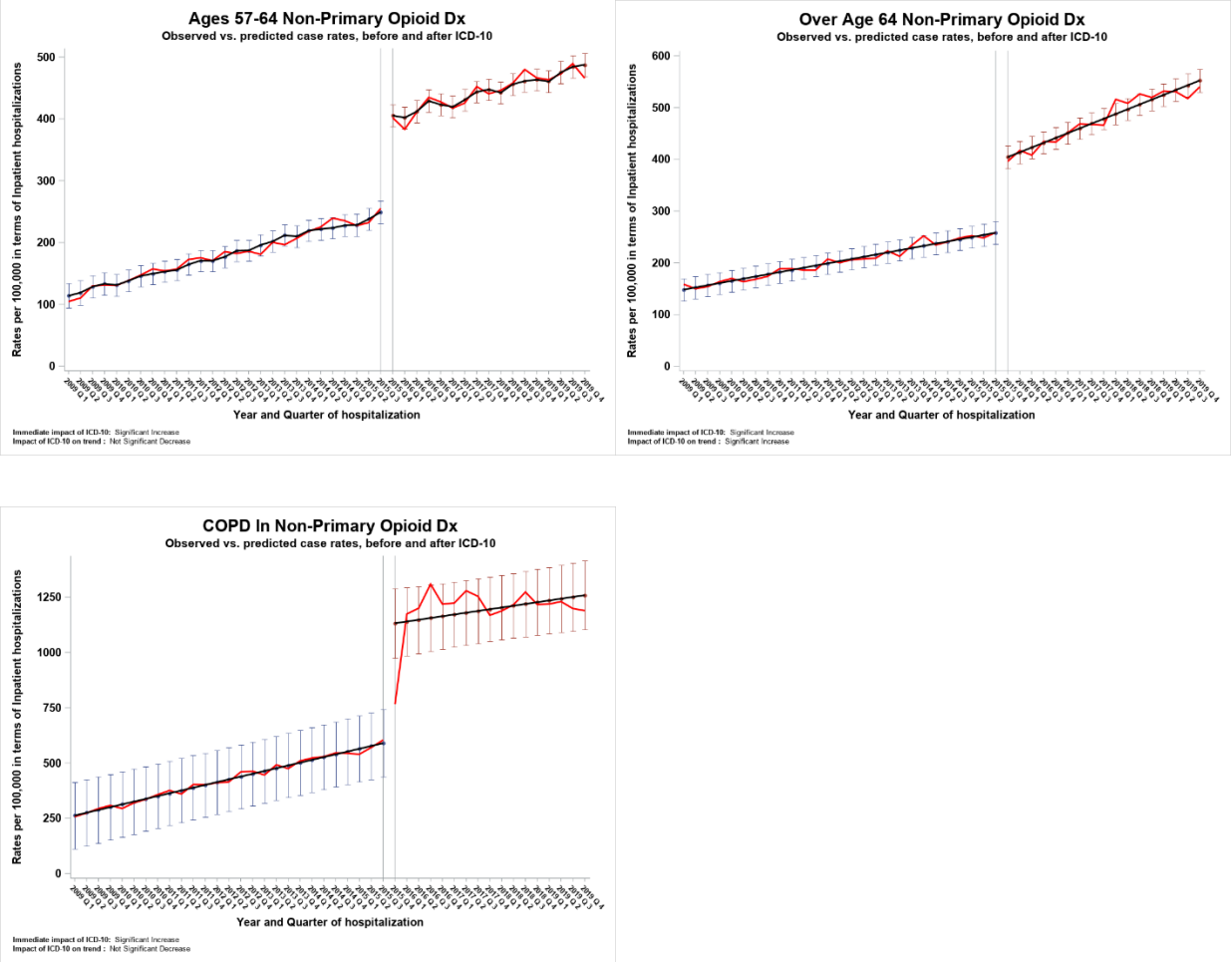


Figure 14. In-Patient Admissions: Subgroups Over Time - Non-Primary Diagnosis Opioids
Quarterly hospital prevalence estimates for segments within inpatient admissions where an opioid code was the not the primary diagnosis but was still present. The reference lines delineate when the change from the ICD-9 to the ICD-10 occurred. The red line markers and estimates represent observed quarterly rates during both time periods. The black line represents the predicted regression models with 95% confidence intervals.

Discussion

In this paper we examined the immediate impact of the switch from ICD-9 to ICD-10 on October 15, 2015, on both Florida ED and IP rates of diagnosis indicative of opioid dependence, abuse, or use, along with trends in rate changes after the transition to ICD-10. The study period encompassed 11 years, and we also examined changes in admission rates in a range of

sociodemographic and clinical subgroups. We observed that nearly all subgroups saw an immediate increase in the final quarter of 2015, often large in scope, and that did not return to the levels observed with ICD-9 diagnoses. Overall, the switch to ICD-10 saw a larger increases in rates of emergency department visits compared to in-hospital admissions.

We also observed that there were differences in the trends occurring post ICD modification between the emergency department and inpatient groups. The immediate impact noted in this study was anticipated due to previous evidence coupled with the increased coding burden presented by the formal modifications to the ICD-9 [8, 60]. Therefore, all changes in trend should be carefully evaluated by opioid epidemiologists when examining longitudinal healthcare data that passes over the ICD-9/ICD-10 transition.

Based on the previous analysis of HCUP data, we expected to see a pronounced immediate impact increase in both emergency department and inpatient admission rates, which occurred as anticipated but to a lesser extent for in-patient admissions [8, 60]. After the ICD-10 transition increase, we also expected to see a decreasing trend post ICD-10 in inpatient admissions where the primary diagnosis was opioid driven, as well as those where the number of co-morbid conditions was small or non-existent, due to stringent laws passed in 2014 by Florida state legislature. These laws and policies included the ability to purchase anti-overdose medications for at home administration, coupled with improved physician education on opioid prescribing. This decreasing rate during the ICD-10 period was also consistent with a Florida reported 3-year decrease in opioid overdose deaths, which has since start to climb post 2019 [3].

With the transition to ICD-10, we also observed increases in the rate per 100,000 of persons with greater than five co-morbid conditions in both inpatient and emergency department admissions where opioids were the primary diagnosis. After the transition to ICD-10 there was a

significant decrease in the rates among persons with less than 3 comorbidities. These results are consistent with our hypothesis that persons abusing opioids are surviving longer and developing a greater number of co-morbid conditions as they age and with continued use. We also observed a statistically non-significant increase in the trend of admission without any co-morbid conditions. We anticipated that newer opioid users would still present for admission due to issues often associated with newer use, such as overdose. We further did not expect to see a decrease in any of the co-morbid conditions, although we believe some explanation can be found in the enhanced intervention strategy adopted in Florida over the past six years. This has resulted in improved outcomes for opioid abuse such as the ability to self-administer anti-overdose medications in the community. This may have resulted in a greater number of patients surviving overdose at home and choosing not to be evaluated by a physician for reasons like trying to avoid stigma and fear of criminal prosecution.

Limitations

A limitation of our analysis is strict reliance on ICD-based codes that have suboptimal accuracy. That is, we were not able to evaluate the extent to which the positive and negative predictive value of the codes may have changed with the transition (since we did not review medical record to confirm/refute diagnoses). We could only assess changes in the relative frequency of code documentation, making it difficult to disentangle changes in coding accuracy from changes in documentation practices or changes in the true underlying prevalence of the conditions under study.

In addition, we observed few significant changes in trends in the rates within socio-demographic characteristics of any group, except for those under the age of 18 and for non-white admissions, which increased in both opioid primary and non-primary admits. The Substance

Abuse and Mental Health Services Administration (SAMHSA) has recently been attempting to explain the phenomena we observed in our data [16]. They, along with others, have launched a concerted effort over the past 3 years to expose the public to the impact of the opioid epidemic on the black and black Hispanic communities, and these studies have shown that opioid related morbidity and mortality in these groups has been increasing recently at rates that have been climbing steadily toward their white counterparts [14, 16].

Conclusion

We investigated the immediate and short-term impacts of the ICD-9/10 transition on rates and trends of inpatient and emergency department encounters in which there was an opioid-related diagnosis documented (primary or secondary). Overall, there were generally large increases in rate in each subgroup, while secular changes post ICD-10 transition were split between emergency department (mostly increasing) and inpatient (mostly decreasing) admission except for the number of co-morbid conditions at admission, which have been increasing regardless of admission status. The identified level changes could be from the large increase in available opioid related codes and hospital staff's inexperience with the new coding system, while the temporal differences and the increasing amount of co-morbid conditions may be related to public health policies designed to limit prescription opioid abuse, put into place during the year of the transition period. This work may be helpful to researchers and policy makers focusing on opioids by allowing them to continue to rely on opioid related data generated from ICD codes.

In addition, our work can be replicated (scalable) in that the coding scheme and statistical analysis are straightforward and could easily be re-coded to work for other states. Policy makers and healthcare administrators may also use this information to help estimate and prepare for the

increased burden of admissions related to opioids where the complexity of co-morbid conditions appears to be increasing. Finally, this study can be used to continue to evaluate the periodic changes to the ICD system, especially considering the proposed ICD-11 due to come out in 2022.

Chapter 5:
Discussion and Conclusions

This dissertation set out to characterize and explain the prevalence and factors associated with the Florida opioid epidemic from 2009 to 2019 by expounding on existing areas of research through three contributions. The first paper examined the association of pharmaceutical marketing of opioids, utilizing frequency of contact and the US dollar value of efforts such as lunches, speaking fees, and honoraria, on the prescribing rates of different Florida physicians. The second paper focused on a geospatial analysis of non-fatal opioid overdoses in Florida counties, looking for clusters of positive (much higher rates) spatial autocorrelation to explain factors associated with Florida counties that may have higher or lower than average opioid overdoses, which can then be studied further. The final paper was an examination of hospital discharge data in Florida of the immediate and secular changes in co-morbidity profiles of admission events related to opioid diagnoses relative to the mandatory ICD-9 to ICD-10 coding switch in quarter 4 of 2015. The following is a brief discussion of the results, contribution, and interpretation of each of these papers.

Pharmaceutical Marketing of Opioids in Florida and Prescriber Behavior

A person's first encounter with opioids is often while under the care of a physician, making understanding factors underlying prescribing behavior vital. However, the impact that pharmaceutical marketing has on this behavior is an area of limited research. What data exists suggests that there is a link, and that the highest levels of acceptance of transfers of value (not

necessarily just marketing) is associated with higher prescription rates. However, there was no dose-response relationship and we found lower prescription rates in groups below the highest level threshold. This study sought to contribute to the existing body of work by providing additional state-level data as well as by implementing improved, easily replicated methods of analysis to better account for confounding (e.g., propensity score matching/balancing) and to better isolate the association between opioid marketing efforts and opioid prescribing rates by physicians.

This study found that both the dollar value and frequency of opioid marketing efforts received were associated with higher individual physician prescribing rates during the time of the study, when compared to other physicians of similar characteristics that had not received marketing efforts [4, 21, 53, 66]. However, this effect was only present in physicians that had annual contact with marketers more than twice, becoming more pronounced at higher frequencies [24]. This study was limited by its use of Florida Medicare data which impacts some of its generalizability. Moreover, the study was limited to physicians on the assumption that advanced practice registered nurses (APRN) and physicians' assistants (PA) are directly supervised by medical doctors (MD/DO). Matching physicians from Medicare part D to the Sunshine Act database was performed by name and zip code as there were no other identifiers, there may also be some residual confounding associated with peer-to-peer influence on prescribing behavior. Finally, there exists the possibility of some reverse causal effect, wherein the prescribers with higher opioid prescribing rates are simply getting more attention from the pharmaceutical sales teams.

This paper continues to support other findings that pharmaceutical marketing influences the behavior of physicians, and that this is present in physicians who prescribe opioids, further

adding to the work by differentiating frequency and dollar value of marketing efforts as well as physician practice type [21, 24, 53, 66]. These findings were somewhat unexpected because it was thought that the dollar value of any marketing effort would have the highest association with increased opioid prescribing rather than the frequency of contact with the marketing salesforce, supporting theories around the psychological effect of pharmaceutical marketing [9-11, 24]. This study suggests that future work should be directed towards understanding how opioid sales and marketing efforts mediate prescribing patterns in exposed physicians, in addition to understanding and quantifying the role that a physician peer may influence another physician's prescribing habits, suggesting an opening for future work focused on mediation analysis to provide information on specific causal pathways to opioid prescribing. This in turn, could lead to much more specific targeted interventions [21, 53, 66, 67].

Sociodemographic Geospatial Analysis

Opioid researchers have been using GIS for years to better understand the geospatial distribution of opioid overdose and opioid deaths [37, 40, 42, 68]. However, they haven't made use of more robust features of GIS such as the assessment of latent spatial clusters, reducing understanding of this phenomenon [38, 47-49, 69]. This study sought to contribute to the existing body of work by state agencies, adding georeferenced data on non-fatal opioid overdose, as well as contributing advanced GIS and statistical modeling to account for both temporal and spatial autocorrelation. Data was collected from four separate sources and aggregated to the county level and then projected on to raster map layers, which were created with the R programming language. Using ArcGIS to begin to assess for spatial independence, suspected groupings were statistically tested for general and localized clustering [49]. Clusters were further analyzed and modeled using eigenvector spatial filtering (ESF) to adjust for spatial dependence to assist with

regression that was also adjusted multiple observations over time. This adds a new dimensionality and allows this study to evaluate the effects of a variety of exposures across time points allowing us to look for potential trends in clustering of opioid overdoses [38, 45, 47, 49].

This study found that clusters of counties where physicians had a greater exposure, a greater number of treatment resources per, the populace was a higher percent non-white, and/or a higher percent non-Hispanic were associated with statistically significant, separate, clusters of both emergency department encounters and inpatient admissions related to opioid overdose. There were no significant findings related to the main outcome of interest, pharmaceutical marketing of opioids to physicians.

This study was limited by several things: (1) non-fatal overdose counts and therefore calculated rates may be underestimated due to individual ability to self-treat opioid overdose in the community without medical intervention; (2) SDI score was taken at the county level which may skew estimates of poverty because most Fl counties have both poor and wealthy communities of varying size; (3) higher SDI counties may lack fiscal resources to report deaths in a timely and accurate manner; and (4) it is difficult to quantify the area effect opioid marketing may have on non-fatal opioid overdose(s) due to issues with prescription medication diversion to other areas (such as patients selling their prescription opioids to make money) and any effects representing local provider interaction with one another.

This paper supports the current efforts of Florida to continue to better understand the factors associated with the current opioid crisis. Furthermore, based on this analysis, county-level clusters of non-fatal opioid overdose in Florida can be tracked and evaluated statistically. Moreover, the evaluation of spatial autocorrelation (clustering) allows researchers to understand what variables might be associated with clusters of high non-fatal opioid overdoses. Finally, it

suggests that in general, more detailed analysis of the opioid epidemic is not only possible, but that many modern GIS applications and techniques offer a graphical user interface (removing the need to write code) making this accessible to the lay researcher. This study suggests that future work could be focused on obtaining more granular (zip code/neighborhood level) for fatal (such as death certificate data) and non-fatal opioid overdose, which would help account for the limitation of the Social Deprivation Index composite variable. Other work should focus on a mixed methods evaluation of both negative and positive autocorrelated clusters of fatal and non-fatal opioid overdose, which could help explain individual provider interaction on opioid prescribing behavior. Finally, tracking, or quantifying prescription opioid product diversion may allow for a more accurate assessment of communities where physicians are frequently exposed to opioid product marketing.

Examining the immediate and secular impact of opioid related admissions relative to changes in the ICD-9/ICD-10

Healthcare providers in the United States rely on electronic medical records (EMR) to keep track of patient care. These records require standardization which is done through the International Classification of Diseases (ICD) now on its 10th revision [57]. As of October 2015, the number of available opioid-related diagnoses codes increased from 25 to 108 [57]. Using Florida inpatient and emergency department hospital discharge data obtained from AHCA, this study set out to examine both the secular changes in the number of opioids related admits and the number of opioid-related, co-morbid conditions from 2009-2020 as well as the trend and level shift of opioid related admissions. Data was available at the quarterly level by year and de-identified to the ‘incident’ or presenting problem which were aggregated to the quarter by year, estimating prevalence for primary and non-primary opioid diagnosis and admission and

separated by ICD-9/10 for ease of interpretation. Interrupted time series using segmented regression was used to estimate both the immediate and secular changes present in the data.

This study was consistent with the more descriptive H-CUP (2017) report on impact of the ICD transition, however, the present study added to the overall data by stratifying co-morbid conditions and by adding statistical rigor to reporting the observed data [60]. We found that between 2009-2020 there were more than one million opioid-related admissions in Florida, that all data were immediately affected by the transition, however, only some showed changes in trend, additionally statistically significant trend increases were observed in the number of co-morbid conditions over time and minimal but significant increases were observed in individual conditions relative to opioids. This study faced four limitations (1) it used Florida hospital data so it may be difficult to generalize to other states or to the U.S. (2) AHCA data was 'event' only data, each event counts as one observation in that given quarter and there is no identifying data so that individuals could be followed over time and multiple admissions could be controlled for statistically (3) there was a steep learning curve for hospitals and much confusion occurred immediately post-transition, raising questions of reliability (4) the ED codes were limited to only 9 and did not capture any person with more than 9 co-morbid conditions related to opioids.

The research suggests in Florida that the immediate level change was statistically significant, while the increase in trend occurred mostly on IP admissions. The abrupt change can be explained by staff limitations, and hospital policy, coupled with the new coding scheme which added new levels of complexity to cases. The change in trend is a little more difficult to explain but the answer could be two-fold. One, the increase in IP admits related to opioids could be that individuals with long term opioid use (LTU) are developing more co-morbid conditions as they age (both from opioid use and the effects of aging), that those conditions are increasing in

severity resulting in inpatient admission. Two, opioid mitigations efforts in Florida were at least partially succeeding (1) less overdose trips to the ED due to self -treat OD (2) fewer new people are using and overdosing enough to necessitate medical intervention. This easily replicable study suggests that researchers should scrutinize longitudinal opioid data that falls withing the noted timeframe. This methodology can also be used by states to anticipate the burden of future ICD changes.

Final Discussion

This dissertation contributed to the body of work on the opioid epidemic by expanding on the literature focused on the association of pharmaceutical marketing with physician opioid prescription writing, addressing geospatial considerations and expanding existing GIS approaches with more robust statistical approaches, and utilizing more advanced statistical processes to evaluate the longitudinal effect of policy changes in diagnostic criteria on emergency and inpatient hospital admissions. The combined and replicable methodological approach of this analysis makes it a unique effort that other states can utilize in support of their own efforts to combat the influence of the opioid epidemic. The researchers have several recommendations and/or caveats based, in part, upon the body of work present in this dissertation: First, mitigation efforts focused on the reduction of inflated opioid prescription rates should either limit activities that allow for high frequency contact between providers and sales reps (such as lunches) or limit the amount of direct contact between pharmaceutical sales and providers to less than seven contacts in a year [10, 11, 24]. Second, from a GIS perspective, this study allowed the researchers to look at clusters of counties where non-fatal opioid overdoses occurred. These methods may allow others to do the same, thus our recommendation is a mixed methods study, starting with interviews of the community leaders and data gathering to increase

spatial-temporal granularity in the counties where extreme rates are occurring. When attempting to replicate our results, care should be taken, as the techniques outlined in paper two are often computationally intensive and should only be used in areas where clustering of the outcome of interest is highly suspected [45, 49]. Finally, regarding researchers examining hospital discharge or Medicaid/care claims data on opioid-related admissions spanning the ICD-9 to ICD-10 coding periods, our suggesting is that they continue to rely on analytical strategies that include stratification by period, owing to the changes observed in immediate effect of the transition coupled with the relatively large change in the number of diagnostics codes increases the complexity and interpretation of any results [11, 12, 24, 38, 49, 60, 62, 63].

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Appendix A: Literature Review

Introduction

There are many different theories associated with the increase in fatal and non-fatal opioid overdose in the United States since the late 1990s [1, 4]. This ranges from neurobiological theories, comparing genetic traits of those diagnosed with substance abuse disorders, to examining how the social determinants of health (including built environment) can mediate an exposure to opioids [1, 4]. Other theories have suggested that the differing pharmacological properties of new synthetic opioids may mediate drug overdose deaths [5]. There are also some that posit that there was a change in opioid prescribing patterns of physicians, and those patterns might be related to marketing efforts of opioid producing big pharma [4]. Some researchers postulate that public health policy changes related to the treatment of pain in the early 21st century is related to increased prescribing of opioids by physicians (leading to addiction), including the American Pain Society's efforts throughout the 1990s [4]. Additionally, many in Florida have attributed the rise and fall of the so called "pill mills" to a subsequent rise in opioid use and abuse in Florida and across the southern United States [1, 4]. Finally, concerns have been identified in the evaluation of hospital level opioid overdose data over time due to the changeover from classification schemes at the end of 2015 [8]. The primary purpose of this literature review is to examine the current research and any knowledge gaps associated with the rise of the opioid epidemic.

Neurophysiology of Addiction

Drugs work by affecting the brain and brain chemistry. Brain cells communicate via neuro-transmitters that signal the open/close of receptor sites (like logic gates in a simple computer) [19]. Drugs interfere with the signaling process by either disrupting transmission or activating receptors that don't need to be active [19]. Substances like opioids and marijuana have chemical structures that are similar enough to the brain's natural ones that they are able to attach to receptors, however the message they give the cell becomes distorted and the brain's perception of other messages can become quite abnormal [19]. Other types of drugs like methamphetamines and cocaine prevent the brain from recycling (called re-uptake) chemicals (serotonin, norepinephrine, etc.) that balance mood and alertness appropriately. This can cause euphoria and the illusion of focus/alertness. Drugs act on specific parts of the brain, most notably the area that perceives reward for pleasurable activities such as eating, socializing, and sex; this is also where users learn to habituate those behaviors that bring the user the most pleasure [19]. Drug use can become one of these habits with repeat exposure a user's sense of pleasure begins to decrease, affecting all of their pleasurable activities, and it becomes difficult to enjoy anything without the presence of the substance of choice [19]. This increased level tolerance to the substance of choice eventually leads to the process of addiction, which includes a combination of psychological and physiological dependence starting a cycle in the that's difficult to break; wherein the brain begins to manufacture stressful feelings when the perceptions are no longer dulled by the abuse of the drug [19]. The individual begins to develop behavioral patterns that revolve around the habitual use of the drug, their life starts to become a focus of getting high or getting drugs to get high, often disrupting the regular course of life [4]. Unfortunately, continued use has been associated with a higher risk of non-fatal and fatal overdose [4, 19]. More research

is needed to evaluate secular changes in health complications and co-morbidities in patients designated as a long-term opioid user [4, 19].

Neurobiological Vulnerabilities

The biology of addiction is just now beginning to be researched and answering why different individuals can be exposed to the same frequency and duration of an addictive substance with only a portion displaying the symptoms of a SUD is a difficult question [19, 70]. Researchers have noted that SUD tends to run in families (genetics), and that social exposure to drug use and stress can also contribute to risks [70]. Studies have estimated that the four highest inheritable risks for addiction are alcohol, caffeine, opioids, and cocaine, in that order [71].

Genetic personality traits such as novelty seeking and impulsivity have also been associated with the promotion of addictive behavior in those prone to do so [19, 71]. Other familial traits that can potentially result in psychiatric disorders, thereby enhancing vulnerability through negative indications, may also make one more likely to utilized addictive substances in an attempt to mitigate symptoms, most notably the family of anxiety disorders [19, 71]. There are also two types of genetic environment that may be considered, both correlation and interaction [71]. Gene-environment correlation occurs when a person's genes are corelated with the likelihood of an increased use of an addictive substance (exposure) leading to outcomes such as a gene linked to heavy smoking and subsequent increased risk of lung cancer [71].

Gene-level interaction occurs when a person's genetic makeup (genotype) modifies the outcome to an environmental exposure such as an individual's specific response to a traumatic event [71, 72]. It has been documented that all of the personality disorders in the Diagnostic and Statistical Manual of Psychiatric Disorders 5th edition (DSM V) can be modestly to moderately inheritable, and that they can develop through an individual's reaction to trauma exposure [7]. It has been further elucidated that those persons with personality disorders (psychiatric

impairments) are more likely to use substances, thus modifying the outcome of substance abuse/addiction [42, 70]. The genes being investigated for the promulgation of SUDs are catechol-O-methyl transferase (COMT) and the serotonin transporter (SLC6A14) which regulate individual expression of serotonin, norepinephrine, and dopamine (reward chemicals in the brain) [71, 72]. However, the results are mixed and tend to vary by region, while gene discovery related to substance abuse disorders is still new, although promising [71]. The takeaway is that while scientists are starting to be able to identify individuals at greater genetic risk of substance abuse, they still have a long way to go before the utilization of proper mitigation strategies with genetic data, such as genetic counseling to potential parents or targeted gene therapy, can become effective [71, 72].

Differing Pharmacological Properties in Newer Opioids

Even though the different pharmacological properties haven't made much difference in who becomes addicted and what they use, newer lab-created opioids are responsible for at least part of the increase in overdose-related deaths associated with opioid abuse [1, 73]. An important factor is that most new, illicit use, drugs are simply higher dose, synthetic, concentrations of older opioids, allowing the user to utilize less of the drug for the same effect [1, 42]. Traditional (opium, heroin, morphine, codeine) opioids are derived from the poppy plant after certain levels of processing [4]. In the past 70 or so years drug companies have sought to reduce dependence on poppy producers by creating synthetic versions of opium poppy derivatives [4]. The result was much stronger drugs (oxycodone, oxycontin, fentanyl, tramadol, fentanyl analogues, methadone) at much lower prices, in some cases more than 1500 times more potent than the traditional substances, ostensibly to treat pain from issues like end stage cancer [74]. Originally it was just a matter of illicit product diversion from pharmaceutical companies; however, a number of enterprising organic chemists went into business for themselves and began manufacturing

these drugs, as well as creating new ones (called analogues), solely for the purposes of illicit distribution, which is not FDA regulated and as such has no quality control [42]. The results of this criminal manufacture of synthetic opioids is that strength varies across labs and, without chromatography or spectroscopy, it is almost impossible to determine accurate dosing [42]. The other side effect is that this manufacture is inexpensive and drug dealers frequently mix it with more traditional substances of abuse in an effort to increase their store of the more expensive substances (heroin, morphine), but they are not providing this information to their 'customers' [42]. The user then proceeds to use what they normally would use, and accidentally overdoses and dies, because both the dealer and the customer were not aware of the strength of the product [42]. Some manufactured drugs are so strong that a few grains could kill a seasoned user with years of tolerance. This strength and concentration makes the drug both smaller and much easier to transport and hide from authorities, which continues to increase its appeal to the illicit substance trade. The figure below, a graph from Keiser Permanente, shows five-fold rise from 2011 (16 per 1500k persons) to 2018 (150+ per 1500k persons) of synthetic opioid deaths in the United States [34]. The reality is that new opioids are inexpensive, easy to manufacture, and easier to hide and transport than traditional analogues, making them an increasingly viable alternative for drug dealers to turn to. Researchers have an adequate understanding of the pathophysiology of death from opioids (regardless of strength), so the focus of research efforts have been on overdose prevention public service announcements, surviving overdose(s) in the community, and combating illicit sales. More research is needed in expanding and integrating the tracking of both illegal and prescription opioid movement (diversion), opioid overdose occurrence, and evaluating current mitigation strategies.

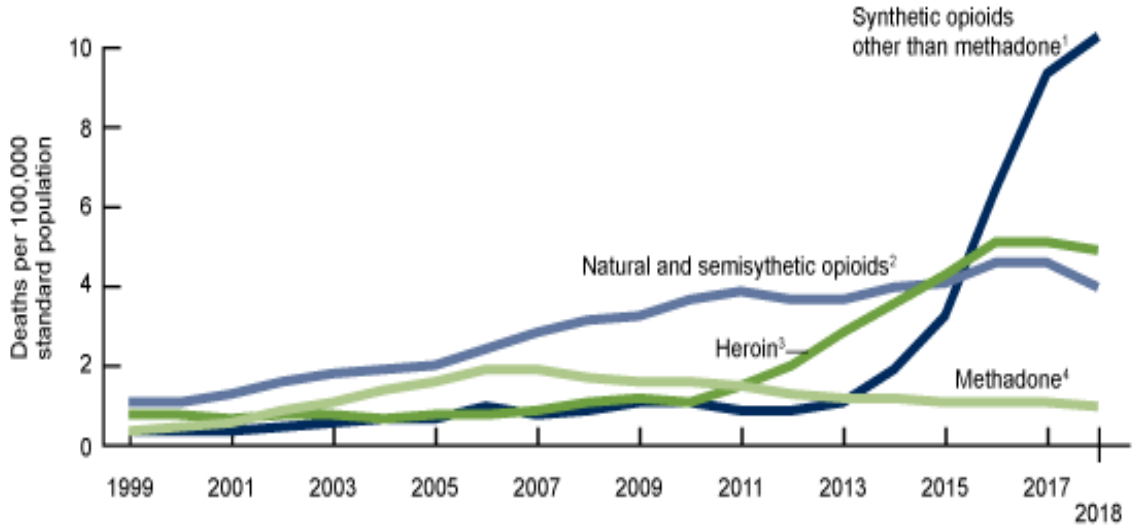

Figure 15: Changing Physician Prescribing Patterns and Pharmaceutical Marketing

In 1999, the amount of morphine milligram equivalents (MME) prescribed per 100 persons was 180 MME (far in excess of other developed countries) and by 2010 the number had increased to 780 MME per 100 persons [23]. This number dropped to around 640 MME per 100 persons by 2015 [23]. MME more accurately reflects the amount in milligrams beings dispensed in each prescription. Rates are a little harder to come by, the IQVIA XPONENT data base has data for 2006 and up available online, which is where most of the relevant studies on these rates have derived their data from. The CDC reports opioid prescribing rates, in 2006, 72.4 per 100 persons (215,917,663 written scripts / 298,400,000 population). The 2010 rate increased to 81.2 per 100 persons with a 780 MME, before coming back down to the almost 2006 rate in 2015, however, the strength of those prescriptions was still three times higher than what was being used in 1999 [2, 20, 23]. Rates in 2018, were 51.4 per 100 persons with MME of 543.3 (993,917,021 (written scripts)/318,600,000 (population), below 2006 values [2, 22, 23]. With these numbers comes a large variation in prescribing patterns amongst states in 2006. Oklahoma, Louisiana, Tennessee, West Virginia (129.2 the highest), Kentucky, and Indiana, all presented

rates over 107 per 100 persons, and in 2018 only minor changes in these numbers were observed. Despite these changing prescribing patterns, overdose deaths from opioids are still very high (in excess of 20 per 100k persons), causing some to question if enough is being done to mitigate the over prescribing of opioids [25]. Studies have also tried to link these prescribing patterns to overall influence by drug manufacturers to physicians through marketing related payments such as meals and fancy conferences at exotic locations [21, 25]. They have found that even a small amount of marketing effort (under $100) could lead to statistically significant changes in prescribing rates [21, 24]. Opioid prescribing has changed since the late 1990s, increasing drastically by 2010, before trending slightly downward to where it is today. Furthermore, new research has begun to highlight the role that aggressive pharmaceutical marketing has played in physician over prescribing of opioids, although this is still in its infancy and more work is needed to effectively tease out the level of influence 'big pharma' played [2, 20, 22-25, 53].

Proliferation of Pain Clinics and Subsequent Implementation of Pain Clinic Laws

Pain clinics began shortly after Purdue Pharma released its newest drug, oxycontin, which it aggressively marketed to physicians as a safe alternative ("less addictive") to other opioids like morphine [27, 28]. The first pain clinics to exist were in Florida, owned and operated by two brothers, Jeff and Christopher George, starting The South Florida Pain Clinic in Broward and Palm Beach counties, where they were estimated to have earned in excess of $40 million US [28]. Their clinics were set up to be vertically integrated, with a person to falsify MRI reports, a physician to diagnose chronic pain, and a pharmacy that only dispensed pain meds (cheaply acquired from Purdue Pharma for pennies a pill) cash only, starting at $10 a pill, it's estimated that they provided over 500 million pills to persons all over the United States, making them legal drug kingpins (by the Narcotics Kingpin Act of 1999) [28]. People from all

over the country drove to Florida to take advantage of these businesses, sometimes buying thousands of pills at a time for diversionary resale in other states [28]. By the time the clinics peaked in 2010, 90 of the nation's top opioid prescription writers were found within Florida's borders and 85% of the oxycodone prescribed in the US was written in Florida [28]. During this year Florida saw its highest spike in overdose death rates related to synthetic opioids nearly triple that of 1999. The reason it was so easy for pill mills to proliferate in Florida was the complete lack of any viable prescription monitoring systems in place, allowing for them to stay "under the radar." Not only were the laws less restrictive, but the market was ready due to the U.S. incursion into Afghanistan, one of the largest opium producing nation in the world, which limited the amount of heroin and morphine that entered the U.S. illegally. The dealers in illicit opiates needed to keep their customers addicted on the cheap and Florida pill mills made it easy to do [13, 28, 29]. Lawmakers attempted to rectify this, however, Purdue began to lobby strongly in Florida and donated more than $4 million between 2006-2015 [13]. Eventually, even big pharma money couldn't stop the public outcry and news agency reporting of the pill mill crisis, and then Governor (Scott, now a Florida Senator) was encouraged to reverse his position, agreeing to the state narcotics tracking system, and laws were passed to prevent the continued vertical integration of pain clinics (they couldn't provide pills on site anymore) [13]. Many shut down, others continued to operate regularly harassed by police. Eventually, most closed lowering age adjusted overdose death rates for several years and making pills too expensive to use regularly, however, illicit labs are making low-cost synthetic opioids and manufacturing fake pills. Additionally some of the population has switched back to heroin which has become more available [13, 27]. Pill mills changed the face of the opioid epidemic for the worse, they were

responsible for getting millions of pills to thousands of people across the US, fanning the fires of opioid overdoses and associated deaths.

American Pain Society (APS)

The APS was an influential, professional membership calling itself "a multidisciplinary community of scientists, clinicians and other professionals." It was founded in 1977, with the express goal of researching pain, publishing the *Journal of Pain* for many years. It is most noted for the (now infamous) introduction of pain as the 5th vital sign in 1996, the society claimed that they hoped by elevating pain to the level of essential information would allow for its evaluation and management improving patient perception of outcomes [75]. Essentially they were successful in this endeavor launching specialized pain related trainings and sending out extensive "tool boxes" ostensibly to teach physicians the "science" of pain management, however it was more focused on breaking down the barriers to getting patients to take pain medications (pg. 9), arguing against the restrictive regulation of controlled substances (pg. 11) and a patient's right to comfort (pg. 20) [75, 76]. This received heavy buy in from Joint Commission on Health Care (JACHO) and the Department of Veterans Affairs (VA) [75]. While it did get physicians to look at patient discomfort much more closely, it has now been (dis)credited with encouraging the over prescription of opioid analgesics [75]. This, coupled with a series of lawsuits alleging damages due its role in the epidemic, led to bankruptcy in 2019 and subsequent dissolution by January of 2020 [75].

ICD-9 vs ICD-10

The differences in ICD-9 versus ICD-10 with regards to opioids are quite large, most notable was that it increased from 20 to 100 individual diagnosis codes [8]. The official transition date

from ICD-9-CM to ICD-10-CM for inpatient and outpatient diagnoses (death certificates have been using ICD-10 since 1999) was October 1, 2015; however, administrative problems including the addition of data make it likely that when examining data within 2 years of this date there could be discontinuity as care facilities worked to make the transition. A study by the Healthcare Cost and Utilization Project (HCUP) using inpatient data from Colorado, Kentucky, and Minnesota, examined the change in opioid related diagnoses before and after the transition [8]. Despite the increase in available codes, the study noted that only 25% of the codes were being utilized [8]. The HCUP-based analysis also noted several significant increases in opioid-related inpatient stays between the ICD-9/290 which differed by age group: 65+ (55.7%), 45-64 (20.8%), and 25-44 (2.2%), suggesting that such differences are worth looking at in other states such as Florida [8]. Other issues noted with the change are codes in the ICD10 that have no equivalent in the ICD9, such as “unspecified opioid use” which has 14 codes that don’t match, and the addition of a “complicated” and “continuous” series of codes; giving rise to some ambiguity creating descriptions like “opioid use, unspecified, uncomplicated” or “opioid use, unspecified, with unspecified opioid induced disorder”. This might suggest that such code usage could be subjective, where the ICD9 tended to focus on whether the diagnosis involved opioid use, user addiction, and history of use [8]. The newer codes attempt to provide for every contingency imaginable that could be associated with opioid use such as “adverse effect of opium, first encounter” or “adverse effect opiate agonist” and “methadone causing adverse effects in therapeutic use” which adds to the difficulty of performing an analysis that includes the transition period [8]. More research is needed to better understand the both the immediate and secular impact of the coding transition which will allow decision makers to evaluate potential strategies for future code revisions and updates.

Conclusion

The purpose of this review was to examine the current public health research as it relates to the ongoing opioid epidemic of the twenty-first century, specific to topics that impact this dissertation. It can be noted from the bodies of work examined that the severity scope and persistence of this outbreak is unprecedented, and that little success has been achieved and rates of fatal and non-fatal opioid overdose remain far above pre-epidemic levels [1, 3-5]. Research has focused primarily on the individual, such as the biology of addiction although gaps exist to better understand temporal pathophysiology as well as neurological vulnerabilities that could lead to fatal and non-fatal opioid overdose [19, 70-72]. Other work has started to examine external influences on fatal and non-fatal opioid overdose such as the social determinants of health, neighborhood influences, physician opioid prescribing behavior, opioid marketing efforts to physicians, and to some degree geographic impact, however this research represents newer efforts and gaps still exist in understanding the role that pharmaceutical companies, physician prescribing behavior, hospitals, and geographical distribution played. This body of work serves as a review of the current knowledge of the opioid epidemic and recommends further evaluation of physicians' opioid prescribing, pharmaceutical marketing efforts of opioids in relation to complex interplay of geography and sociodemographic characteristics on opioid overdose and overdose death in the hopes that it will help better inform multi-prong mitigation strategies by decision makers.

Appendix B: ICD-9 and ICD-10 Codes

Diagnosis code	Description
ICD-9-CM diagnosis codes	
304.00	Opioid type dependence, unspecified
304.01	Opioid type dependence, continuous
304.02	Opioid type dependence, episodic
304.03	Opioid type dependence, in remission
304.70	Combinations of opioid type drug with any other drug dependence, unspecified
304.71	Combinations of opioid type drug with any other drug dependence, continuous
304.72	Combinations of opioid type drug with any other drug dependence, episodic
304.73	Combinations of opioid type drug with any other drug dependence, in remission
305.50	Opioid abuse, unspecified
305.51	Opioid abuse, continuous
305.52	Opioid abuse, episodic
305.53	Opioid abuse, in remission
965.00	Poisoning by opium (alkaloids), unspecified
965.01	Poisoning by heroin
965.02	Poisoning by methadone
965.09	Poisoning by other opiates and related narcotics
970.1	Poisoning by opiate antagonists
E850.0	Accidental poisoning by heroin
E850.1	Accidental poisoning by methadone
E850.2	Accidental poisoning by other opiates and related narcotics
E935.0	Heroin causing adverse effects in therapeutic use
E935.1	Methadone causing adverse effects in therapeutic use
E935.2	Other opiates and related narcotics causing adverse effects in therapeutic use
E940.1	Adverse effects of opiate antagonist

ICD-10-CM diagnosis codes	
Opioid abuse/dependence	
F11.10	Opioid abuse, uncomplicated
F11.120	Opioid abuse with intoxication, uncomplicated
F11.121	Opioid abuse with intoxication, delirium
F11.122	Opioid abuse with intoxication, with perceptual disturbance
F11.129	Opioid abuse with intoxication, unspecified
F11.14	Opioid abuse with opioid-induced mood disorder
F11.150	Opioid abuse with opioid-induced psychotic disorder, with delusions

F11.151 Opioid abuse with opioid-induced psychotic disorder, with hallucinations
F11.159 Opioid abuse with opioid-induced psychotic disorder, unspecified
F11.181 Opioid abuse with opioid-induced sexual dysfunction
F11.182 Opioid abuse with opioid-induced sleep disorder
F11.188 Opioid abuse with other opioid-induced disorder
F11.19 Opioid abuse with unspecified opioid-induced disorder
F11.20 Opioid dependence, uncomplicated
F11.21 Opioid dependence, in remission
F11.220 Opioid dependence with intoxication, uncomplicated
F11.221 Opioid dependence with intoxication, delirium
F11.222 Opioid dependence with intoxication, with perceptual disturbance
F11.229 Opioid dependence with intoxication, unspecified
F11.23 Opioid dependence with withdrawal
F11.24 Opioid dependence with opioid-induced mood disorder
F11.250 Opioid dependence with opioid-induced psychotic disorder, with delusions
F11.251 Opioid dependence with opioid-induced psychotic disorder, with hallucinations
F11.259 Opioid dependence with opioid-induced psychotic disorder, unspecified
F11.281 Opioid dependence with opioid-induced sexual dysfunction
F11.282 Opioid dependence with opioid-induced sleep disorder
F11.288 Opioid dependence with other opioid-induced disorder
F11.29 Opioid dependence with unspecified opioid-induced disorder

Opioid use

F11.90 Opioid use, unspecified, uncomplicated
F11.920 Opioid use, unspecified with intoxication, uncomplicated
F11.921 Opioid use, unspecified with intoxication delirium
F11.922 Opioid use, unspecified with intoxication, with perceptual disturbance
F11.929 Opioid use, unspecified with intoxication, unspecified
F11.93 Opioid use, unspecified, with withdrawal
F11.94 Opioid use, unspecified, with opioid-induced mood disorder
F11.950 Opioid use, unspecified with opioid-induced psychotic disorder, with delusions
F11.951 Opioid use, unspecified with opioid-induced psychotic disorder, with hallucinations
F11.959 Opioid use, unspecified with opioid-induced psychotic disorder, unspecified
F11.981 Opioid use, unspecified with opioid-induced sexual dysfunction
F11.982 Opioid use, unspecified with opioid-induced sleep disorder
F11.988 Opioid use, unspecified with other opioid-induced disorder
F11.99 Opioid use, unspecified, with unspecified opioid-induced disorder

Poisoning

T40.0X1A Poisoning by opium, accidental (unintentional), initial encounter
T40.0X1D Poisoning by opium, accidental (unintentional), subsequent encounter
T40.0X2A Poisoning by opium, intentional self-harm, initial encounter
T40.0X2D Poisoning by opium, intentional self-harm, subsequent encounter

T40.0X3A Poisoning by opium, assault, initial encounter
T40.0X3D Poisoning by opium, assault, subsequent encounter
T40.0X4A Poisoning by opium, undetermined, initial encounter
T40.0X4D Poisoning by opium, undetermined, subsequent encounter
T40.1X1A Poisoning by heroin, accidental (unintentional), initial encounter
T40.1X1D Poisoning by heroin, accidental (unintentional), subsequent encounter
T40.1X2A Poisoning by heroin, intentional self-harm, initial encounter
T40.1X2D Poisoning by heroin, intentional self-harm, subsequent encounter
T40.1X3A Poisoning by heroin, assault, initial encounter
T40.1X3D Poisoning by heroin, assault, subsequent encounter
T40.1X4A Poisoning by heroin, undetermined, initial encounter
T40.1X4D Poisoning by heroin, undetermined, subsequent encounter
T40.2X1A Poisoning by other opioids, accidental (unintentional), initial encounter
T40.2X1D Poisoning by other opioids, accidental (unintentional), subsequent encounter
T40.2X2A Poisoning by other opioids, intentional self-harm, initial encounter
T40.2X2D Poisoning by other opioids, intentional self-harm, subsequent encounter
T40.2X3A Poisoning by other opioids, assault, initial encounter
T40.2X3D Poisoning by other opioids, assault, subsequent encounter
T40.2X4A Poisoning by other opioids, undetermined, initial encounter
T40.2X4D Poisoning by other opioids, undetermined, subsequent encounter
T40.3X1A Poisoning by methadone, accidental (unintentional), initial encounter
T40.3X1D Poisoning by methadone, accidental (unintentional), subsequent encounter
T40.3X2A Poisoning by methadone, intentional self-harm, initial encounter
T40.3X2D Poisoning by methadone, intentional self-harm, subsequent encounter
T40.3X3A Poisoning by methadone, assault, initial encounter
T40.3X3D Poisoning by methadone, assault, subsequent encounter
T40.3X4A Poisoning by methadone, undetermined, initial encounter
T40.3X4D Poisoning by methadone, undetermined, subsequent encounter
T40.4X1A Poisoning by synthetic narcotics, accidental (unintentional), initial encounter
T40.4X1D Poisoning by synthetic narcotics, accidental (unintentional), subsequent encounter
T40.4X2A Poisoning by other synthetic narcotics, intentional self-harm, initial encounter
T40.4X2D Poisoning by other synthetic narcotics, intentional self-harm, subsequent encounter
T40.4X3A Poisoning by other synthetic narcotics, assault, initial encounter
T40.4X3D Poisoning by other synthetic narcotics, assault, subsequent encounter
T40.4X4A Poisoning by synthetic narcotics, undetermined, initial encounter
T40.4X4D Poisoning by synthetic narcotics, undetermined, subsequent encounter
T40.601A Poisoning by unspecified narcotics, accidental (unintentional), initial encounter
T40.601D Poisoning by unspecified narcotics, accidental (unintentional), subsequent encounter
T40.602A Poisoning by unspecified narcotics, intentional self-harm, initial encounter
T40.602D Poisoning by unspecified narcotics, intentional self-harm, subsequent encounter
T40.603A Poisoning by unspecified narcotics, assault, initial encounter

T40.603D Poisoning by unspecified narcotics, assault, subsequent encounter
T40.604A Poisoning by unspecified narcotics, undetermined, initial encounter
T40.604D Poisoning by unspecified narcotics, undetermined, subsequent encounter
T40.691A Poisoning by other narcotics, accidental (unintentional), initial encounter
T40.691D Poisoning by other narcotics, accidental (unintentional), subsequent encounter
T40.692A Poisoning by other narcotics, intentional self-harm, initial encounter
T40.692D Poisoning by other narcotics, intentional self-harm, subsequent encounter
T40.693A Poisoning by other narcotics, assault, initial encounter
T40.693D Poisoning by other narcotics, assault, subsequent encounter
T40.694A Poisoning by other narcotics, undetermined, initial encounter
T40.694D Poisoning by other narcotics, undetermined, subsequent encounter

Adverse effects

T40.0X5A Adverse effect of opium, initial encounter
T40.0X5D Adverse effect of opium, subsequent encounter
T40.2X5A Adverse effect of other opioids, initial encounter
T40.2X5D Adverse effect of other opioids, subsequent encounter
T40.3X5A Adverse effect of methadone, initial encounter
T40.3X5D Adverse effect of methadone, subsequent encounter
T40.4X5A Adverse effect of synthetic narcotics, initial encounter
T40.4X5D Adverse effect of synthetic narcotic, subsequent encounter
T40.605A Adverse effect of unspecified narcotics, initial encounter
T40.605D Adverse effect of unspecified narcotics, subsequent encounter
T40.695A Adverse effect of other narcotics, initial encounter
T40.695D Adverse effect of other narcotics, subsequent encounter

Long-term use of opiates

Z79.891 Long-term (current) use of opiate analgesic