PRESCRIPTION OPIOID EPIDEMIC IN PENNSYLVANIA: LESSONS FROM MEDICARE AND MEDICAID

by

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ABSTRACT

This dissertation seeks to provide evidence for interventions that large health systems can utilize to help mitigate the prescription opioid epidemic in Pennsylvania.

Chapter one introduces the research problem

Chapter two examines the potential for machine-learning approaches to better understand the heterogeneity of opioid use in Medicare. What constitutes potentially high-risk use of prescription opioids in Medicare is not clearly known. Using novel techniques of machine-learning, we identify five groups of Medicare beneficiaries with potentially high-risk opioid use patterns. We observe that these groups differ not only on measures of opioid use but also on important demographic characteristics, clinical characteristics and mortality.

Chapter three examines the associations between physician prescribing specialties and opioid-related outcomes of opioid-use disorder (OUD), misuse, and overdose. Little is known about the variations in risk of OUD, misuse, and overdose by type of opioid prescribing specialties. Using data from Pennsylvania Medicaid, we examine the associations between the index and dominant opioid prescribing specialty and OUD, misuse, and overdose. We observe that Medicaid enrollees who receive their index opioid prescription or a majority of their prescriptions from specialties that treat chronic pain -pain medicine and physical medicine and rehabilitation- are at higher risk for OUD and misuse compared to primary care.

Chapter four examines the associations between adherence to antidepressant medications among individuals with mood disorders and opioid use. Literature shows that antidepressants have anti-nociceptive effects in mitigating pain among individuals with mood disorders. Using Pennsylvania Medicaid data, we examine whether adherence to antidepressants among individuals with major depressive disorders (MDD) or anxiety disorders is associated with reduced opioid use. We observe that enrollees with MDD and no cancer, who achieve ≥ 20% adherence have significantly lower hazards ratios for opioid use than those who achieve <20% adherence.

This dissertation has important implications for public health. Our findings provide evidence for interventions that health-systems can use to: (i) identify high-risk beneficiaries who use opioids, (ii) support evidence-based prescribing in settings where patients are at an elevated risk for adverse outcomes of opioid use, and (iii) increase adherence to antidepressant medications among individuals with MDD.

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To my grandmother, Mary, who taught me the value of humility

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1 CHAPTER ONE: INTRODUCTION

The United States has seen an increase in drug overdose deaths from 2000 to 2014, with nearly half a million individuals dying due to drug overdoses.[1] Of the 28,647 prescription drug overdose deaths in 2014, 61% were due to opioids.[2] Pennsylvania (PA) is one of the main states impacted by this epidemic. PA ranked 9th among states in the number of age-adjusted drug overdose deaths per 100,000 people from 2011-2013.[3]

With the goal of providing evidence-based approaches to inform implementation of policies and help mitigate the prescription opioid epidemic in PA, this dissertation uses data from two large-health systems - PA Medicare and Medicaid. These health systems are ideal for studying utilization of prescription opioids. Medicare and Medicaid provide health care for nearly a third of the state's populations, but likely account for a larger share of the state's users of prescription opioids. For example, for every 100 persons in 2012, physicians in PA prescribed 88.9 opioid prescriptions,[4] a rate 8% higher than the national average.[4] In 2012, 1/3rd of Medicare enrollees used opioids for non-cancer pain.[5] Further, PA ranked in the top 10 states on providers who wrote >3,000 prescriptions for Schedule II controlled substances in Medicare Part D in 2012.[6] Past studies have shown that opioid utilization for treating chronic non-cancer pain in Medicaid nationally is twice as high as compared to commercially insured population.[7] From 2007 to 2012, long-term opioid use in the PA Medicaid increased from 13.9% to 16.8%[8] and the prevalence of opioid use disorder (OUD) increased by 56% from 2007 to 2011.[8] These data contain valuable

information on opioid utilization and offer an ideal opportunity to study important policy-relevant questions . This dissertation is composed of three manuscripts. A broad overview of the three chapters is provided in the following paragraphs.

Chapter two (manuscript one) examines the potential for machine-learning approaches to better understand the heterogeneity of opioid use in Medicare Part D. High-risk use of opioid medications in Medicare has been on the rise. The 2016 Comprehensive Addiction and Recovery Act has authorized a "lock-in" program to limit high-risk use of opioid medications by restricting the number of opioid prescribers/pharmacies for some beneficiaries.[9] What constitutes "high-risk use" of prescription opioids among the elderly or disabled Medicare beneficiaries is subject to debate. Further, little is known about the characteristics of those with high-risk use of opioid medications. In this chapter, we advance the science of identifying sub-groups of Medicare beneficiaries with "high-risk" opioid use patterns using novel unsupervised machine-learning techniques. These techniques handle complex interactions among variables of interest. We identify five distinct groups that differ not only on measures of opioid use, but also on demographic and clinical characteristics, and mortality. We also observe that dual and disabled beneficiaries obtain prescriptions from far more prescribers and pharmacies than the non-dual, non-disabled elderly.

Chapter three (manuscript two) examines the associations between physician prescribing specialties and opioid-related outcomes of OUD, misuse, and overdose. Opioids are prescribed for acute and chronic pain by numerous specialties for both short and long-term pain. However, there is little information on the variations in risk of OUD, misuse, and overdose by type of opioid prescribing specialties. Using data from PA Medicaid (2007-2015), we examine the associations between the index and dominant opioid prescribing specialty and OUD, misuse, and overdose. We report differences in rate of adverse events associated with opioid use based on the provider

specialties from whom opioid-naive Medicaid enrollees obtain their first prescription, and a majority of their prescriptions. Our results show that Medicaid enrollees who receive their index opioid prescription or a majority of their prescriptions from specialties that treat chronic pain -pain medicine and physical medicine and rehabilitation- are at higher risk for OUD and misuse than those who receive their index prescriptions or a majority of their prescriptions from primary care. The differences in adverse events may arise from the clinical needs of patients seeking care from certain specialties, from the prescribing behaviors of particular specialties or a combination of both these factors.

Chapter four (manuscript three) examines the associations between adherence to antidepressant medications among individuals with mood disorders and opioid use. Individuals with psychiatric illnesses are not only highly likely to receive opioid medications, but are also at highest risk for adverse consequences of opioid use such as abuse, misuse, and overdose.[10-13] Literature shows that antidepressants have anti-nociceptive effects in mitigating pain among individuals with mood disorders.[14,15] We conduct a longitudinal retrospective study using PA Medicaid data (2007-2015) to examine the associations between adherence to antidepressants and time to the first use of opioid medications. We measure adherence using proportion of days with antidepressant medication during a 180-day period. We observed that enrollees with major depressive disorders and no cancer who achieve ≥ 20% adherence have lower hazards ratios for opioid use compared to those who achieve <20% adherence. The implications of our findings will be discussed in detail in the respective chapters.

2 CHAPTER TWO: USING UNSUPERVISED MACHINE LEARNING TO IDENTIFY HIGH-RISK OPIOID USE IN MEDICARE

ABSTRACT

Background: In an effort to address rising opioid overdose deaths, payers including Medicare are implementing surveillance programs to identify high-risk opioid use. Most algorithms for identifying individuals at risk are based on some combination of information on opioid dose, duration of use, and number of unique opioid prescribers and pharmacies. Unfortunately, these algorithms are often based on arbitrary thresholds and seldom account for potentially complex interactions among these variables. We explored the potential for machine-learning approaches to identify groups of Medicare enrollees based on several measures of opioid use, and examined differences in clinical characteristics and mortality rates.

Methods: We included all fee-for-service beneficiaries enrolled in Medicare Part D in Pennsylvania who initiated new episodes of prescription opioid use (n= 186,799) after excluding beneficiaries with metastatic cancer, long-term care or hospice use. We used the mean, maximum, and range of three variables to examine opioid use: morphine milligram equivalents (MME)/ day, number of unique opioid prescribers, and number of unique pharmacies. We used *k*-means clustering to jointly assess the clustering variables. We compared demographic, enrollment, clinical (e.g. pain diagnoses), and other medication use (e.g. antidepressants) characteristics using chi-square and Kruskal Wallis tests. We also compared hazard ratios for all-cause mortality among groups using cox proportional hazards regression.

Results: Using optimal cluster selection criteria, we identified five groups and reported the mean of the maximum values across all episodes per beneficiary on variables of interest. The largest

group making up 70.9% of the sample (n=132,469) filled opioid prescriptions from a mean maximum of 1.3 [standard deviation (SD)= 0.5] prescribers, from 1.0 (SD= 0.2) pharmacy and had a mean maximum MME/day of 44.7 (SD= 37.6). By contrast, the highest use group was small (n=1,192, 0.6%) and filled opioid prescriptions from a mean maximum of 9.1 (SD= 4.4) prescribers and 6.0 (SD=2.4) pharmacies with 125.1 (SD=113.7) MME/day. Hazard ratios for mortality for beneficiaries in the highest use sub-group had was 1.56, 95% Confidence Interval =1.27, 1.93 relative to the lowest use group.

Conclusion: The cluster categorization observed in this study can support risk stratification for surveillance based interventions such as prescription-drug monitoring and lock-in programs.

KEYWORDS: Opioids, Medicare, Machine-learning, Prescribers, Pharmacies, Morphine Equivalents

2.1 INTRODUCTION

Medicare Part D spending on commonly abused prescription opioids (e.g. oxycodone, hydrocodone-acetaminophen) reached $4.1 billion in 2015 representing an increase of 165% since its inception in 2006.[16] With this widespread use, concerns have been raised about opioid abuse, misuse, and diversion among Medicare beneficiaries. The Centers for Medicare and Medicaid Services (CMS) have taken several steps in addressing the opioid epidemic in Medicare. For example, in 2013 CMS adopted the Overutilization Monitoring System (OMS) requiring plan sponsors to enhance their use of monitoring tools such as quantity limits and drug utilization reviews.[17] The Medicare Advantage Prescription System (MARx) implemented in 2014 enables monitoring of point-of-sale of prescription opioids and allowing plan sponsors to identify aberrant users.[18] The Comprehensive Addiction and Recovery Act-2016 authorizes Medicare to implement a recipient restriction (lock-in) program.[9] Lock-in programs, whereby select enrollees who overuse prescription opioids are restricted to a designated prescriber and/or pharmacy, have been adopted by most state Medicaid programs although the criteria used to determine eligibility vary widely across all states.[19]

There are important challenges to implementation of these surveillance efforts in Medicare. First, there is a lack of consensus on what constitutes overutilization.[19-21] Algorithms to identify overuse or high-risk opioid use often rely on some combination of information on the number of opioid prescribers, number of pharmacies where opioid prescriptions are filled, and/or dose and duration of use. For example, in some cases, a threshold of obtaining opioid prescriptions from ≥5 unique providers is considered as doctor shopping in Medicare.[22] Recently, CMS used a threshold of > 120 morphine milligram equivalents (MME)/day over 90 days and obtaining opioid prescriptions from > 3 prescribers and filling prescriptions at > 3 pharmacies during a 12-month

period to measure potential overuse.[23,24] The criteria to measure MME/day were based on an initiative in Washington State.[23,25] These definitions do not take into account the possible interaction between these variables. For example, an enrollee may fill high-dose prescriptions from one provider or pharmacy but may not qualify for surveillance-based interventions using only the number of prescribers and pharmacy criteria given above. A second challenge for Medicare is that most of the prior studies identifying risk factors for prescription opioid use are based on data from Medicaid and commercially insured populations[26-32], the findings of which may not apply to Medicare which is limited to elderly and disabled enrollees.

In this paper, we attempted to advance the science of identifying high-risk sub-groups of Medicare beneficiaries filling opioid prescriptions by applying machine-learning approaches. We used a technique of unsupervised machine learning which uses partitional clustering algorithms (*k*-means) to group large datasets into meaningful sub-groups. Rather than applying arbitrary thresholds, the *k*-means procedure allowed identification of sub-groups based on the distribution of observations across the clustering variables. Although we used the same variables as used by the above-mentioned surveillance programs, there are two important differences to our approach. First, we used more information (mean, maximum and range) on the variables of interest over six-month episodes per beneficiary rather than applying pre-determined thresholds. Second, the *k*-means clustering technique accounted for potential interactions between these variables. The groups were therefore based on a joint assessment of all clustering variables measuring opioid use. Given the little information available on the extent of heterogeneity of opioid use in Medicare, this procedure provided an ideal opportunity to investigate our study objective.

2.2 METHODS

2.2.1 Data Source

We conducted a longitudinal analysis using 2007-2012 data on all fee-for-service Pennsylvania Medicare enrollees with a Part D plan. Pennsylvania is the 5th largest state in terms of total Medicare beneficiaries[33], with high rates of opioid utilization.[4,11,34] We used enrollment files to obtain beneficiary demographic characteristics (e.g. age, race, sex), reason for eligibility (e.g. disabled vs. aged) and presence of low-income subsidy for the Part D benefit, and enrollment duration. We used the inpatient (MEDPAR), outpatient, carrier claims, and home health files to obtain information on beneficiary diagnosis and procedure codes. The Prescription Drug Event (PDE) file included prescription characteristics such as the National Drug Code (NDC), days' supply, date of fill, and dose. We used the Medispan® database to obtain other information on prescription characteristics such as drug name, strength, and active ingredient by NDC.[35] We used the unique provider identifiers (IDs) from the PDE files to identify unique prescribers and pharmacies for this study. Less than 1% of opioid claims had missing IDs for both prescribers and pharmacies.

2.2.2 Study sample

Our analytic cohort included adult fee-for-service, elderly and disabled Medicare enrollees residing in Pennsylvania, with Part D coverage and included enrollees dually eligible for Medicaid. We did not include Medicare Advantage participants as we did not have complete information on their medical claims needed for constructing covariates. We excluded the following group of

enrollees who are likely to have different opioid use patterns – i) those with any metastatic cancer diagnosis identified using International Classification of Diseases, 9th version, Clinical Modification (ICD-9-CM)[36], ii) those residing in long-term care facilities or those obtaining their opioid prescriptions from long-term care pharmacies (using the primary pharmacy type variable in the PDE file), and iii) those receiving hospice services (using place of service codes).

2.2.3 Cohort design and unit of observation

The unit of analysis was the person-level, however, the unit of observation was opioid use episodes observed during the study period for each beneficiary. An episode began with the first prescription of oral, transdermal, or submucosal opioid medication (index event) and ended if there was a gap of six months or more between two consecutive opioid prescriptions **(Figure A.1)**.[37] The index event was preceded by a baseline observation period, in which we required patients to have continuous six-months of enrollment and no opioid prescription fills. Episodes varied in length and each patient could have multiple episodes. Within each episode, we created measures of opioid utilization described in detail below over six-month episodes **(Figure A.2)**. We then created aggregated measures of opioid use across each beneficiaries' episodes (described below). Most PDMP and lock-in programs identify opioid utilization using specific thresholds for number of opioid prescribers, pharmacies or MME observed over varying time intervals. We used a six-month interval over which we observed specific opioid fill patterns to allow for sufficiently long follow-up time.[23,38]

2.2.4 Unsupervised k-means analysis

Clustering is a classification technique that groups observations in a dataset such that observations within a group are as similar as possible on the clustering variable of interest than observations in other groups. We used an unsupervised clustering technique to identify sub-groups of enrollees using opioids primarily due to CMS' policy at the time that claims with diagnoses of substance use disorders would be redacted.[39,40] This policy prevented us from creating relevant outcome variables necessary for *supervised* machine learning algorithms, such as hospitalizations for overdose.

Several unsupervised clustering methods exists and can be classified as partitional, hierarchical, density-based, and grid-based clustering.[41] We used the partitional clustering technique known as *k*-means due to its ability to handle our large sample size. The *k*-means technique works by: i) choosing *k* random points as initial cluster centers, ii) assigning and re-assigning observations to cluster centers till the distance between each observations in a cluster and the cluster centroid reaches a minimum.[42] The choice of '*k*' clusters depends on the *a priori* relationships. Since we did not have any *a priori* assumptions, we varied '*k*' from two to 10 clusters using the 'clusterR' package in R.[43,44] The optimal number of clusters was chosen using the following indices: Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), and sum of the within-cluster-sum-of-squares-of-all-clusters (WCSSE). We compared the ratio of change for each of these indices across all values of the clusters. Since the values of each of these indices may improve with increasing the number of clusters, we chose the optimal cluster number as the one corresponding to the first highest ratio of change **(Table A.1)**.

2.2.5 Clustering variables

We relied on opioid utilization measures often used by payers to identify patients at risk of overdose or other adverse opioid related outcomes. The key difference was that we did not impose arbitrary cut points for the variables of interest but rather used *k*-means to identify distinct clusters based joint assessment of the measures of interest. First, we identified the number of unique opioid prescribers identified in Medicare PDE files during each six-month episode. Second, we identified the number of unique opioid pharmacies associated with a pharmacy claim during the same six-month episode. Third, we included the standardized MME[45] measure that captured the quantity, strength, and the morphine conversion factor. The MME/day was calculated by dividing the total MME by the duration of days supplied. To capture complete information on opioid use across all six-month episodes and to capture variability within individuals, we used the mean, maximum, and range of the above variables each measured over six-month periods across all episodes per beneficiary. For example, for a beneficiary with two episodes, with values of 50 MME/day and 120 for MME/day, we would choose 120 as the maximum value, 85 as the mean, and 70 (120-50) as the range for clustering purposes. This approach yielded a total of nine opioid use measures for each individual in the sample (mean, maximum, and range for each of the three outcomes: MME, number of prescribers and number of pharmacies).

2.2.6 Characteristics of clusters

After identifying the sub-groups (clusters) we compared their characteristics including: 1) demographic and enrollment, 2) clinical diagnoses, and 3) use of other medications. Demographic variables were measured at baseline and included: age at first episode, gender, race/ethnicity, and

place of residence (urban/rural). Enrollment variables included an indicator for Medicare eligibility due to disability, dual-eligibility for Medicaid and receiving low-income subsidy (LIS). For the clinical diagnoses, we compared the sub-groups for presence of at least one ICD-9-CM claim for the following conditions at any point during the six-year observation period with a focus on mental disorders and pain conditions based on prior studies showing these diagnoses to be associated with opioid use[46]: i) adjustment disorders, ii) anxiety disorders, iii) mood disorders, iv) personality disorders, v) other mental health disorders, vi) back pain, vii) neck pain, viii) arthritis/joint pain, ix) headache/migraine, and x) HIV/AIDS. Also, given the high rates of use of other medications with opioids as reported by prior studies[47], we compared use of the following drug classes: i) antidepressants, ii) anticonvulsants, iii) antipsychotics, iv) muscle relaxants, and v) stimulants. Use of other medications was defined as use of drugs from the aforementioned therapeutic classes during the same six-month episodes as opioid use.

2.2.7 All-cause mortality

Since we did not have overdose or opioid-use disorder related outcomes due to CMS redaction, we compared all-cause mortality among the groups. All-cause mortality was identified using the date of death variable.

2.2.8 Statistical analyses

Since the maximum values of the three clustering variables are most likely to be identified by surveillance activities conducted by prescription drug- monitoring programs, lock-in programs and other monitoring activities, in the results section we report the maximum values for a given

variable for beneficiaries in each cluster. To compare differences in the groups across all clustering variables, we performed Kruskal-Wallis tests. To compare differences in the groups across non-clustering variables, we performed Chi-square tests for categorical variables (e.g. gender, race) and one-way analysis of variance for continuous variables (e.g. age at first episode). To compare all-cause mortality among the groups, we conducted cox proportional hazards regression where we controlled for demographic characteristics - age, gender, race (white/ non-white); enrollment characteristics - dual eligibility for Medicaid, presence of low-income subsidy, presence of disability; and, baseline comorbid conditions including (i) adjustment disorders, ii) anxiety disorders, iii) mood disorders, iv) personality disorders, v) other mental health disorders, vi) back pain, vii) neck pain, viii) arthritis/joint pain, ix) headache/migraine, and x) HIV/AIDS. Finally, we included a modified Elixhauser comorbidity index.[48] We used SAS 9.4. for data management and other statistical analyses.[49] This study was designated as exempt from University of Pittsburgh's Institutional Review Board.

2.3 RESULTS

2.3.1 Characteristics of study sample

There were 895,047 beneficiaries who were enrolled in fee-for-service Medicare and a stand-alone Part D plan in Pennsylvania between 2007 and 2012. After applying the inclusion and exclusion criteria, we had a final sample size of 186,799 beneficiaries with a total of 310,779 episodes **(Figure A.3)**. This cohort was predominantly white (87.8%), female (61.4%) and lived in urban areas (85.0%). The mean age for this cohort was 64.2 years (standard deviation

(SD)=15.7), reflecting the large proportion (37.7%) of under-65 disabled Medicare enrollees in our sample **(Table 2.1)**. Approximately 69% enrollees participated in the Part D low-income subsidy program. Enrollees had a mean of 1.7 (SD=1.0) and a median of 1 episode (minimum=1, maximum= 8).

Table 2.1 Patient-level cohort characteristics 2007 to 2012

Total	**186,799**
Age, Mean (± SD)	64.2 (15.7)
Gender, n (%)	
Female	114,623 (61.4)
Race, n (%)	
White	163,912 (87.8)
Black	16,088 (8.6)
Hispanic	2,407 (1.3)
Other	4,392 (2.3)
Residence, n (%)	
Urban	158,679 (85.0)
Disabled, n (%)	70,420 (37.7)
Dual-eligible, n (%)	100,752 (53.9)
Low-income subsidy, n (%)	127,927 (68.5)
Eligible opioid use episodes	
Mean (SD)	1.7 (1.0)
Median (min-max)	1 (1-8)

SD = standard deviation; min=minimum; max=maximum

2.3.2 Characteristics of clustering variables

We identified five groups based on the cluster selection criteria discussed above **(Table A.1)**. We present the maximum values on the clustering variables in this section. The largest group with the lowest values on all variables of interest (hereafter 'low dose, few providers' group) constituted 70.9% (n=132,469) of all beneficiaries **(Table 2.2)**. The maximum number of opioid prescribers per beneficiary across all episodes in the low dose, few providers group was, on average, 1.3 (SD=0.5) prescribers and the mean maximum number of pharmacies was 1.0 (SD=0.2). The mean maximum MME/day per beneficiary across episodes was 44.7 (SD=37.6).

Beneficiaries in group 2 (hereafter '*moderate dose, moderate pharmacies, few providers*' group; n=36,740; 19.7%) had slightly higher unique prescribers (3.0, SD=0.9), pharmacies (1.7, SD=0.6) and MME/day (62.2, SD=53.1) compared to the *low dose, few providers* group. Similarly, beneficiaries in group 3 (hereafter '*moderate dose, moderate provider*s' group; n=10,503; 5.6%) had slightly higher unique prescribers (4.4, SD=1.6), pharmacies (3.2, SD=0.9) and MME/day (97.3, SD=101.6) compared to the *low dose, few providers* or *moderate dose, moderate pharmacies, few providers* groups. Group 4 (hereafter '*high dose, few provide*rs' group; n=5,895; 3.2%) had the highest mean maximum MME/day of 168 (SD=158.5) compared to the other four groups. However, this group obtained prescriptions from a maximum of 2.0 (SD=0.9) unique prescribers and 1.3 (SD= 0.6) unique pharmacies over a six-month period. Group 5 (hereafter '*high dose, multiple providers*' group) was small (n=1,192; 0.6%), but had a markedly higher number of unique prescribers (9.1, SD=4.4) and pharmacies (6.0, SD=2.4) compared to other groups. The MME/day for the *high dose, multiple providers* was 125.1 (SD= 113.7).

Table 2.2 Characteristics of the groups based on clustering variables

Total beneficiaries N=186,799	**Low dose, few providers n=132,469 (70.9%)**	**Moderate dose, moderate pharmacies, few providers n=36,740 (19.7%)**	**Moderate dose, moderate providers n=10,503 (5.6%)**	**High dose, few providers n=5,895 (3.2%)**	**High dose, multiple providers n=1,192 (0.6%)**	***P***
Maximum values of clustering variables						
Morphine Milligram Equivalents per day, mean (SD)	44.7 (37.6)	62.2 (53.1)	97.3 (101.6)	168 (158.5)	125.1 (113.7)	<0.0001
Number of unique prescribers, mean, (SD)	1.3 (0.5)	3.0 (0.9)	4.4 (1.6)	2.0 (0.9)	9.1 (4.4)	<0.0001
Number of unique pharmacies, mean (SD)	1.0 (0.2)	1.7 (0.6)	3.2 (0.9)	1.3 (0.6)	6.0 (2.4)	<0.0001
Mean of clustering variables						
Morphine Milligram Equivalents per day, mean (SD)	39.1 (32.6)	43.5 (38.9)	63.5 (67.5)	99.8 (116.0)	76.3 (47.9)	<0.0001
Number of unique prescribers, mean (SD)	1.2 (0.4)	1.9 (0.7)	2.4 (0.9)	1.4 (0.4)	4.4 (2.2)	<0.0001
Number of unique pharmacies, mean (SD)	1.0 (0.2)	1.3 (0.4)	1.9 (0.6)	1.1 (0.2)	3.1 (1.2)	<0.0001
Range of clustering variables						
Morphine Milligram Equivalents per day, mean (SD)	10.4 (24.1)	33.9 (40.0)	60.9 (78.2)	120.9 (118.9)	88.4 (92.0)	<0.0001
Number of unique prescribers, mean (SD)	0.2 (0.4)	1.7 (1.0)	3.2 (1.6)	1.0 (0.9)	7.7 (4.3)	<0.0001
Number of unique pharmacies, mean (SD)	0.0 (0.1)	0.6 (0.5)	2.1 (0.9)	0.3 (0.6)	4.7 (2.3)	<0.0001

SD= standard deviation; The values represent the mean of the maximum/mean/range across all six-month episodes. The Kruskal Wallis statistical tests were performed to compare differences in the clustering variables across sub-groups.

2.3.3 Demographic and enrollment characteristics by groups

Compared to the other groups, beneficiaries in the low dose, few providers group had an average age of 66.5 years (SD=15.0) **(Table 2.3)** with the fewest disabled (30.2%) beneficiaries. By contrast, beneficiaries in the *high dose, multiple providers* group were the youngest (42.7, SD=10.8 years) and had the highest proportion of disabled (97.6%) and dual-eligible (90.6%) beneficiaries compared to the other groups. The *high dose, few providers* group that had the highest mean maximum MME/day had a mean age of 63.8 (SD=15.8) years with 38.7% disabled and 49.4% dual-eligible beneficiaries.

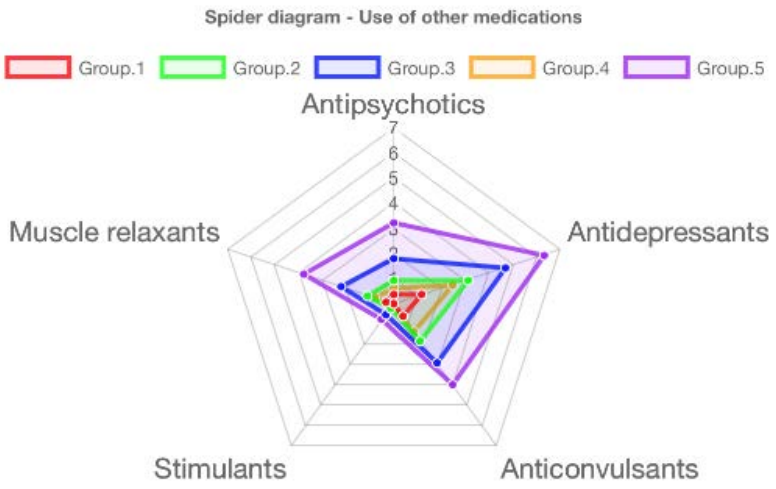
Table 2.3 Demographic and enrollment characteristics of the groups

Total beneficiaries N=186,799	**Low dose, few providers =132,469 (70.9%)**	**Moderate dose/moderate pharmacies/few providers n=36,740 (19.7%)**	**Moderate dose/moderate providers n=10,503 (5.6%)**	**High-dose, few providers n=5,895 (3.2%)**	**High dose, multiple providers n=1,192 (0.6%)**	***P***
Age at first episode, mean (SD)	66.5 (15.0)	60.5 (15.7)	51.0 (14.5)	63.8 (15.8)	42.7 (10.8)	<0.0001
Female, n (%)	80,837 (61.0)	23,099 (62.9)	6,044 (57.6)	4,031 (68.4)	612 (51.3)	<0.0001
White, n (%)	116,873 (88.2)	32,012 (87.1)	8,665 (82.5)	5,407 (91.7)	955 (80.1)	<0.0001
Disabled, n (%)	40,004 (30.2)	18,736 (51.0)	8,241 (78.5)	2,284 (38.7)	1,155 (96.9)	<0.0001
Dual eligible, n (%)	66,576 (50.3)	22,126 (60.2)	8,057 (76.7)	2,912 (49.4)	1,081 (90.6)	<0.0001
LIS, n (%)	87,054 (65.7)	27,083 (73.7)	9,049 (86.2)	3,578 (60.7)	1,163 (97.6)	<0.0001
Urban living area, n (%)	112,998 (85.3)	30,768 (83.8)	9,019 (85.9)	4,823 (81.8)	1,071 (89.9)	<0.0001

LIS=Low-income subsidy, SD= Standard Deviation; One-way analysis of variance was performed to compare differences across groups for continuous variables and chi-square tests for categorical variables.

2.3.4 Use of other medications use by groups

Use of other medications is represented in **Figure 2.1** via a spider-diagram which shows the mean maximum number of prescription fills for all groups based on the following therapeutic classes: 1) antipsychotics, 2) antidepressants, 3) anticonvulsants, 4) muscle relaxants, and 5) stimulants. The two groups with the highest use of both psychiatric medications and muscle relaxants were the *high dose, multiple providers* and *moderate dose, moderate providers* groups. The mean maximum number of fills for the *high dose, multiple providers* group were: 3.2 (SD=4.7) for antipsychotics, 6.3 (SD=5.4) for antidepressants, 4.0 (SD=4.6) for anticonvulsants, and 3.8 (SD=3.8) for muscle-relaxants. The *moderate dose, moderate providers* group has slightly lower use of other medications than the *high dose, multiple providers* group, yet filled comparatively more prescriptions than the remaining three groups as follows: 1.8 (SD=3.9) for antipsychotics, 4.7 (SD=5.0) for antidepressants, 2.9 (SD=3.9) for anticonvulsants, and 2.2 (SD=3.0) for muscle-relaxants. The ranges of other medication use for the remaining groups were as follows: 1) antipsychotics, 0.4 (SD=2.0) to 0.9 (SD=2.8), 2) antidepressants, 1.2 (SD=2.7) to 3.1 (SD=4.2); 3) anticonvulsants, 0.6 (SD=2.0) to 1.8 (SD=3.2), 4) muscle relaxants, 0.3 (SD=0.9) to 1.1 (SD=2.1).



Note: This figure represents the distribution of the mean of the maximum values of prescriptions fills for antipsychotics, antidepressants, anticonvulsants, stimulants, and muscle relaxants across the five groups. There were significant differences in the maximum prescription fills across the five subgroups as observed by Kruskal Wallis tests. Group 1= Low dose, few providers; Group 2= Moderate dose, moderate pharmacies, few providers; Group 3= Moderate dose, moderate providers; Group 4= High dose, few providers; Group 5= High dose, multiple providers

Figure 2.1 Spider diagram representing use of other medications by groups

2.3.5 Presence of comorbid conditions by groups

We found that the *high dose, multiple providers* group had the highest prevalence of mental health conditions as follows **(Table 2.4)**: any mental illness (91.4%), anxiety disorders (76.5%), mood disorders (83.4%), adjustment disorders (17.6%), other mental health disorders (30.5%). Similarly, we also found the highest prevalence of physical health conditions in the *high dose, multiple providers* group as follows: any chronic pain (99.2%), back pain (94.9%), neck pain (73.8 %), arthritis/joint pain (97.1%), and headache/migraine (38.0%). Across the remaining three groups, the prevalence of any mental illness was ranging from 43% to 78.5%, and prevalence of any chronic pain was from 87.7% to 98.1 %.

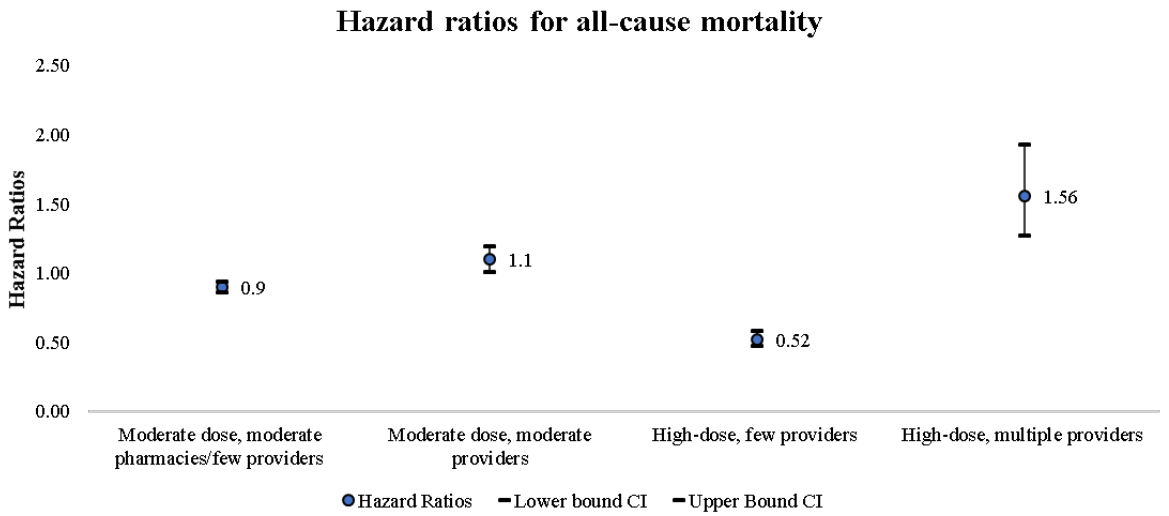
Table 2.4 Comorbid conditions among clusters at any given time during the observation period (2007-2012)

Total beneficiaries N=186,799	Low dose/few providers =132,469 (70.9%)	Moderate dose/moderate pharmacies/few providers n=36,740 (19.7%)	Moderate dose/moderate providers n=10,503 (5.6%)	High-dose, few providers n=5,895 (3.2%)	High dose, multiple providers n=1,192 (0.6%)
Any mental health	43.0	62.8	78.5	58.4	91.4
Adjustment disorders	4.3	7.4	11.7	7.2	17.6
Anxiety disorders	25.9	40.7	56.2	38.5	76.5
Mood disorders	29.2	48.6	66.6	42.8	83.4
Psychotic disorders	6.8	9.4	14.6	7.9	23.9
Other mental health disorders	6.5	11.8	19.0	11.3	30.5
Any chronic pain	87.7	96.2	98.1	97.4	99.2
Back pain	57.0	79.1	88.3	79.9	94.9
Neck pain	28.9	45.1	59.4	47.2	73.8
Arthritis/joint pain	81.1	91.1	93.4	93.4	97.1
Headache/migraine pain	6.9	14.0	24.1	13.2	38.0
HIV/AIDS	0.8	1.4	2.7	0.8	3.7

Note: The numbers represent column percentages or prevalence of conditions within each group as measured by the presence of at least one ICD9 diagnosis claim (inpatient, outpatient, or professional) at any time during the observation period (2007-2012); Chi-square tests were performed to compare differences in prevalence of comorbid conditions across all five groups; Any pain refers to the presence of either back, neck pain, arthritis/joint pain, or headache/migraine during the observation period; *All differences were significant at the p=0.001 level*

2.3.6 Hazard ratios for of all-cause mortality

Finally, we investigated the hazard ratios of all-cause mortality associated with specific groups. The *low dose, few providers* group was used as the reference group since this group had the least utilization with respect to the clustering variables. We observed that beneficiaries who had the highest values on the number of prescribers and pharmacies had the highest hazard ratios for all-cause mortality relative to beneficiaries in the *low dose, few providers* group. Beneficiaries in the *high dose, multiple providers* had 1.56 [95% CI=1.27, 1.93] times higher hazards of all-cause mortality compared to beneficiaries in the *low dose, few providers* group **(Figure 2.2)**. Beneficiaries in the *moderate dose, moderate providers* had 1.10 [95% CI=1.01, 1.19] times higher odds of all-cause mortality compared to beneficiaries the *low dose, few providers* group.



Adjusted for gender, age, disability status, dual eligibility, low-income subsidy, median duration of opioid use episodes, baseline disorders including (adjustment disorders, anxiety disorders, personality disorders, other mental health disorders, back pain, neck pain, headache/migraine, and arthritis/join pain), and baseline Elixhauser index. All hazards ratios were significant at the 0.001 level. CI= Confidence Intervals. The lower and upper bound refer to the 95% Wald Confidence Limits

Figure 2.2 Hazard ratios for all-cause mortality associated with each group

2.4 DISCUSSION

Using techniques of cluster analysis, we examined opioid use patterns across six-month periods per beneficiary. Our study found markedly heterogeneous opioid use among Pennsylvania Medicare beneficiaries and had three key findings. First, the cluster analysis found five distinct groups based on the number of prescribers, pharmacies, and MME/day. There were large magnitude of differences in opioid use measures across the five sub-groups. Since the groups were based on a joint assessment of all clustering variables, the clustering technique improves on existing approaches and yielded groups that may not have been identified using other approaches. For example, beneficiaries in the *high dose, multiple providers* group had the highest values on number of prescribers and pharmacies but not on MME/day. Second, the groups with the highest values on opioid use measures also significantly differed in use of antipsychotics, antidepressants, anticonvulsants, and muscle-relaxants and the prevalence of mental illnesses and pain diagnoses. And, third, the group with the highest values on number of prescribers and pharmacies (*high dose, multiple providers* and *moderate dose, moderate providers*) had the highest hazard ratios for all-cause mortality compared to the groups with the least values on the three clustering variables of interest.

Rather than using pre-specified thresholds, the *k*-means technique used in this study offered the benefits of identifying potentially high-risk enrollees who use opioids by accounting for potential interactions between important variables measuring opioid use. Due to the CMS-initiated redaction of substance-abuse claims[39,40], we could not measure adverse outcomes of opioid use - overdose and opioid-use disorder. Therefore, we could not investigate how risk of overdose or opioid-use disorder varies with changes in opioid utilization patterns. Prescription drug monitoring programs and lock-in programs typically have access mainly to prescription data on controlled

substances. The lock-in programs run by several state Medicaid programs often rely on a retrospective review of prescriber, pharmacy, and other opioid prescription characteristics to identify beneficiaries eligible for surveillance-based interventions (e.g. restriction opioid prescriptions to one-provider).[19] In a way, these techniques often rely on "unsupervised" approaches like that used this study to identify patients at risk. The technique used in this paper improves on existing approaches by shedding light on the interactions between important variables used by surveillance programs to measure opioid overuse or abuse when other data such as clinical diagnoses are not available.

Many studies have previously examined characteristics of opioid use such as MME/day and doctor/pharmacy shopping among young or middle-aged adults.[27-30,50] In this study, we examined characteristics of opioid use in a disabled or elderly Medicare population. CMS has recently employed a threshold of >120 MME/day over 90 days and/or obtaining opioid prescriptions from > 3 prescribers and filling prescriptions at > 3 pharmacies during the same period as indicators of over utilization.[23] Although we measure MME over the entire six-month episode and not 90 days, beneficiaries in the *high dose, multiple providers* group (0.6% of the sample) would meet those criteria.

Our findings reflect that Medicare beneficiaries who could potentially be classified under the *high dose, multiple providers* category appear to have complex health needs. In our study, beneficiaries who obtained prescriptions from multiple providers (*high dose, multiple providers* and *moderate dose, moderate providers* groups) had higher proportion (over 75%) of disabled and dual-eligible (low-income) beneficiaries compared to the other groups. We also observed higher prevalence of back pain, neck pain, mood disorders and high use of other medications in these groups. For example, beneficiaries in the *high dose, multiple providers* group had on an average,

a maximum of six prescriptions of antidepressants, four prescriptions of muscle-relaxants and four prescriptions anticonvulsants during the six months of opioid use. We cannot ascertain whether these beneficiaries were intentionally seeking opioid prescriptions from multiple doctors and pharmacies or simply seeking treatment for complex health needs from multiple providers with unintended consequences for opioid prescribing. Therefore, before implementing policies to reduce overutilization of prescription opioids, our findings highlight that it is important to recognize that those with potentially high-risk opioid use may have complex healthcare needs. The heterogeneity we observed in our study implies that policies having a "one-size fits all" approach may not help reduce opioid overuse. Instead of using definitive thresholds, existing surveillance efforts can be improved by first ascertaining the health needs of the population.

Currently, upon identifying overutilization, Part D plan sponsors can conduct prescriber/pharmacy and/or patient-specific education and outreach interventions.[51] If these efforts are not successful, recent legislation allows restriction of opioid use among these beneficiaries.[9] However, little is known about the impact of such restrictions on pain treatment for Medicare beneficiaries with complex medical and behavioral health needs. Managing the health needs of this population may require delivery system reforms that allow integration of behavioral health and treatment of substance use disorders with physical health care models such that continuity of care is available for these patients. The Screening, Brief Intervention and Referral to Treatment (SBIRT)[52,53] model or the Collaborative Opioid Prescribing model[54] are examples of integrated service delivery systems that may be useful in this context. Our results can be utilized by current legislation for designing restriction programs in Medicare.[9] Restriction programs have been in existence since the late 1970s[55], and have shown to be successful in reducing opioid abuse and overdose.[56] However, these programs have largely been implemented in Medicaid. Given that

Medicaid beneficiaries are more likely to be at risk for adverse outcomes of opioid over utilization such as overdose than other populations[57], the eligibility criteria used by Medicaid to enroll patients in restriction programs may not apply to Medicare. Although this study does not identify the right thresholds for doctor/pharmacy shopping or MME/day, the results provide some direction into the average values on these measures in the Pennsylvania fee-for-service Medicare population.

Our study has some potential limitations. First, our data cannot identify prescriptions not paid for by Medicare. For example, cash payments for prescriptions (e.g. Medicare coverage gap) cannot be captured. Second, prescriptions filled by an enrollee are not necessarily consumed by that enrollee. However, both these issues are observed in most health care claims since they do not capture variables such as blood tests or urine drug screens information that can help validate medication consumption. In the absence of substance-abuse claims, we examined differences in all-cause mortality among the sub-groups. An important limitation was that cause of death was not available. We used the date of death to identify all-cause mortality. Finally, limiting our analyses to only Pennsylvania Medicare claims reduces the external validity of our findings. Despite these limitations, our study utilized a six-year longitudinal cohort to answer essential and timely policy-relevant questions.

2.5 CONCLUSIONS

The clustering technique used in this study identified five distinct groups that differed not only on measures of opioid use, but also differed on demographic, clinical, and other medication use characteristics. More importantly we observed that dual and disabled beneficiaries obtained prescriptions from far more prescribers and pharmacies than the non-dual, non-disabled elderly.

The opioid utilization of pattern of disabled and dual-eligible enrollees could possibly be an outcome of their health status. Health systems and state-level policies may need to ascertain the health needs of these beneficiaries before implementing recipient restriction policies.

3 CHAPTER THREE: ASSOCIATIONS BETWEEN THE SPECIALTY OF OPIOID PRESCRIBERS AND OPIOID ADDICTION, MISUSE AND OVERDOSE OUTCOMES

ABSTRACT

BACKGROUND: Opioids are prescribed for acute and chronic pain by numerous specialties. We sought to examine the associations between prescriber specialty and the likelihood of opioid use disorder, misuse, and opioid overdose among Medicaid enrollees initiating opioid treatment. Our findings have implications for where to target efforts to educate both prescribers and patients about the safety of opioid use.

METHODS: We conducted a longitudinal retrospective study using Pennsylvania Medicaid data (2007-2015). We constructed an incident cohort of 434,612 enrollees initiating new episodes of opioid treatment without history of opioid addiction or overdose at baseline. We attributed patients to one of ten prescriber specialties using the first opioid prescriber's specialty, and alternatively, the dominant prescriber writing a majority of the patient's opioid prescriptions. We estimated adjusted rate ratios (ARR) for three opioid-related risks (OUD, misuse, and overdose) adjusting for demographic and clinical characteristics.

RESULTS: Patients who were first prescribed opioids by pain medicine/anesthesiology had higher ARR for OUD (1.53, 95% confidence interval (CI) =1.25, 1.88), misuse (1.62, 95% CI= 1.36, 1.92), and overdose (2.12, 95% CI= 1.08, 4.14) compared to patients initiating opioid episodes with primary care practitioners (PCPs). Patients first prescribed opioids by physical medicine and rehabilitation specialists were also more likely to develop OUD (1.33, 95% CI=1.13,

1.57), misuse (1.61, 95% CI= 1.41, 1.84), and overdose (1.84, 95% CI= 1.07, 3.19) compared to patients initiating opioids with PCPs. Findings were largely similar when patients were attributed to specialty based on the dominant opioid prescriber specialty.

CONCLUSION: We reported differences in adverse events associated with opioid use based on the provider specialties from whom opioid-naive Medicaid enrollees obtain their first prescription, and a majority of their prescriptions. These differences may arise from the clinical needs of patients seeking care from certain specialties or from the prescribing behaviors of particular specialties or both. These findings suggest that interventions directed towards patients and providers may benefit from targeting certain settings.

KEYWORDS: Opioids, Prescriber Specialty, Medicaid, Overdose, Misuse, Opioid-Use Disorder

3.1 INTRODUCTION

There are concerted efforts at the federal, state, and local level to mitigate the effects of opioid misuse and abuse and its adverse consequences including opioid overdose and death in the US. Opioid prescribing has been a particular focus of intervention and policy efforts. Several federal organizations and national associations for chronic pain have promulgated guidelines for initiating opioids and assessing risks/benefits for patients on long-term opioid therapy, typically used for chronic pain.[58-61] States and health systems are implementing a myriad policies to address the opioid overdose epidemic, many of which have focused on influencing prescribing behavior through restrictions (e.g. limiting the days' supply for initial opioid prescriptions) and prescription drug monitoring programs.[62-65]

One of the challenges in improving the quality of opioid use is that opioids are prescribed in many settings (e.g. inpatient, outpatient, and post-acute), by many different specialties for both short and long-term pain treatment, and for many types of pain (e.g. back pain or arthritis/joint pain). Interventions to improve the quality of opioid prescribing may benefit from targeting these interventions to prescribers most likely to treat high-risk patients; however, the evidence-base for such targeting is limited. Recent evidence shows that certain characteristics of the initial opioid prescriptions (e.g. number of days' supply) can determine the future course of opioid-related events including long-term dependency on opioids.[66-70] Relatively little is known about the relationship between the specialty of the prescriber initiating opioid treatment and adverse opioid events. A recent study showed that a greater number prescriptions from primary care providers were associated with highest number of opioid overdose deaths compared to other specialists.[71] It is not known whether the specialty of the opioid prescriber is correlated with non-mortality outcomes such as opioid use disorder (OUD) or misuse.

To inform the targeting of interventions to improve opioid prescribing and reduce the risks associated with opioid use, we examine the association between opioid prescriber specialty and opioid-related adverse outcomes among patients initiating a new episode of opioid treatment. To improve our understanding of the association between prescriber specialty and patient outcomes over the course of an episode of opioid treatment, we apply two methods for attributing patients to prescribers (and ultimately their specialty group). First, we identify the specialty of the prescriber responsible for the first opioid prescription. Second, we identify the specialty of the dominant prescriber responsible for the majority of opioid prescriptions for a particular patient. Our study setting is a large Medicaid program as Medicaid enrollees have a high risk of opioid overdose.[57,72]

3.2 METHODS

3.2.1 Description of data

We conducted longitudinal analyses using Pennsylvania (PA) Medicaid data (January 2007 through December 2015), which included data on all enrollees including fee-for-service and managed care enrollees. We obtained the data directly from the Department of Human Services (DHS). PA is one of largest Medicaid programs by expenditures and monthly enrollment.[73,74] The demographics (except lower Hispanic population) and healthcare utilization trends in PA Medicaid are similar to those seen in other state Medicaid programs.[75,76]

We used enrollment files to obtain beneficiary demographic characteristics (e.g. age, race, sex), reason for eligibility (e.g. disabled/chronically ill, children and families), enrollment duration, and insurance type (fee-for-service vs. managed care programs). We used the medical

claims (inpatient, outpatient, and professional) to obtain information on beneficiary diagnosis and procedure codes. The pharmacy claims included prescription characteristics such as the National Drug Code (NDC) from which we obtained type of opioid [short-acting opioid (SAO)/ long-acting opioid (LAO)], days' supply, date of fill, and dose. We used the Medispan® data to obtain additional information on prescription characteristics (e.g. drug name, strength, and active ingredient by NDC).[35] We used the unique provider identifiers (IDs) from the pharmacy files to identify provider specialties for this study.

3.2.2 Study sample and cohort design

Our analytic sample included enrollees aged ≥18 to ≤64 years, having at least one prescription for an opioid medication. Our analyses were limited to individuals not dually eligible for Medicare or those over 65 years of age since data on their prescription utilization cannot be observed in Medicaid. Furthermore, given likely differential opioid use patterns, we excluded enrollees with any cancer diagnosis, those residing in long-term care for ≥ 90 days, or enrollees using hospice services.

We created an incident cohort of enrollees initiating opioid treatment episodes. The cohort selection is shown in the appendix **(Figure B.1)**. An episode of opioid treatment started with the first opioid prescription (index event) and ended if there was a gap of ≥ 6 months between two consecutive opioid prescriptions.[37] For patients with multiple opioid treatment episodes, we limited our primary analyses to the first observed episode. The index event was preceded by a 6-month baseline period during which patients must have had: (1) six-months of continuous enrollment defined as enrollment of at least 15 days for six consecutive months, (2) no opioid

prescription fill, (3) no diagnosis of OUD or claim for prescription opioid or heroin overdose, and (4) no medication-assisted therapies for treating OUD.

3.2.3 Outcome variables

There were three primary outcomes of interest: OUD, opioid misuse, and opioid overdose. First, we constructed a dichotomous measure of diagnosis of OUD identified using diagnosis codes in medical claims (**Table B.1**) as defined by International Classification of Diseases, Ninth Revision (ICD-9) and the International Classification of Diseases, Tenth Revision (ICD-10) implemented near the end of our study period. Second, we used pharmacy claims to construct a measure of misuse based on a previously validated measure.[38] Misuse is calculated by assigning a score to the following utilization measures: i) number of unique opioid prescribers (≤2 prescribers=0, 3-4 prescribers=1, ≥5 prescribers=2), ii) number of unique pharmacies (≤2 pharmacies=0, 3-4 pharmacies=1, ≥5 pharmacies=2), iii) days supplied of opioids of SAO (≤185 days=0, 186-240 days=1, >240 days=2), and iv) days supplied for LAO (≤185 days=0, 186-240 days=1, >240 days=2) during two consecutive 180-day periods. We used a dichotomized measure of misuse defined as a score ≥ 2. For lengthy opioid episodes with multiple two-180 day periods, the maximum misuse score was used. The third outcome was an overdose (due to prescription opioids) event that resulted in an emergency department (ED) visit or hospitalization identified using ICD-9/ICD-10 opioid poisoning codes observed in professional, outpatient or inpatient claims files.

3.2.4 Main explanatory variable

The main explanatory variable -opioid prescriber specialty-required linking prescribing provider identifiers to information on specialty, and assigning patient-episodes to specialty groups using two approaches to attribution. First, we obtained the prescribing provider ID from the pharmacy claims which represent filled prescriptions, and the type of specialty from the provider file provided by the PA-DHS. Pharmacy claims were missing information on prescribing provider ID approximately 25% of the time. Our statistical approaches to handle this missing information is discussed below.

After linking prescribing provider identifiers to the Medicaid provider file, we constructed 10 categories of provider specialties based on highest frequency among opioid prescribers: Dentistry; Emergency Medicine (EM); Obstetrics/Gynecology (OB/GYN); Pain Medicine/Anesthesiology; Primary Care Practitioners (PCPs) which included Family/General Practice and Internal Medicine; Physical Medicine and Rehabilitation (PM&R); Podiatry; Psychiatry; Surgery; and other specialties. We could not differentiate pain medicine specialists from anesthesiologists since they were coded as one specialty in the provider file provided by PA-DHS. The 'other' category included physician specialties that could not be classified in the above-mentioned categories as well as a small number of advanced practice providers (e.g. nurse practitioners) who accounted for less than 1% of opioid prescriptions.

We implemented two approaches to attribute patients to one of the 10 specialty groups. First, we attributed patients to a specialty based on the specialty of their first opioid prescriber (i.e., the provider responsible for writing the first opioid prescription filled). Our second alternative was to attribute patients to a specialty based on the specialty of the dominant prescriber in the first episode. For this, we counted the number of opioid fills per specialty group (aggregating if

necessary in the case of multiple unique prescribers of the same specialty). The specialty that prescribed the majority of opioid prescriptions in the episode was considered the dominant prescribing specialty. In some cases, there were equal number of prescription claims from two or more specialties. For this purpose, we created two additional dummy variables. One of the variables represented episodes that had ties between the number of prescriptions from PCPs and another non-PCP specialties (1=tie, 0= no tie), and another variable represented episodes that had ties between non-PCP prescriber specialties.

3.2.5 Covariates

We included patient-level socio-demographic characteristics such as age, gender, race (White or other), eligibility category (disabled/chronically ill, Medicaid expansion, families with children), insurance type (fee-for-service/managed care), and the following characteristics (yes/no) measured during the 6-month baseline prior to the index opioid fill: comorbid conditions including non-opioid substance use disorders (alcohol abuse/dependence, other drug abuse/dependence), mental health conditions (mood, anxiety, other mental health conditions), chronic pain conditions (back pain, neck pain, headache/migraine, and arthritis/join pain) [77], and baseline use of other benzodiazepine and muscle relaxants, and ED visits. Buprenorphine use in the episode was also included as a covariate. Finally, we included a Elixhauser comorbidity index which was modified based on the above conditions being removed.[48]

3.2.6 Statistical approach

We conducted multivariable regression analyses using generalized linear models. To account for the varying length of episodes, we used the log link function and Poisson distribution where the offset variable was the natural log of the days of observation. We conducted two separate analyses using the alternate approaches to attributing patients to specialties (i.e., first vs. dominant prescriber). We compared adjusted rate ratios of the specialty groups to PCPs, the reference category.

We observed that approximately 28% of the enrollees had missing provider IDs for the first prescription while 21% of the enrollees had missing provider IDs for majority of their prescriptions**.** We used two approaches handle missing data. First, we conducted a complete case analysis by excluding the prescription fills within episode with missing provider IDs. Second, we imputed the provider IDs using Multiple Imputation Chained Equations (MICE) and compared the results. The prescriber specialties were imputed based on all the covariates described above. Since the results from the complete-case and MICE analyses were largely similar, we present the complete-case analyses in the main paper while the results from the imputations are provided in the appendix (Appendix B). All analyses were conducted with SAS 9.4.[49] This study was designated as exempt from University of Pittsburgh's Institutional Review Board.

3.3 RESULTS

3.3.1 Descriptive analyses

The patient-level demographic characteristics are provided in **Table 3.1.** From 2007-2015, there were a total of 434,612 Medicaid enrollees initiating opioid treatment who met the inclusion/exclusion criteria. The average age was 30.7 [standard deviation (SD) =11.1] years. Enrollees were predominantly female (67.4%), white (58.1%), and/or living in urban locations (85.2%). A majority were enrolled in managed care organizations (93.7%) as opposed to fee-for-service. The average duration of the first episode was 72.0 (SD=218.6) days with a median of 1 day (minimum=1, maximum=3097 days). The overall prevalence of OUD, misuse and overdose in our study sample was 5%, 3.5%, and 0.2%, respectively. We observed that PCPs were the first opioid prescribers for 17.9% of patients, dentists were the first opioid prescribers for 20.7% of patients, while EM physicians were the first opioid prescribers for 15.7% of patients **(Table 3.2)**. Pain medicine/anesthesiologists and PM&R specialists were the first opioid prescribers for 0.3% and 0.4% patients respectively. PCPs (19.1%), Dentists (21.5%), EM physicians (13.6%) were the dominant prescribers for majority of the patient episodes in our study sample.

Table 3.1 Patient-level cohort characteristics 2007-2015 (N=434,612)

Characteristics	n (%)
Age in years, Mean (SD)	30.7 (11.1)
Female	292,751 (67.4)
Race	
White	252,613 (58.1)
Black	124,354 (28.6)
Other	57,645 (13.2)
Urban living area	370,426 (85.2)
Type of eligibility at first episode	
Disabled/Chronically Ill	98,532 (22.7)
Families with Children	288,220 (66.4)
Expansion	26,678 (6.1)
Other	21,451 (4.8)
Type of health plan	

Table 3.1 Continued	
Managed care	407,152 (93.7)
Fee-for-service	27,460 (6.3)
Prevalence of outcomes	
OUD	21,700 (5.0)
Misuse	15,386 (3.5)
Overdose	981 (0.2)
Duration of episode (days)	
Mean (SD)	72.0 (218.6)
Median (Minimum-Maximum)	1 (1-3079)
Duration of follow-up (days)	
Mean (SD)	1030 (782.7)
Median (Minimum-Maximum)	801 (1-3106)

OUD= Opioid use disorder, SD=standard deviation

Table 3.2 Distribution of patient episodes across prescriber specialties under each attribution rule

	Index Prescribers		***Dominant Prescribers***	
	N	%	N	%
Dentistry	90,156	20.7	93,513	21.5
Emergency Medicine	68,166	15.7	59,118	13.6
Obstetrics/Gynecology	39,212	9.0	35,712	8.2
Pain Medicine/Anesthesiology	1,068	0.3	1,491	0.3
Physical Medicine and Rehabilitation	1,707	0.4	2,247	0.5
Podiatry	2,313	0.5	2,970	0.7
Primary Care	77,564	17.9	82,998	19.1
Psychiatry	1,062	0.2	1,032	0.2
Surgery	19,206	4.4	22,226	5.1
Other	14,334	3.3	13,990	3.2
Combination of other specialties [a]	N/A		13,298	3.1
Combination of primary care and other specialty [b]	N/A		14,790	3.4
Missing	119,824	27.6	91,227	21.0
Total	434,612	100.00	434,612	100.00

[a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b] Refers to episodes where prescription claims from primary care and other non- primary care specialty are equal

3.3.2 Associations between OUD and prescriber specialty

The first set of analyses focused on the relationship between the index prescribing specialty in the episode and OUD. As seen in **Table 3.3**, for patients whose first opioid prescribers were from pain medicine/anesthesiology, the adjusted rate ratio (ARR) for OUD were 1.53, [95% confidence interval (CI)=1.25 1.88] compared to those patients whose first prescribers were PCPs. Similarly, for patients whose first prescribers were PM&R specialists, the ARR for OUD were

1.33 (95% CI=1.13, 1.57) compared to those patients whose first prescribers were PCPs. However, patients initiating opioid treatment with specialties more likely to treat acute pain had lower risk for OUD than patients initiating treatment with PCPs. The ARRs for OUD were 0.86 (95% CI=0.82, 0.90) for dentistry, 0.63 (95% CI=0.59, 0.68) for OB/GYN, 0.75 (95% CI=0.60, 0.94) for podiatry, and 0.74 (95% CI=0.69, 0.80) for surgery. The ARR for OUD for patients whose first prescribers were EM (1.02, 95% CI= 0.97, 1.07) or psychiatrists (1.08, 95% CI=0.90, 1.30) were not significantly different than for PCPs.

Table 3.3 Adjusted rate ratios for associations between prescribing specialty and opioid use disorder

	Index prescriber		***Dominant prescriber***	
Parameters	***ARR***	***P***	***ARR***	***P***
Dentistry	0.86 [0.82, 0.90]	<.0001	0.83 [0.80, 0.87]	<.0001
Emergency Medicine	1.02 [0.97, 1.07]	0.48	1.00 [0.96, 1.05]	0.91
Obstetrics/Gynecology	0.63 [0.59, 0.68]	<.0001	0.55 [0.51, 0.59]	<.0001
Pain medicine/Anesthesiology	1.53 [1.25, 1.88]	<.0001	1.31 [1.13, 1.52]	0.0004
Physical Medicine and Rehabilitation	1.33 [1.13, 1.57]	0.0006	1.20 [1.06, 1.36]	0.0031
Podiatry	0.75 [0.60, 0.94]	0.01	0.81 [0.68, 0.97]	0.02
Psychiatry	1.08 [0.90, 1.30]	0.41	1.16 [0.98, 1.38]	0.09
Surgery	0.74 [0.69, 0.80]	<.0001	0.76 [0.71, 0.81]	<.0001
Other	0.86 [0.79, 0.94]	0.0005	0.89 [0.82, 0.96]	0.0026
Combination of other specialties[a]	N/A		0.84 [0.77, 0.91]	<.0001
Combination of primary care and other specialty[b]	N/A		1.01 [0.94, 1.08]	0.77
Primary Care	Reference		Reference	

Poisson distribution with log link function is used; Model is offset using the natural log of the days of follow-up to account for varying length of exposure to opioid treatment; ARR= Adjusted Rate Ratios; [a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b]Refers to episodes where prescription claims from primary care and other non- primary care specialty are equal; Model is adjusted for demographic characteristics (age in years, race, urban/rural living area), enrollment characteristics (eligibility category, managed care/fee-for-service), baseline comorbid conditions (alcohol abuse/dependence, non-opioid drug abuse/dependence, adjustment disorders, mood disorders, anxiety disorders, back pain, neck pain, arthritis/join pain, headache/migraine, HIV/AIDS), and baseline use of benzodiazepines, muscle relaxants, and visits to emergency departments; Adjusted rates for all covariates included in this model are shown in Appendix B

The second set of analyses focused on the relationship between the dominant prescribing specialty in the episode and OUD. These results were similar to the associations observed between index opioid prescribing specialty and OUD. As seen in **Table 3.3**, when the dominant prescribing specialty was pain medicine/anesthesiology the ARR for OUD was 1.31 (95% CI = 1.13, 1.52) relative to PCPs. Patients whose dominant opioid prescribers were PM&R specialists also had

higher ARR for OUD (1.20, 95 % CI = 1.06, 1.36) compared to those patients who obtained majority of their opioid prescriptions from PCPs. The ARR for OUD were significantly lower when patients obtained majority of their prescriptions from dentistry, OB/GYN, podiatry, and surgery compared to those patients who obtained majority of their opioid prescriptions from PCPs. The ARR for OUD for psychiatry was 1.16 (95 % CI= 0.98, 1.38), but the relationship was not significant at the p=0.05 level. Similarly, in case of ties, when patients obtained the same number of prescriptions from PCPs and other specialties, the ARR for OUD was 1.01 (95% CI=0.94, 1.08), but the relationship was not significant.

3.3.3 Associations between misuse and prescriber specialty

Patients whose first opioid prescriptions were written by pain medicine/anesthesiology had an ARR of 1.62 (95% CI=1.36, 1.92) for misuse relative to PCPs, while those by PM&R had an ARR of 1.61 (95% CI=1.41, 1.84) relative to index prescriptions by PCPs **(Table 3.4)**. For index prescriptions from other specialties (EM, Dentistry, OB/GYN, Surgery, and Others), the ARR for misuse were significantly lower relative to index prescriptions from PCPs. The direction and magnitude of these associations between specialty and misuse were largely similar when patients were attributed to specialty groups on the basis of the dominant specialty, prescribing the majority of opioids in the episode.

Table 3.4 Adjusted rate ratios for associations between prescribing specialty and misuse

	Index prescriber		*Dominant prescriber*	
Parameters	***ARR***	***P***	***ARR***	***P***
Dentistry	0.39 [0.36, 0.41]	<.0001	0.26 [0.25, 0.28]	<.0001
Emergency Medicine	0.78 [0.74, 0.82]	<.0001	0.41 [0.39, 0.43]	<.0001
Obstetrics/Gynecology	0.46 [0.42, 0.50]	<.0001	0.15 [0.13, 0.17]	<.0001
Pain Medicine/Anesthesiology	1.62 [1.36, 1.92]	<.0001	1.86 [1.68, 2.07]	<.0001
Physical Medicine and Rehabilitation	1.61 [1.41, 1.84]	<.0001	1.66 [1.51, 1.81]	<.0001
Podiatry	0.76 [0.62, 0.93]	0.01	0.97 [0.85, 1.11]	0.69
Psychiatry	1.00 [0.81, 1.24]	0.99	0.76 [0.61, 0.94]	0.01
Surgery	0.66 [0.61, 0.71]	<.0001	0.67 [0.63, 0.71]	<.0001
Other	0.79 [0.72, 0.86]	<.0001	0.62 [0.57, 0.67]	<.0001
Combination of other specialties [a]	N/A		0.43 [0.39, 0.48]	<.0001
Combination of primary care and other specialty[b]	N/A		0.78 [0.73, 0.83]	<.0001
Primary Care	Reference		Reference	

Poisson distribution with log link function is used; Model is offset using the natural log of the days of follow-up to account for varying length of exposure to opioid treatment; ARR= Adjusted Rate Ratios; [a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b] Refers to episodes where prescription claims from primary care and other non- primary care specialty are equal; Model is adjusted for demographic characteristics (age in years, race, urban/rural living area), enrollment characteristics (eligibility category, managed care/fee-for-service), baseline comorbid conditions (alcohol abuse/dependence, non-opioid drug abuse/dependence, adjustment disorders, mood disorders, anxiety disorders, back pain, neck pain, arthritis/join pain, headache/migraine, HIV/AIDS), use of burprenorphine, baseline use of benzodiazepines, muscle relaxants, and visits to emergency departments; Adjusted rates for all covariates included in this model are shown in appendix B

3.3.4 Associations between overdose and prescriber specialty

Similar to OUD and misuse, the ARR for overdose for patients whose first opioid prescriptions were from pain medicine/anesthesiology (2.12, 95% CI=1.08, 4.14) and PM&R (1.84, 95% CI=1.07, 3.19) were significantly higher relative to PCPs **(Table 3.5)**. The ARR for overdose when index prescriptions were obtained from dentistry (0.66, 95% CI= 0.53, 0.82), EM (0.74 95% CI=0.59, 0.91) and OB/GYN (0.37, 95% CI=0.25, 0.55) were significantly lower relative to PCPs. However, these results were sensitive to our attribution method; when the dominant specialty was used instead of the index specialty there were no significant differences between PCPs and either pain medicine/anesthesiology (1.04, 95% CI=0.57, 1.90) or PM&R (1.31, 95% CI=0.84, 2.05) in the risk of overdose (**Table 3.5)**.

Table 3.5 Adjusted rate ratios for associations between prescribing specialty and prescription opioid overdose

	Index prescriber		*Dominant prescriber*	
Parameters	***ARR***	***P***	***ARR***	***P***
Dentistry	0.66 [0.53, 0.82]	0.0002	0.59 [0.48, 0.73]	<.0001
Emergency Medicine	0.74 [0.59, 0.91]	0.0049	0.62 [0.50, 0.77]	<.0001
Obstetrics/Gynecology	0.37 [0.25, 0.55]	<.0001	0.31 [0.20, 0.47]	<.0001
Pain medicine/Anesthesiology	2.12 [1.08, 4.14]	0.03	1.04 [0.57, 1.90]	0.90
Physical Medicine and Rehabilitation	1.84 [1.07, 3.19]	0.03	1.31 [0.84, 2.05]	0.23
Podiatry	0.94 [0.38, 2.29]	0.89	0.63 [0.28, 1.42]	0.26
Psychiatry	1.48 [0.76, 2.89]	0.25	1.19 [0.59, 2.40]	0.63
Surgery	0.64 [0.45, 0.90]	0.01	0.59 [0.44, 0.80]	0.001
Other	1.16 [0.84, 1.61]	0.36	0.85 [0.61, 1.19]	0.35
Combination of other specialties[a]	N/A		0.70 [0.48, 1.02]	0.06
Combination of primary care and other specialty[b]	N/A		0.93 [0.69, 1.25]	0.64
Primary Care	Reference		Reference	

Poisson distribution with log link function is used; Model is offset using the natural log of the days of follow-up to account for varying length of exposure to opioid treatment; ARR= Adjusted Rate Ratios; [a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b]Refers to episodes where prescription claims from primary care and other non-primary care specialty are equal; Model is adjusted for demographic characteristics (age in years, race, urban/rural living area), enrollment characteristics (eligibility category, managed care/fee-for-service) , baseline comorbid conditions (alcohol abuse/dependence, non-opioid drug abuse/dependence, adjustment disorders, mood disorders, anxiety disorders, back pain, neck pain, arthritis/join pain, headache/migraine, HIV/AIDS), use of burprenorphine, and baseline use of benzodiazepines, muscle relaxants, and visits to emergency departments; Adjusted rates for all covariates include in this model are shown in the appendix

3.4 DISCUSSION

We examined the association between opioid prescriber specialty and opioid-related risks among patients initiating treatment in a large Medicaid cohort. Our findings show that patients receiving opioid prescriptions from pain medicine/anesthesiology, PM&R, and PCPs are at greater risk. Patients treated with opioids by these specialties were consistently at greater risk for developing OUD and opioid misuse, although their risk of overdose was sensitive to how specialty group was assigned. Our findings have implications for the targeting of interventions to reduce opioid-related risks.

Opioids are prescribed by many different specialties for both acute and chronic pain. Our results are in agreement with a previous study which showed that specialties more likely to

prescribe opioids for chronic pain had higher risks of opioid related deaths.[71] Using data from the medical examiner, prescription drug monitoring program and controlled substance database from the state of Utah, the study found that anesthesiologists, pain medicine specialists, and physicians from PM&R has 2.0, 2.6, 2.1 times higher opioid-related fatalities respectively for every 1000 prescriptions compared to internal medicine physicians.[71] In addition to mortality-related outcomes, our study also found higher ARR for non-mortality outcomes of OUD and misuse among specialties that prescribe opioids for chronic pain after adjusting for diagnoses of chronic pain. The literature on opioid prescribing by specialists more likely to prescribe opioids for acute pain - dentists, OB/GYN, and orthopedic surgeons - has been mixed. Although some studies have reported higher likelihood of prescribing an opioid by prescribers from dentistry and surgery compared to those from family medicine and general practice[71,78,79], the opioid-related fatalities among patients who received prescriptions from dentistry, OB/GYNs, and orthopedic surgery is reported to be lower relative to those receiving prescriptions from internal medicine physicians.[71] In our study, we observed that incident patients newly prescribed opioids from dentistry, OB/GYN, and surgery had significantly lower ARR of OUD, misuse or overdose compared to those who received their prescriptions from PCPs. Recent research suggests that emergency medicine is a potential gateway to long-term opioid use.[67,80] In this study, we observed that ARR for misuse and overdose were significantly lower when emergency medicine physicians were the first or dominant prescribers in an episode than PCPs.

We were not able to identify the underlying causes of differences in opioid-related risks by specialty which may be related to significant differences in patient factors, provider behavior or both. Patients receiving opioid treatment from pain medicine and PM&R specialists are more likely to have chronic non-cancer pain[81] and may have complex physical, behavioral and

psychosocial issues often requiring inter-disciplinary care.[46,82,83] Evidence on the quality of opioid prescribing by pain management and PM&R specialists is scarce. Interestingly, a prior study showed a steady increase in rates of opioid prescribing by these two specialties between 2007 to 2012.[78] We observed that pain management and PM&R specialists were the index or dominant prescribers for a small proportion of patients. By contrast, PCPs were index or dominant prescribers for a majority of patients in our study sample and had higher risk of adverse events compared to other acute pain treating specialties (dentistry, surgery, OB/GYN). Our findings highlight that policies can potentially be targeted toward specific physician specialties to allow early opportunity to intervene by screening patients, suggesting behavior changes or referring high-risk cases to medication treatment. Given the high-volume of opioid prescribing among specialties like PCPs[71,78,79], effective targeting of interventions may, in turn, depend on factors such as patient-volume, patient-risk for adverse outcomes, or a combination of both. More studies are required to better understand how such factors can influence the targeting of interventions.

A number of efforts are underway to reduce adverse consequences of opioid exposure. In 2014, the PA-DHS established Centers of Excellence with the aim of providing coordinated care to patients with OUD.[84] These efforts can potentially be expanded to patients seeking care from specialists from pain medicine and PM&R and PCPs. Health systems could monitor prescribing practices and communicate with prescribers about aberrant prescribing patterns. In addition, health systems could also encourage increased physician participation in continuing education programs which are being organized by the Substance Abuse and Mental Health Services Administration.[85] Our study helps in contributing evidence that could be used by organizations currently developing strategies for pain management.

3.4.1 Strengths and Limitations

Study strengths include our focus on patients initiating opioid treatment with no history of OUD or overdose in the baseline period, detailed information on prescriber specialty, and two approaches to attributing patient-episodes to specialty groups. The results of this study, however, should be viewed in light of some key limitations. First, although we adjust for patient level comorbidities, demographic, and enrollment variables, there are several unmeasured confounders (e.g. severity of pain) that cannot be accounted for given the nature of observational data. Second, limiting our analyses to only PA Medicaid claims reduces the external validity of our findings. Third, our data cannot identify events that occur outside of the health system. For example, cash payments for prescriptions cannot be captured if enrollees choose not to use insurance and we cannot determine which prescription fills are subject to diversion. Also, we measure overdose events (fatal and non-fatal) that received medical attention but do not capture overdoses in the community. However, these issues are observed in most health care insurance claims since they do not capture clinical information that can help in validating medication consumption. Fourth, OUD diagnosis is often under-coded in claims data.[86] Patients receiving an OUD diagnosis may, in fact, represent a unique population of patients who have talked to their physician about their OUD or their aberrant prescription use may have alerted their physicians. Finally, we imputed the provider specialties when provider IDs were missing. Although the results were largely similar to the complete-case analysis, imputations may not accurately reflect real-world scenarios.

3.5 CONCLUSIONS

Our findings indicate that patients receiving opioid prescriptions from pain medicine/anesthesiology, PM&R, and PCPs are at greatest risk of OUD, misuse or overdose. The results of this paper provide evidence for targeted physician and health-systems level interventions to reduce adverse effects of over prescribing of opioids.

4 CHAPTER FOUR: MOOD DISORDERS, ANTIDEPRESSANTS AND OPIOID USE: THE ROLE OF ADHERENCE

ABSTRACT

BACKGROUND: Patients with psychiatric illnesses are both more likely to be prescribed an opioid medication and experience adverse consequences of opioid exposure such as abuse, misuse, and overdose. Many antidepressants promote analgesia, and successful treatment of depression reduces the bothersomeness of pain. Many patients, however, do not take antidepressant medications as prescribed and discontinue their use prematurely. Describing the link between antidepressant medication adherence (a modifiable behavior) and subsequent opioid use may provide insight into another approach to reduce the epidemic of opioid abuse. This study examines the relationship between adherence to antidepressant medications among individuals with mood or anxiety disorders and its association with opioid use.

METHODS: We conducted a longitudinal retrospective study using Pennsylvania Medicaid data (2007-2015). We constructed a cohort of 18 to 64-year-old enrollees initiating antidepressant treatment who had a diagnosis for major depressive disorders (MDD) or anxiety disorders. We measured adherence using proportion of days covered (PDC) over a 180-day period after initiation of antidepressant treatment and censored our follow-up time to two years after end of adherence measurement period. We conducted Cox proportional hazards regression analyses to examine the effect of adherence on opioid use.

RESULTS: Our findings show that there were no significant differences in adjusted hazards for opioid use (0.94, 95% CI=0.87, 1.01) among the adherent (PDC ≥ 80%) and non-adherent

enrollees (PDC <80%) with MDD and no cancer. However, using the multi-category definitions of adherence and PDC<20% as reference category, the adjusted hazard ratios for opioid use were as follows: 20% ≤ PDC <40% = 0.76, (95% CI= 0.68, 0,85), 40% ≤ PDC <60% = 0.80, (95% CI= 0.70, 0.90), 60% ≤ PDC <80% = 0.79 (95% CI= 0.70, 0.90, and PDC ≥ 80% = 0.77 (95% CI = 0.70, 0.86). Proportional hazards assumptions for these models were violated. For enrollees with anxiety and no cancer, the adjusted hazards of opioid use were significant lower (0.84, 95% CI= (0.72, 0.99) for the 40% ≤ PDC <60% category (reference = PDC<20%). Among enrollees with MDD and anxiety and any cancer, there were no significant relationships between adherence and opioid use.

CONCLUSION: Within the limitations of our study, we observed that enrollees with MDD and no cancer who achieve ≥ 20% PDC have significantly lower baseline hazard ratios for opioid use than enrollees with PDC<20%. Further research is required to confirm our findings.
KEYWORDS: Mood disorders, Depression, Anxiety, Antidepressants, Adherence, Opioids

4.1 INTRODUCTION

Significant policy efforts are underway to mitigate the opioid epidemic in the United States. Opioid prescribing has been an important focus of policy interventions.[2,58] It is established that not only is there high comorbidity among depression and anxiety with chronic non-cancer pain[87-93], but individuals with these psychiatric diseases are more likely to be prescribed opioids.[10,12,94-98] More troubling, patients with psychiatric illnesses who are prescribed opioids experience an elevated risk of adverse consequences use such as abuse, misuse, and overdose.[99-104] Increased opioid prescribing among these patients with chronic pain and depression and/or anxiety is referred to as "adverse selection,"[105,106] and is inconsistent with professional prescribing and clinical care guidelines.[58]

There is substantial evidence to support the bi-directional nature of mood disorders and pain.[107-113] Of specific interest in the context of the opioid epidemic is the pre-existence of mood disorders and subsequent onset of pain. Patients with depression experience abnormalities of the serotonergic and noradrenergic systems, which has been suggested to play a role in the development of physical pain symptoms.[114] Evidence from placebo-controlled studies shows that treatment with antidepressants can mitigate these abnormalities and help in improving pain symptoms.[14,15] A less understood relationship and an emerging line of inquiry is the adherence to antidepressant medications among individuals with mood disorders and its association with opioid use.

In this study, we examined the associations between adherence to antidepressant therapy among individuals with mood disorders and future opioid use. To inform the targeting of interventions aimed at addressing the opioid epidemic, it is important to understand in what subgroups of patients unnecessary exposure of opioids can be minimized. Studies have shown

that adherence to antidepressant medications is usually low ranging from 13% to 56%.[115] If high adherence to antidepressants is associated with reduce use of opioid medications, then interventions can be targeted toward increasing adherence to antidepressant medications. The setting for this study is a large Medicaid program as Medicaid enrollees have high prevalence of comorbid mental illnesses and are also at a higher risk for adverse outcomes of opioid use.[57,72]

4.2 METHODS

4.2.1 Description of data

We conducted retrospective longitudinal analyses using Pennsylvania (PA) Medicaid data. We obtained data on all enrollees in either the fee-for-service or and managed care programs between January 2007 and December 2015 directly from Department of Human Services (DHS). PA is one of largest Medicaid programs in the US by expenditures and monthly enrollment.[73,74] The demographic characteristics (except lower Hispanic population) and healthcare utilization trends in PA Medicaid are similar to those seen in other state Medicaid programs.[76,102]

We used enrollment files to obtain beneficiary demographic characteristics (e.g. age, race, sex), reason for eligibility (e.g. disabled/chronically ill, children and families), enrollment duration, and insurance type (fee-for-service vs. managed care programs). We used the medical claims (inpatient, outpatient, and professional) to obtain information on beneficiary diagnosis and procedure codes. The pharmacy claims included prescription characteristics such as the National Drug Code (NDC) from which we obtained days' supply, date of fill, and dose. We used the

Medispan® data to obtain additional information on prescription characteristics including drug name, strength, and active ingredient by NDC.[35]

4.2.2 Study sample and cohort design

Our analytic cohort included enrollees aged ≥18 to ≤64 years, who were not dually eligible for Medicare since we could not observe data on their prescription utilization. In addition, we excluded enrollees who met the following criteria: 1) receiving a diagnosis for bipolar disorders/schizophrenia, other psychosis-related disorders, paranoid state, drug-induced depression depressive-type psychosis, Alzheimer's disease, Parkinson's disease, and dementia, and 2) residing in long-term care for ≥ 90 days, or enrollees using hospice services. The International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) codes for the exclusion diagnoses are provided in the appendix (Appendix C).

We created two separate cohorts of enrollees with a diagnosis of major depressive disorders (MDD) or anxiety disorders initiating antidepressant treatment. The cohort selection is shown in the appendix (**Figure C.1)**. The first prescription for an antidepressant medication was treated as an index event. The index event was preceded by a 6-month baseline period during which enrollees had to meet the following criteria: having six-months of continuous enrollment defined as enrollment of at least 15-days for six consecutive months and no prescription fills for antidepressants or opioids. Enrollees were required to have a diagnosis of MDD or anxiety disorder at some point during the six-months prior to the index antidepressant fill or within 30 days after antidepressant the index fill **(Appendix Figures C.2 and C.3)**. Since there was a significantly high prevalence of cancer in both the MDD (n=3,733, 25.4%) and anxiety cohorts (n=2,597; 25.5%)

(**Table 4.1**), we stratified our analyses into the follow four sub-groups: 1) MDD and no cancer, 2) MDD and presence any cancer, 3) anxiety disorders and no cancer, 4) anxiety disorders and presence of any cancer.

4.2.3 Main explanatory variable

The main independent variable for the analysis was adherence to antidepressant medications. Adherence was measured using proportion of days covered (PDC). The PDC is defined as the number of days covered with antidepressants between the first and the last prescription divided by the required duration of therapy. We chose a six-month time frame since it is considered as the minimum required duration of therapy to achieve both the acute and maintenance phase of treatment.[116] The PDC calculations also accounted for the number of days of overlap for individuals taking >1 antidepressant concurrently and were capped at 1.0. The Pharmacy Quality Alliance has endorsed using of PDC[117] as superior to other adherence measures such as the medication possession ratio as it may over-estimate the true prescription fill rate. We used two definitions of adherence for our analysis. First, we used the conventional dichotomous definition of adherence, where patients achieving ≥80% PDC are considered adherent. The 80% threshold is widely used. However, studies have found this threshold to be arbitrary and not always sensitive to clinically important differences in the levels of adherence.[118] We therefore used another categorical measure of adherence where we grouped adherence into the following five categories: (PDC <20%, 20%≤PDC<40%, 40%≤PDC<60%, 60%≤PDC<80%, PDC ≥ 80%).

4.2.4 Outcome variable

Our outcome variable of interest was the time to the first prescription of oral, transdermal, or submucosal opioid medication. We measured opioid use in the 180 days after the measurement period for antidepressant adherence had ended.

4.2.5 Covariates

We included patient-level socio-demographic characteristics such as age, gender, race (White, Black or Other), eligibility category during the first opioid prescription (disabled/chronically ill, families with children, other), and insurance type (fee-for-service/managed care). We also included indicators for the following comorbid conditions for which ICD-9 codes were present during the six-month baseline period prior to the index opioid fill: substance use disorders (alcohol abuse/dependence, non-opioid drug abuse/dependence), mental health conditions (adjustment disorders, other mental health conditions), chronic pain conditions (back pain, neck pain, headache/migraine, and arthritis/join pain).[77] We also included a modified Elixhauser comorbidity index[48] which did not include those conditions identified separately above.

4.2.6 Statistical Analyses

The association between adherence to antidepressants and opioid use was estimated using Kaplan Meier survival plots. We used the long-rank tests for equality of survival functions to test for differences in the survival curves. We conducted Cox proportional hazards regression and

estimated adjusted hazard ratios and 95% confidence intervals (CI) to assess the relationship between adherence and opioid use adjusting for the above-mentioned covariates. We undertook a step-wise approach to assess the relationship between the adherence measures and opioid use in the presence of covariates. We first analyzed uni-variable or unadjusted models, where we evaluated the relationship between adherence measures and opioid use. Next we explored the impact of adjusting for i) demographic variables, ii) enrollment variables and iii) other comorbid conditions on opioid use. Proportionality assumptions were tested using the interaction of the adherence measures with follow-up time. Since a nine-year time duration would be too long to explore the impact of adherence on opioid use, for our main analyses, we censored the follow-up time to a two-year period after the end of the adherence measurement period. We also conducted sensitivity analyses, where the follow-up period was censored to one-year. All analyses were conducted with SAS 9.4. and Stata.[49,119] This study was designated as exempt from University of Pittsburgh's Institutional Review Board.

4.3 RESULTS

4.3.1 Characteristics of study cohort

4.3.1.1 MDD cohort

The demographic characteristics of the MDD and anxiety cohort are provided in **Table 4.1.** From 2007-2015, there were a total of 14,670 Medicaid enrollees initiating antidepressant treatment who met the inclusion/exclusion criteria for the MDD cohort. Of these, 45.2% (n=6,630) filled at least one opioid prescription after antidepressant adherence was measured (i.e. 180-days

initiation of antidepressant therapy). The average age of the cohorts with and without opioid use was 33.8 (SD=11.7) and 33.7 (SD=12.4) years respectively (p=0.54). The group with opioid use had significantly higher proportion of females (opioid use, 80.2% vs. no opioid use, 68.5%; p <0.0001), managed care enrollees (opioid use, 97.6 % vs. no opioid use, 92.3%; p <0.0001), and those qualifying for Medicaid under the disabled/chronically ill category (opioid use, 27.3% vs. no opioid use, 25.3%; p=0.007) and families with children (opioid use, 65.5% vs. no opioid use, 58.7%; p <0.0001) categories. In addition, there was a significantly (p<0.0001) higher prevalence of any cancer among individuals with opioid use (34.6%) compared to the non-opioid use (17.9%).

Table 4.1 Characteristics of enrollees with major depressive disorders and anxiety

	MDD cohort			***Anxiety cohort***		
	Opioid use (n=6,630)	**No opioid use (n=8,040)**	***P***	**Opioid use (n=4,217)**	**No opioid use (n=5,950)**	***P***
Demographics						
Age at first antidepressant prescription, mean (SD)	33.8 (11.7)	33.7 (12.4)	0.54	32.8 (11.1)	32.6 (12.0)	0.32
Female, n (%)	5,318 (80.2)	5,506 (68.5)	<0.0001	3,346 (79.4)	4,110 (69.1)	<0.0001
Urban living area, n (%)	5,422 (81.8)	6,570 (81.7)	0.93	3,368 (79.9)	4,767 (80.1)	0.76
White, n (%)	4,299 (64.8)	5,752 (71.5)	<0.0001	3,196 (75.8)	4,680 (78.6)	0.0007
Black, n (%)	1,286 (19.4)	1,177 (14.6)	<0.0001	572 (13.6)	629 (10.6)	<0.0001
Other, n (%)	1,045 (15.8)	1,111 (13.8)	0.0009	449 (10.6)	641 (10.8)	0.84
Eligibility categories						
Disabled/Chronically Ill, n (%)	1,808 (27.3)	2,033 (25.3)	0.007	1,037 (24.6)	1,448 (24.3)	0.77
Families with Children, n (%)	4,340 (65.5)	4,717 (58.7)	<0.0001	2,885 (68.4)	3,509 (59.0)	<0.0001
Other, n (%)	482 (7.3)	1,290 (16.0)	<0.0001	295 (7.0)	993 (16.7)	<0.0001
Managed care enrollees, n (%)	6,472 (97.6)	7,423 (92.3)	<0.0001	4,118 (97.7)	5,511 (92.6)	<0.0001
Any Cancer, n (%)	2,292 (34.6)	1,441 (17.9)	<0.0001	1,469 (34.8)	1,128 (19.0)	<0.0001

MDD = Major Depressive Disorders; SD = standard deviation; Differences between categorical variables were tested using chi-square tests. Differences between continuous variables were tested using independent-samples t-tests.

4.3.1.2 Anxiety cohort

The demographic characteristics of the cohort with anxiety were similar to the MDD cohort. From 2007-2015, there were a total of 10,167 Medicaid enrollees initiating antidepressant treatment who met the inclusion/exclusion criteria. Of these, 41.5% (n=4,217) had at least one

opioid prescription fill after antidepressant adherence was measured (i.e. 180-days initiation of antidepressant therapy). The average age of the cohorts with and without opioid use was 32.8 (SD=11.1) and 32.6 (SD=12.0) years respectively (p=0.32). The group with opioid use had significantly higher proportion of females (opioid use, 79.4% vs. no opioid use, 69.1%; p <0.0001), managed care enrollees (opioid use, 97.7% vs. no opioid use, 92.6%; p <0.0001), and those qualifying for Medicaid under the families with children eligibility category (opioid use, 68.4% vs. no opioid use, 59.0%; p <0.0001). There was a significantly (p<0.0001) higher prevalence of any cancer among individuals with opioid use (34.8%) compared to the non-opioid use group (19.0%).

4.3.2 Adherence measures

4.3.2.1 MDD cohort

As explained in the methods section, we stratified our analyses based on the presence of cancer in both the MDD and anxiety cohorts. In the MDD cohort, there were 10,937 (74.5%) beneficiaries who did have cancer. Among these enrollees, using the dichotomous definition of adherence (PDC ≥80%), we observed that there were significantly fewer adherent enrollees in the opioid use sub-group (opioid use sub-group =31.9 % vs. no opioid use sub-group =36.0%, p<0.0001) **(Table 4.2)**. Among enrollees with MDD and any cancer (n=3,733; 25.5%) there was a significantly lower proportion of enrollees meeting PDC ≥80% criterion (opioid use sub-group =37.5% vs. no opioid use sub-group =40.3%, p=0.09).

Table 4.2 Distribution of enrollees according to categories of proportion of days covered

	MDD COHORT			ANXIETY COHORT		
			NON-CANCER			
	Opioid use (n=3,142)	**No opioid use (n=7,795)**	***P***	**Opioid use (n=2,046)**	**No opioid use (n=5,524)**	***P***
Using continuous measure of PDC						
Mean (SD)*	0.57 (0.30)	0.61 (0.29)	<0.0001	0.60 (0.30)	0.62 (0.29)	0.0005
Median (Min-Max)$^{\phi}$	0.50 (0.03-1.00)	0.64 (0.01-1.00)	<0.0001	0.60 (0.05-1.00)	0.67 (0.02-1.00)	0.004
Using dichotomous categories of PDC						
PDC <80%	2,139 (68.1)	4,986 (64.0)	<0.0001	1,319 (64.5)	3,363 (60.9)	0.0043
PDC ≥80%	1,003 (31.9)	2,809 (36.0)		727 (35.5)	2,161 (39.1)	
Using multiple categories of PDC						
PDC <20%	544 (17.3)	848 (10.9)	<0.0001	318 (15.5)	613 (11.1)	<0.0001
20% ≤ PDC <40%	660 (21.0)	1,749 (22.4)		411 (20.1)	1,145 (20.7)	
40% ≤ PDC <60%	504 (16.0)	1,213 (15.6)		294 (14.4)	824 (14.9)	
60% ≤ PDC <80%	431 (13.7)	1,176 (15.1)		296 (14.5)	781 (14.1)	
PDC ≥80%	1,003 (31.9)	2,809 (36.0)		727 (35.5)	2,161 (39.1)	
			CANCER			
	Opioid use (n=1,679)	**No opioid use (n=2,054)**	***P***	**Opioid use (n=1,028)**	**No opioid use (n=1,569)**	***P***
Using continuous measure of PDC						
Mean (SD)*	0.61 (0.30)	0.63 (0.30)	0.047	0.59 (0.31)	0.63 (0.30)	0.004
Median (Min-Max)$^{\phi}$	0.63 (0.01-1.00)	0.67 (0.03-1.00)	<0.0001	0.61 (0.01-1.00)	0.67 (0.02-1.00)	0.02
Using dichotomous categories of PDC						
PDC <80%	1049 (62.5)	1,227 (59.7)	0.09	654 (63.6)	926 (59.0)	0.02
PDC ≥80%	630 (37.5)	827 (40.3)		374 (36.4)	643 (41.0)	
Using multiple categories of PDC						
PDC <20%	265 (15.8)	261 (12.7)	0.05	175 (17.0)	210 (13.4)	0.06
20% ≤ PDC <40%	297 (17.7)	393 (19.1)		190 (18.5)	280 (17.8)	
40% ≤ PDC <60%	252 (15.0)	297 (14.5)		143 (13.9)	214 (13.6)	
60% ≤ PDC <80%	235 (14.0)	276 (13.4)		146 (14.2)	222 (14.2)	
PDC ≥80%	630 (37.5)	827 (40.3)		374 (36.4)	643 (41.0)	

MDD = Major Depressive Disorders; PDC = Proportion of days covered; *Mean PDC compared using independent two-sample t-tests; $^{\phi}$ Medians compared using Wilcoxon rank sum tests.

4.3.2.2 Anxiety cohort

We observed similar findings in the anxiety cohort. There were 7,570 (74.4%) who did not have cancer. Among these enrollees, there were significantly fewer adherent enrollees (PDC ≥80%) who had opioid use (opioid use sub-group=35.5 % vs. no opioid use sub-group=39.1%, p<0.0001). Similarly, among enrollees with anxiety and presence of any cancer, the opioid use sub-group had significantly fewer adherent enrollees compared to the non-opioid use sub-group (opioid use sub-group =36.4 % vs. no opioid use sub-group =41.0%, p=0.02).

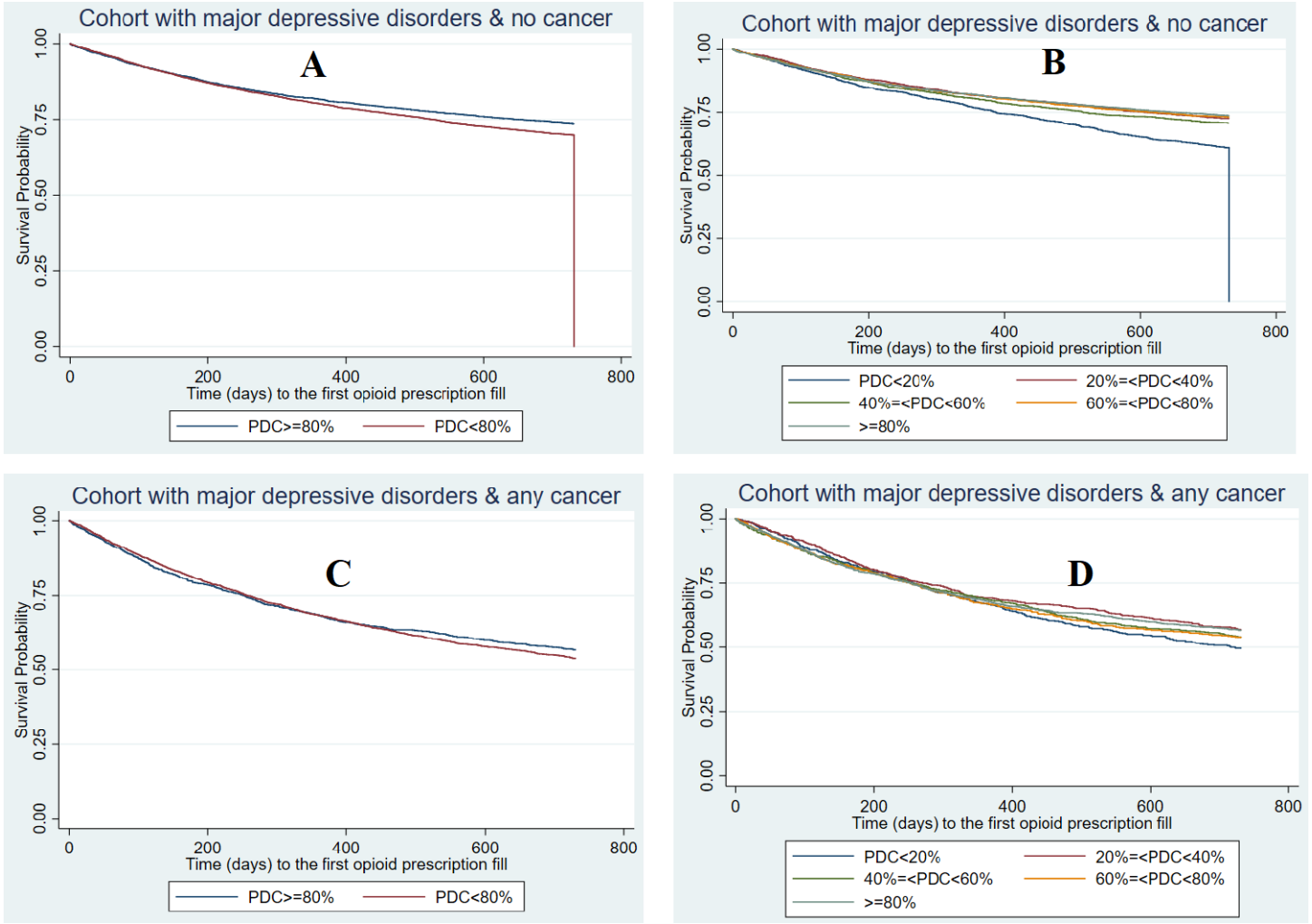
4.3.3 Kaplan-Meier estimates

4.3.3.1 MDD cohort

We constructed Kaplan-Meier survival plots and conducted log-rank tests for equality of survivor functions to study the relationship between adherence to antidepressant therapy and opioid use. In the MDD cohort without cancer **(Figure 4.1A)**, the median time for opioid use in the MDD and no cancer cohort was 231.5 days (minimum=1, maximum= 731). There were statistically significant differences in the Kaplan-Meier survival curves using both the dichotomous (χ^2 (1) = 13.2, p=0.0002) and multi-category definitions of adherence (χ^2 (4) = 81.2, p=<0.0001) **(Figure 4.1B)**. For the MDD and any cancer cohort, the median time to opioid use was 221days (minimum=1, maximum=728). There were no statistically significant differences in the Kaplan-Meier survival curves in the MDD cohort with any cancer using both the dichotomous (χ^2 (1) = 1.6, p=0.21) and multi-category definitions of adherence (χ^2 (4) = 7.1, p=0.13) **(Figures 4.1C and 4.1D)**.

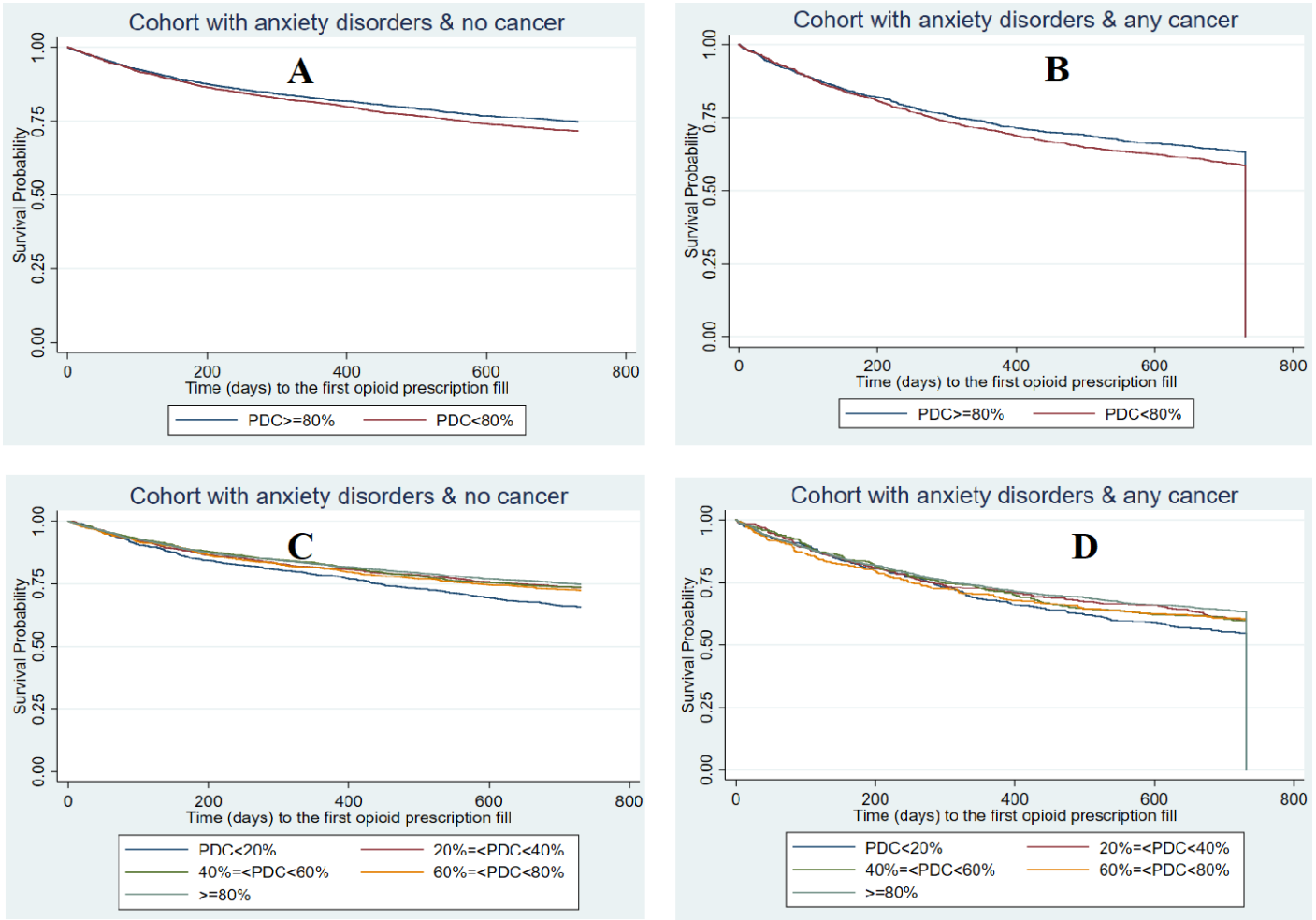
4.3.3.2 Anxiety cohort

For the cohort with anxiety and no cancer, the median time to opioid use was 210 days. There were statistically significant differences (χ^2 (1) = 0.69, p=0.005) in the survival curves using the dichotomous **(Figure 4.2A)** and multi-category (χ^2 (4), = 28.3, p<0.0001) definitions of adherence **(Figure 4.2C)**. In the cohort with anxiety and any cancer, there were statistically significant differences (χ^2 (4), = 4.72, p=0.03) in the survival curves using the dichotomous definition of adherence (**Figures 4.2B**), but the differences were not significant using the multi-category definition of adherence, (χ^2 (4), = 7.42, p=0.12) **(Figures 4.2D)**.



Note: Unadjusted Kaplan Meier estimates of opioid use among enrollees with major depressive disorders classified using: (A) dichotomous definition of adherence (PDC ≥80%) among enrollees with no cancer, (B) multi-category definition of adherence among enrollees with no cancer, (C) dichotomous definition of adherence (PDC ≥80%) among enrollees with cancer, and (D) multi-category definition of adherence among enrollees with cancer. Note: The differences in the survival curves were tested using the log-rank tests for equality of survivor functions.

Figure 4.1 Unadjusted Kaplan Meier estimates of opioid use among enrollees with major depressive disorders



Note: Unadjusted Kaplan Meier estimates of opioid use among enrollees with anxiety disorders classified using: (A) dichotomous definition of adherence (PDC ≥80%) among enrollees with no cancer, (B) dichotomous definition of adherence (PDC ≥80%) among enrollees with cancer, (C) multi-category definition of adherence among enrollees with no cancer, and (B) multi-category definition of adherence among enrollees with cancer . Note: Note: The differences in the survival curves were tested using the log-rank tests for equality of survivor functions. .

Figure 4.2 Unadjusted Kaplan Meier estimates of opioid use among enrollees with anxiety disorders

4.3.4 Cox-proportional hazards

We conducted Cox-proportional hazards regressions to assess the relationship between adherence to antidepressants and opioid use adjusting for demographic and enrollment characteristics and presence of comorbid mental illness and pain.

4.3.4.1 MDD cohort

We observed no significant differences in adjusted hazards for opioid use (0.94, 95% CI=0.87, 1.01) among the adherent and non-adherent enrollees using the ≥ 80% PDC criterion in the MDD and no cancer sub-group **(Table 4.3)**. However, using the multi-category definitions of adherence and PDC<20% as reference category, adjusted hazard ratios for opioid use were as follows: 20% ≤ PDC <40% = 0.76, (95% CI= 0.68, 0,85), 40% ≤ PDC <60% = 0.80, (95% CI= 0.70, 0.90), 60% ≤ PDC <80% = 0.79 (95% CI= 0.70, 0.90), and PDC ≥ 80% = 0.77 (95% CI = 0.70, 0.86) **(Table 4.4)**. The proportional hazards assumptions for these models were not met. In the MDD and cancer sub-group, the adjusted hazards of opioid use were significantly lower (0.84, 95% CI= 0.71, 0.99) only for the 20% ≤ PDC <40% category (reference = PDC<20%). In the sensitivity analyses we observed that enrollees achieving 20% ≤ PDC <40% at one-year of follow-up had significantly lower adjusted hazards of opioid use (0.86, 95% CI=0.74, 0.99**) (Appendix Table C.2)**.

4.3.4.2 Anxiety cohort

Using the ≥ 80% PDC criterion, there were no significant differences in opioid use among the adherent and non-adherent enrollees (Adjusted Hazard Ratios=0.97; 95% CI= 0.89, 1.07). The

adjusted hazards of opioid use were significant lower (0.84, 95% CI= (0.72, 0.99) for the 40% ≤ PDC <60% category (reference = PDC<20%). Using both the dichotomous (0.92, 95% CI= 0.80, 1.05) and multi-category (0.85, 95% CI=0.71, 1.02) definitions for adherence, we found no significant differences in the adjusted hazards for opioid use between adherent and non-adherent enrollees in the anxiety cohort who had any cancer.

Table 4.3 Results of Cox proportional hazards models among individuals with major depressive and anxiety disorders - effect of 80% PDC threshold on opioid use

	MDD		Anxiety	
	No cancer	**Cancer**	**No cancer**	**Cancer**
Adherence (Ref= PDC <80%)	0.87 (0.80, 0.93) *	0.94 (0.85, 1.04)	**0.88 (0.80, 0.96) ***	**0.87 (0.77,0.99) ***
Adherence+ Demographic	0.89 (0.83, 0.96) *	0.97 (0.88, 1.08)	**0.90 (0.82, 0.99) ***	**0.87 (0.76, 0.99) ***
Adherence + Demographic + Enrollment	0.91 (0.84, 0.99) *	1.00 (0.99, 1.00)	**0.93 (0.85, 1.02)**	**0.88 (0.77, 0.99) ***
Adherence + Demographic + Enrollment + Comorbid mental health and pain	0.94 (0.87, 1.01)	1.02 (0.92, 1.13)	**0.97 (0.89, 1.07)**	**0.92 (0.80, 1.05)**

Demographic covariates = Age in years, Gender, Race (White, Black or Other), Place of residence (Urban/Rural); Enrollment covariates= Managed care/fee-for-service, Eligibility categories (Disabled/Chronically Ill, Expansion, Families with Children, Others); Comorbid mental health conditions = alcohol and substance abuse disorders, adjustment disorders, other mental health conditions; Comorbid pain conditions = back pain, neck pain, arthritis/joint pain, headache/migraine; MDD = Major Depressive Disorder; PDC=Proportion of days covered; Bold refers to non-violation of proportional hazards assumption; * = $p<0.05$

Table 4.4 Results of Cox proportional hazards models among individuals with major depressive and anxiety disorders - effect of multiple adherence categories on opioid use

	MDD		Anxiety	
	No cancer	**Cancer**	**No cancer**	**Cancer**
Adherence variables only				
20% ≤ PDC <40%	0.67 (0.59, 0.75) **	0.82 (0.70, 0.97) *	0.74 (0.64, 0.86) **	**0.87 (0.71, 1.07)**
40% ≤ PDC <60%	0.72 (0.64, 0.82) **	**0.90 (0.76, 1.07)**	**0.74 (0.63, 0.87) ***	**0.86 (0.69, 1.08)**
60% ≤ PDC <80%	0.65 (0.58, 0.74) **	**0.91 (0.77, 1.09)**	**0.78 (0.67, 0.92) ***	0.88 (0.70, 1.09)
PDC ≥80%	0.64 (0.58, 0.71) **	0.85 (0.73, 0.98) *	0.71 (0.62, 0.81) **	**0.78 (0.65, 0.94)**
PDC<20%	Reference	Reference	Reference	Reference
Adherence + Demographic variables				
20% ≤ PDC <40%	0.68 (0.61, 0.76) **	**0.82 (0.70, 0.97)** *	0.77 (0.66, 0.89) *	**0.87 (0.71, 1.07)**
40% ≤ PDC <60%	0.74 (0.66, 0.84) **	**0.91 (0.77, 1.09)**	**0.76 (0.65, 0.89) ***	**0.87 (0.70, 1.08)**
60% ≤ PDC <80%	0.68 (0.60, 0.77) **	0.93 (0.78, 1.11)	**0.80 (0.69, 0.94) ***	0.88 (0.70, 1.09)
PDC ≥80%	0.67 (0.61, 0.75) **	0.88 (0.76, 1.02)	0.74 (0.65, 0.84) **	**0.78 (0.65, 0.94)**
PDC<20%	Reference	Reference	Reference	Reference
Adherence + Demographic + Enrollment variables				
20% ≤ PDC <40%	0.70 (0.63, 0.79) **	**0.83 (0.70, 0.98) ***	0.79 (0.68, 0.92) *	**0.89 (0.72, 1.09)**
40% ≤ PDC <60%	0.76 (0.68, 0.86) **	**0.91 (0.77, 1.09)**	**0.80 (0.68, 0.93) ***	**0.88 (0.70, 1.09)**
60% ≤ PDC <80%	0.70 (0.61, 0.79) **	0.94 (0.79, 1.12)	**0.84 (0.72, 0.98) ***	0.89 (0.71, 1.11)
PDC ≥80%	0.70 (0.63, 0.78) **	0.89 (0.77, 1.04)	0.78 (0.69, 0.90) *	**0.80 (0.67, 0.96)**
PDC<20%	Reference	Reference	Reference	Reference
Adherent + Demographic + Enrollment +Comorbid mental health and pain				
20% ≤ PDC <40%	0.76 (0.68, 0.85) **	**0.84 (0.71, 0.99) ***	**0.91 (0.79, 1.06)**	**0.91 (0.74, 1.11)**
40% ≤ PDC <60%	0.80 (0.70, 0.90) **	**0.93 (0.78, 1.11)**	**0.84 (0.72, 0.99) ***	**0.90 (0.72, 1.12)**
60% ≤ PDC <80%	0.79 (0.70, 0.90) **	**0.96 (0.80, 1.14)**	**0.95 (0.81, 1.11)**	0.90 (0.72, 1.12)
PDC ≥80%	0.77 (0.70, 0.86) **	0.94 (0.81, 1.09)	**0.90 (0.78, 1.02)**	**0.85 (0.71, 1.02)**
PDC<20%	Reference	Reference	Reference	Reference

Demographic covariates = Age in years, Gender, Race (White, Black or Other), Place of residence (Urban/Rural); Enrollment covariates= Managed care/fee-for-service, Eligibility categories (Disabled/Chronically Ill, Expansion, Families with Children, Others); Comorbid mental health conditions = alcohol and substance abuse disorders, adjustment disorders, other mental health conditions; Comorbid pain conditions = back pain, neck pain, arthritis/joint pain, headache/migraine; MDD = Major Depressive Disorder; PDC=Proportion of days covered; Bold refers to non-violation of proportional hazards assumption; * = $p<0.05$, ** = $p<0.001$

4.4 DISCUSSION

We sought to examine if adherence to antidepressant medications among Medicaid enrollees with MDD or anxiety is associated with future use of opioid medications. Our findings show that: i) after adjusting for demographic, enrollment, and comorbid mental illness and pain characteristics, enrollees with MDD and no cancer with 20% ≤ PDC <40%, 40% ≤ PDC <60%, 60% ≤ PDC <80%, and PDC ≥80% had significantly lower hazard ratios for opioid use than enrollees with PDC<20%, (ii) enrollees who achieve ≥ 80% PDC were not significantly different with respect to opioid use than those with < 80% PDC, and (iii) with the exception of the 20% ≤ PDC <40% category in the MDD and cancer group, there were no significant differences in opioid use among enrollees with cancer and MDD or anxiety.

Prior research has shown that unlike other chronic conditions (e.g. diabetes, hypertension), a large proportion of patients with MDD or anxiety often do not achieve optimal adherence (PDC ≥ 80%) to antidepressant therapy.[120-122] In this study we observed that among both MDD and anxiety cohorts nearly one-third of enrollees achieved PDC ≥ 80%. For both the MDD and anxiety cohorts with no cancer, using the dichotomous definition of adherence and examining its effects of on opioid use in the presence of other covariates, we did not observe any significant associations. However, using the multi-category definition of adherence and <20% PDC as the reference category, we observed that as enrollees in the 20-40%, 40-60%, 60-80%, and ≥80% adherence category had 24%, 20%, 21%, 23% significantly lower hazards of opioid use respectively. For the anxiety group with no cancer, there were 16% significantly lower hazards of opioid use for enrollees achieving 40-60% adherence (vs. PDC <20%). Previous research has shown that the 80%

PDC threshold may not reflect clinically important differences in the level of adherence.[118] In this study, we observed that enrollees in the 20-40%, 40-60%, 60-80% PDC category also performed significantly better than those with <20% PDC in terms of time to first opioid use. This reflects that the 80% PDC threshold may not be an optimal threshold for the associations examined in this study. Prior research has demonstrated that differences exist in adherence to antidepressants from different therapeutic sub-classes.[121] Also, patients with depression are heterogeneous in terms of their symptom experiences due to which efficacy of antidepressants may vary depending on which symptom clusters are being treated, in turn affecting adherence.[123] The findings observed in our study warrant further investigations to examine variations in likelihood of opioid use based on antidepressant therapeutic sub-classes and depression symptom clusters.

Our findings suggest that among patients with MDD and no cancer, adherence to antidepressants, may to some degree, influence the future use of opioid medications. These results, therefore, have potential implications for health systems such as Medicaid with an emphasis on using strategies to improve adherence to antidepressant medications. Recent research has shown that psychosocial interventions that use a personalized strategy to address barriers to adherence, educate patients about depression and antidepressant therapy, and encourage them to communicate with their provider are effective in improving adherence.[124] Care models where pharmacists or case-managers follow up with patients at regular time-intervals to address their concerns on medication use have reported moderate benefit in improving adherence.[125,126] Health systems could potentially implement plan designs that lower out-of-pocket expenditures for enrollees to improve adherence.

To our knowledge, this study is the first to examine adherence to antidepressant use among patients with MDD and anxiety and assess its relationship on use of opioids in a large Medicaid

program. Other study strengths include our focus on patients initiating an anti-depressant treatment in the baseline period with no prior opioid use, focus on patients with and without cancer, and two approaches to measuring PDC thresholds. There are several limitations to our findings. First, the proportional hazards assumption was violated for some of the models which implies that the baseline hazard rates observed in this study may vary with time. Second, measuring prescription fills using administrative data may not represent true adherence. Third, although we adjust for patient level comorbidities, demographic, and enrollment variables, there are several unmeasured confounders that may influence adherence (e.g. patient-prescriber relationship, patient's experience of using antidepressants, healthy-user bias) that cannot be accounted for given the nature of observational data.[127,128] Fourth, limiting our analyses to only PA Medicaid claims reduces generalizability of our findings. Fifth, our data cannot identify events that occur outside of the health system. For example, patients who obtain their prescriptions from other sources such as safety-net programs cannot be captured. Our findings highlight the need for further research on this topic using prospective data that address the limitations listed above.

4.5 CONCLUSIONS

Taking into account the limitations of our study, we observed that enrollees with MDD and no cancer who achieve ≥ 20% PDC had significantly lower baseline hazard ratios for opioid use than enrollees with PDC<20%. The ≥ 80% PDC threshold was not optimal to measure risk of opioid use. With some exceptions, adherence to antidepressants among beneficiaries with cancer was not significantly associated with opioid use. Further studies are required to confirm our findings.

APPENDIX A: TABLES AND FIGURES FOR CHAPTER TWO

Table A.1 Cluster evaluation indices and ratios of change

Bayesian Information Criteria (BIC)			
Cluster numbers	BIC	Change in BIC	Ratio of Change
1	1451385.8		
2	869768.0	-581617.8	
3	687223.0	-182545.0	0.3
4	610695.2	-76527.8	0.4
5	534358.8	-76336.4	1.0
6	466174.0	-68184.8	0.9
7	424984.3	-41189.7	0.6
8	380651.4	-44332.9	1.1
Akaike Information Criteria (AIC)			
Cluster numbers	AIC	Change in AIC	Ratio of Change
1	1451294.5		
2	869585.6	-581708.9	
3	686949.3	-182636.3	0.3
4	610330.3	-76619.0	0.4
5	533902.6	-76427.7	1.0
6	465626.5	-68276.1	0.9
7	379921.5	-85705.0	1.3
8	424345.7	44424.2	-0.5
9	350377.3	-73968.4	-1.7
Within Cluster Sum of Squared Errors (WCSSE)			
Cluster numbers	WCSSE	Change in WCSSE	Ratio of Change
1	1451276.5		
2	869549.6	-581726.9	
3	686895.3	-182654.3	0.3
4	610258.3	-76637.0	0.4
5	533812.6	-76445.7	1.0

Table A.1 continued			
6	465518.5	-68294.1	0.9
7	424219.7	-41298.8	0.6
8	379777.5	-44442.2	1.1
9	350215.3	-29562.2	0.7

Table A.2 International Classification of Disease, 9th edition diagnosis codes for covariates

Adjustment disorders	309.0, 309.1, 309.22, 309.23, 309.24, 309.28, 309.29, 309.3, 309.4, 309.82, 309.83, 309.89, 309.9
Anxiety disorders	293.84, 300.00, 300.01, 300.02, 300.09, 300.10, 300.20, 300.21, 300.22, 300.23, 300.29, 300.3, 300.5, 300.89, 300.9, 308.0, 308.1, 308.2, 308.3, 308.4, 308.9, 309.81, 313.0, 313.1, 313.21, 313.22, 313.3, 313.82, 313.83
Mood disorders	293.83, 296.00, 296.01, 296.02, 296.03, 296.04, 296.05, 296.06, 296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16, 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.40, 296.41, 296.42 296.43, 296.44, 296.45, 296.46, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.7, 296.80, 296.81, 296.82, 296.89, 296.90, 296.99, 300.4, 311
Personality disorders	301.0, 301.10, 301.11, 301.12, 301.13, 301.20, 301.21, 301.22, 301.3, 301.4, 301.50, 301.51, 3015.9, 301.6, 301.7, 301.81, 301.82, 301.83, 301.84, 301.89, 301.9
Psychotic disorders	295
Miscellanous mental health disorders	293.89, 293.9, 300.11, 300.12, 300.13, 300.14, 300.15, 300.16, 300.19, 300.6, 300.7, 300.81, 300.82, 302.1, 302.2, 302.3, 302.4, 302.50, 302.51, 302.52, 302.53, 302.6, 302.70, 302.71, 302.72, 302.73, 302.74, 302.75, 302.76, 302.79, 302.81, 302.82, 302.83, 302.84, 302.85, 302.89, 302.9, 306.0, 306.1, 306.2, 306.3, 306.4, 306.50, 306.51, 306.52, 306.53, 306.59, 306.6, 306.7, 306.8, 306.9, 307.1, 307.40, 307.41, 307.42, 307.43, 307.44, 307.45, 307.46, 307.47, 307.48, 307.49, 307.50, 307.51, 307.52, 307.53, 307.54, 307.59, 307.80, 307.81, 307.89, 310.1, 316, 648.40, 648.41, 648.42, 648.43, 648.44, V40.2, V40.3, V40.31, V40.39, V40.9, V67.3
Back pain	721.3, 721.4, 721.41, 721.42, 721.5, 721.6, 721.7, 721.8, 721.9, 721.90, 721.91, 722.2, 722.30, 722.70, 722.80, 722.90, 722.32, 722.72, 722.82, 722.92, 722.39, 722.73, 722.83, 722.93, 724.0, 724.00, 724.01, 724.02, 724.03, 724.09, 724.1, 724.2, 724.3, 724.4, 724.5, 724.6, 724.7, 724.70, 724.71, 724.79, 724.8, 724.9, 737.1, 737.3, 738.4, 738.5, 756.10, 756.11, 756.12, 756.13, 756.19, 805.4, 805.8, 839.2, 839.42, 846, 846.0, 847.1, 847.3, 847.2, 847.9
Neck pain	721.0, 721.1, 722.0, 722.31, 722.71, 722.81, 722.91, 723.0, 723.1, 723.2, 723.3, 723.4, 723.5, 723.6, 723.7, 723.8, 723.9, 839.0, 839.1, 847.0
Arthritis/joint pain	710-710.9, 725, 726-726.91, 727-727.9, 728-728.9, 729-729.99, 730-730.99, 731-731.8, 732-732.9, 733-733.9, 734, 735-735.9, 736-736.9, 737-737.9, 738-738.9, 739-739.9
Headache/ migraine	346-346.93, 307.81
HIV/AIDS	042, 079.53, 279.10, 279.19, 795.71, 795.8, 795.81, 795.82, 795.83

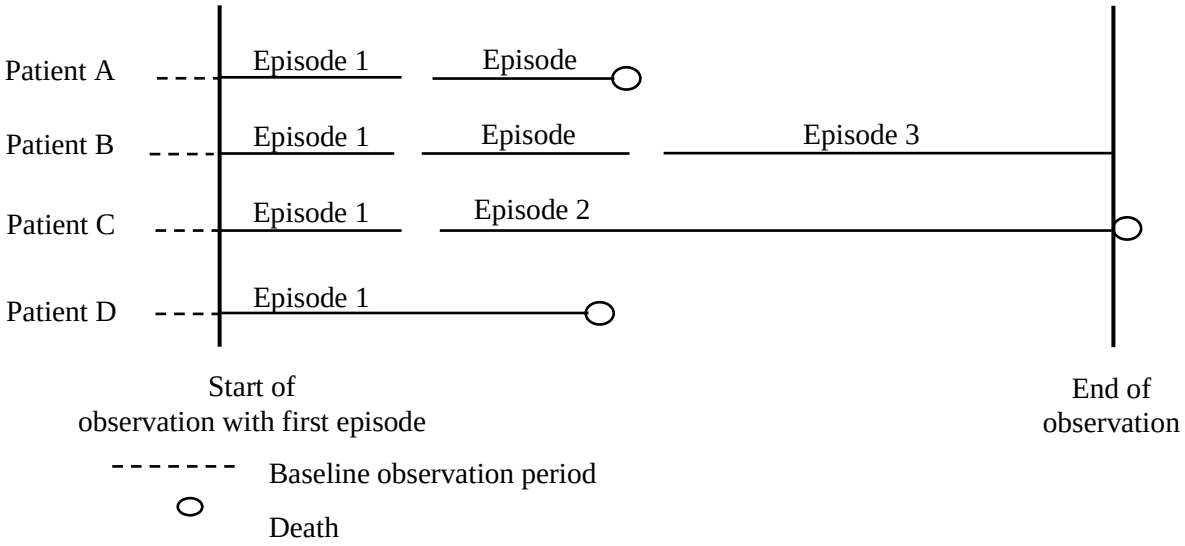


Figure A.1 Establishment of Study Cohort (I)

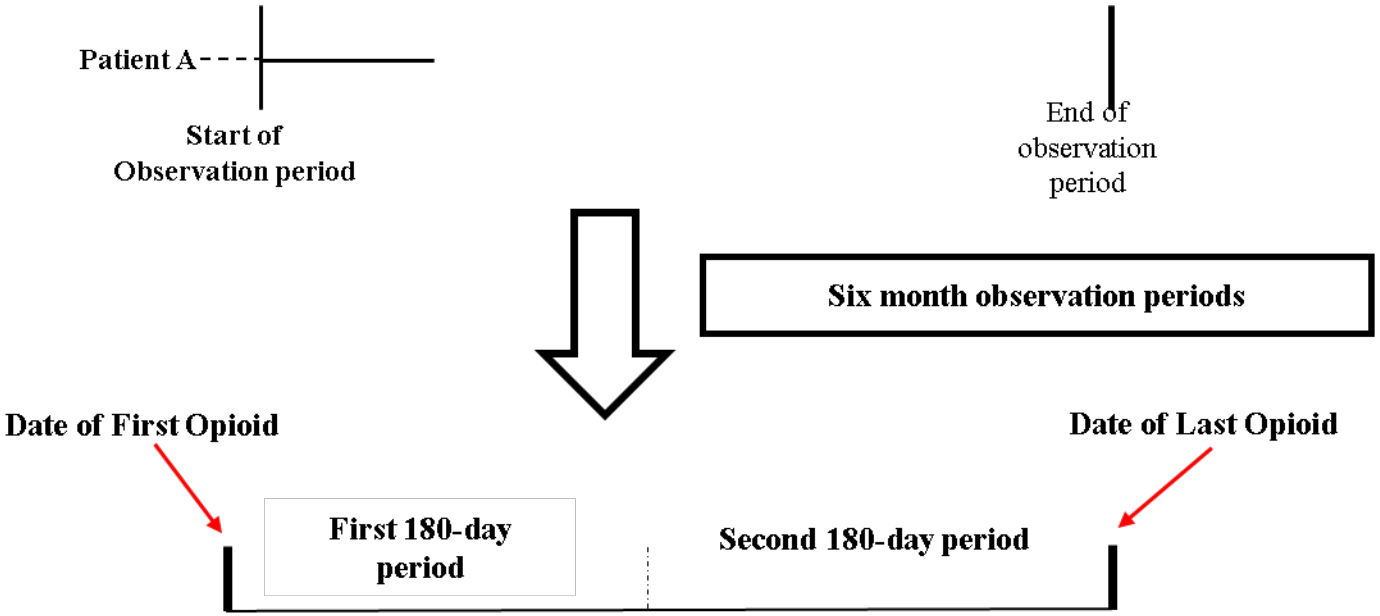


Figure A.2 Establishment of Study Cohort (II)

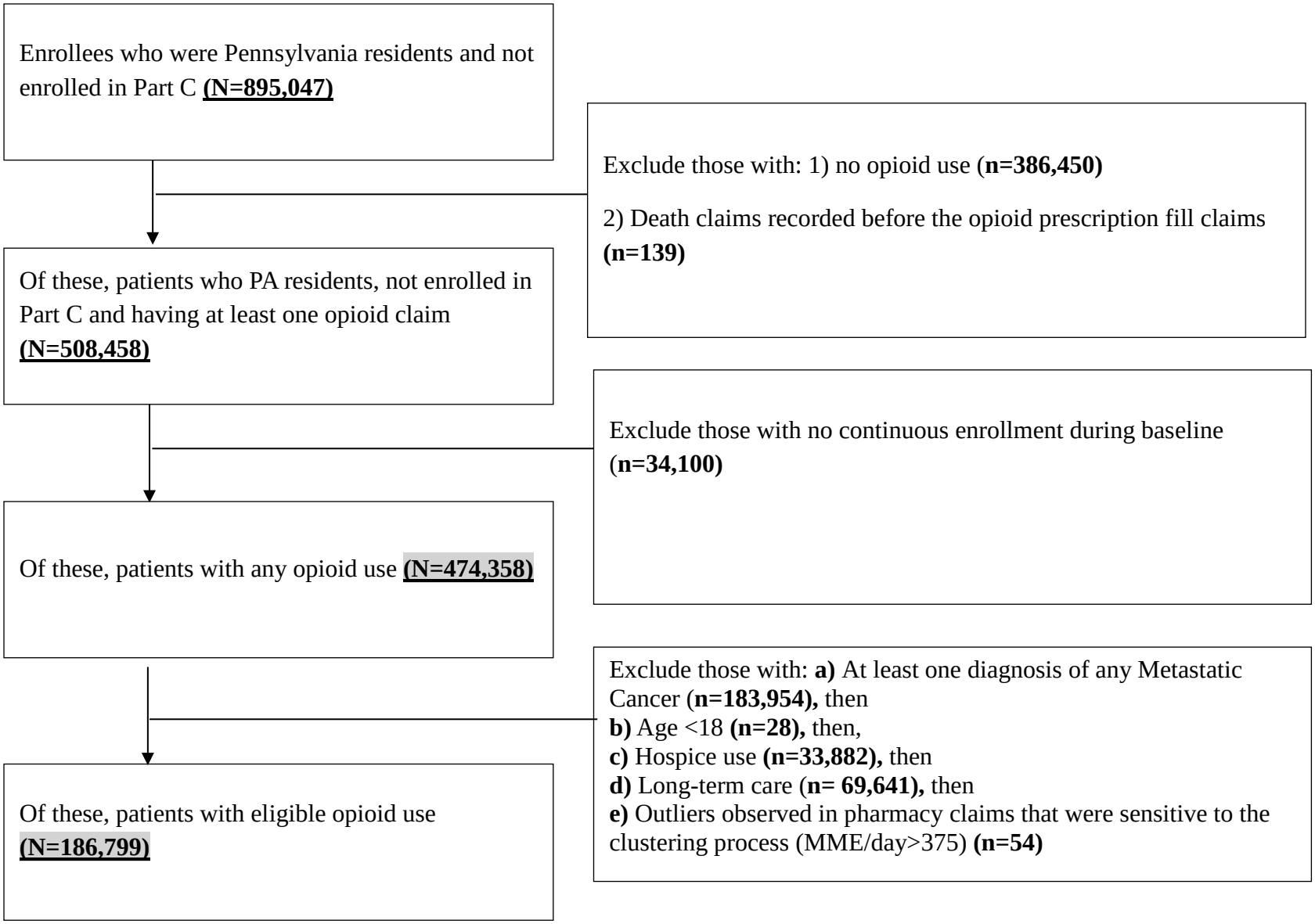
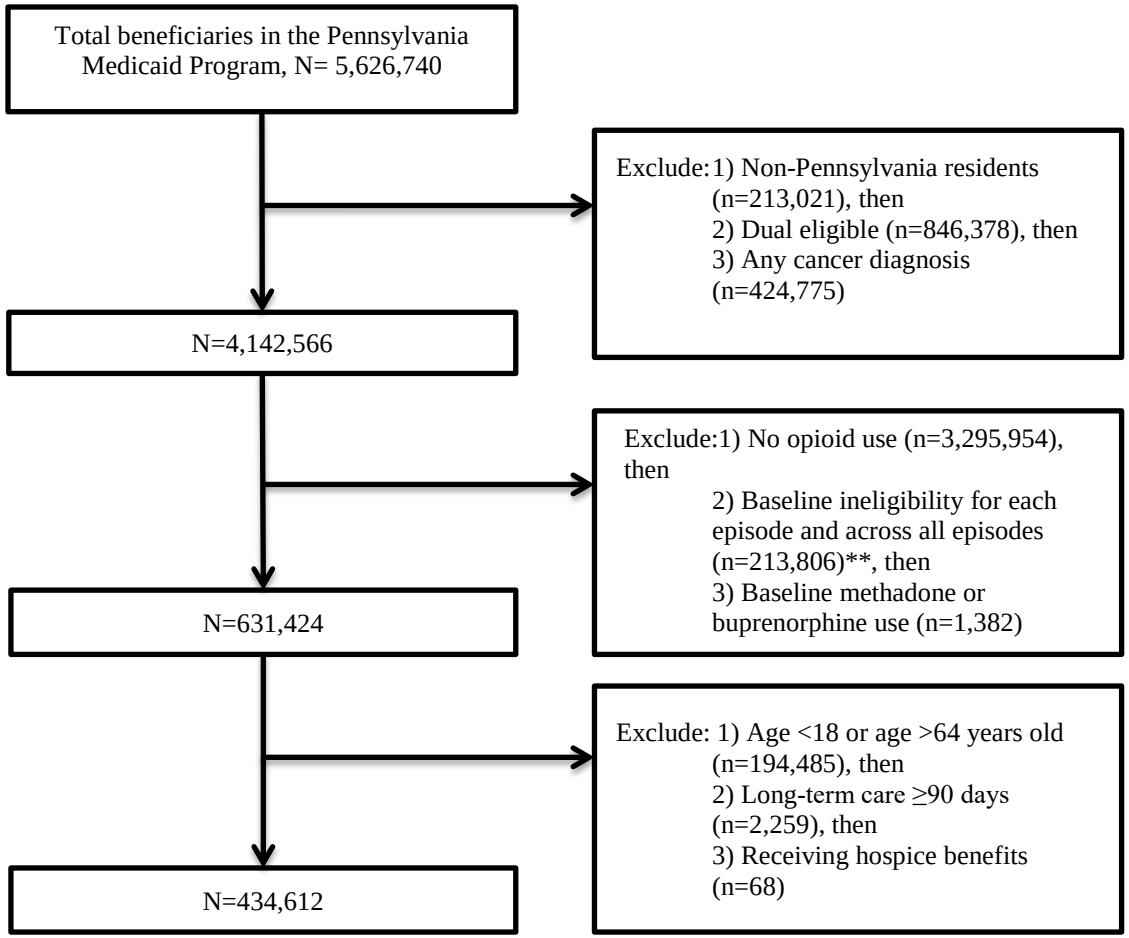


Figure A.3 Sample size flowchart from 2007-2012

APPENDIX B: TABLES AND FIGURES FOR CHAPTER THREE



**Enrollees meeting any three conditions given below for each episode are considered ineligible for that episode and excluded if such ineligibility exists across all episodes:

i) date of index opioid fill < 6 months from first date of enrollment;
ii) date of prescription or heroin overdose < 6 month of index opioid fill;
iii) date of opioid use disorder < 6 months of first date of opioid

Figure B.1 Cohort Selection Flow Chart, Pennsylvania Medicaid: 2007-2015

Table B.1 International Classification of Disease, 9th and 10th edition for opioid-use disorder and overdose

Opioid use disorder	
ICD-9	304.0, 304.00, 304.01, 304.02, 304.03, 304.7, 304.70, 304.71, 304.72, 304.73, 305.5, 305.50, 305.51, 305.52, 305.53
ICD-10	F1110, F11120, F11121, F11122, F11129, F1114, F11150, F11151, F11159, F11181, F11182, F11188, F1119, F1120, F1121, F11220, F11221, F11222, F11229, F1123, F1124, F11250, F11251, F11259, F11281, F11282, F11288, F1129, F1190, F11920, F11921, F11922, F11929, F1193, F1194, F11950, F11951, F11959, F11981, F11982, F11988, F1199
Overdose	
ICD-9	965.00,965.02, 965.09, E.850.1, E.850.2
ICD-10	T401X, T401X1, T401X1A, T401X1D, T401X1S, T401X3, T401X3A, T401X3D, T401X3S, T401X4, T401X4A, T401X4D, T401X4S, T400X1A, T400X3A, T400X4A, T402X1A, T402X1D T402X1S, T402X3A, T402X3D, T402X3S, T402X4A, T402X4D, T402X4S, T402X5A, T402X5D T402X5S, T403X1, T403X1A, T403X1D, T403X1S, T403X3A, T403X3D, T403X3S, T403X4A T403X4D, T403X4S, T403X5A, T403X5D, T403X5S, T404X1, T404X1A, T404X1D, T404X1S T404X3A, T404X3D, T404X3S, T404X4A, T404X4D, T404X4S, T404X5A, T404X5D, T404X5S T40601A, T40603A, T40604A, T40691, T40691A, T40693A, T40694A.
ICD-9: International Classification of Diseases, 9th Revision ICD-10: International Classification of Diseases, 10th Revision	

Table B.2 Associations between prescribing specialty and opioid use disorder showing the adjusted rates for all covariates including prescribing specialty, demographic and enrollment variables, comorbid conditions, and use of other health services

	Index prescriber		*Dominant prescriber*	
Parameters	***Adjusted Rates***	***P***	***Adjusted Rates***	***P***
Dentistry	0.86 [0.82, 0.90]	<.0001	0.83 [0.80, 0.87]	<.0001
Emergency Medicine	1.02 [0.97, 1.07]	0.48	1.00 [0.96, 1.05]	0.91
Obstetrics/Gynecology	0.63 [0.59, 0.68]	<.0001	0.55 [0.51, 0.59]	<.0001
Pain medicine/Anesthesiology	1.53 [1.25, 1.88]	<.0001	1.31 [1.13, 1.52]	0.0004
Physical Medicine and Rehabilitation	1.33 [1.13, 1.57]	0.0006	1.20 [1.06, 1.36]	0.0031
Podiatry	0.75 [0.60, 0.94]	0.01	0.81 [0.68, 0.97]	0.02
Psychiatry	1.08 [0.90, 1.30]	0.41	1.16 [0.98, 1.38]	0.09
Surgery	0.74 [0.69, 0.80]	<.0001	0.76 [0.71, 0.81]	<.0001
Other	0.86 [0.79, 0.94]	0.0005	0.89 [0.82, 0.96]	0.0026
Combination of other specialties[a]	N/A		0.84 [0.77, 0.91]	<.0001
Combination of primary care and other specialty[b]	N/A		1.01 [0.94, 1.08]	0.77
Primary Care	Reference		Reference	
Demographics				
Female	0.60 [0.58, 0.62]	<.0001	0.61 [0.59, 0.63]	<.0001
Age at first episode, years	0.99 [0.99, 1.00]	<.0001	0.99 [0.99, 0.99]	<.0001
White	2.41 [2.31, 2.52]	<.0001	2.34 [2.25, 2.42]	<.0001
MCO	2.15 [1.95, 2.36]	<.0001	2.15 [1.97, 2.35]	<.0001
Urban	1.16 [1.11, 1.21]	<.0001	1.16 [1.12, 1.21]	<.0001
Eligibility Category (reference = Families with Children)				
Disabled/Chronically Ill	1.44 [1.38, 1.50]	<.0001	1.44 [1.39, 1.50]	<.0001
Expansion	3.02 [2.75, 3.32]	<.0001	3.10 [2.85, 3.36]	<.0001
Other	1.58 [1.48, 1.69]	<.0001	1.57 [1.48, 1.66]	<.0001
MME/day (reference <20)				
20-49.9	0.93 [0.88, 0.97]	0.0008	0.97 [0.94, 1.01]	0.17
50-99.9	0.97 [0.92, 1.03]	0.29	0.98 [0.93, 1.03]	0.37
≥100	1.12 [1.02, 1.22]	0.02	1.44 [1.34, 1.54]	<.0001
Comorbid conditions[c]				
Alcohol abuse/dependence	1.15 [1.08, 1.23]	<.0001	1.13 [1.07, 1.20]	<.0001
Non-opioid drug abuse/dependence	3.11 [2.97, 3.26]	<.0001	2.98 [2.85, 3.10]	<.0001
Adjustment disorders	0.81 [0.73, 0.90]	0.0001	0.83 [0.76, 0.92]	0.0001
Anxiety disorders	1.18 [1.13, 1.24]	<.0001	1.18 [1.13, 1.23]	<.0001

Table B.2 Continued				
Mood disorders	1.27 [1.22, 1.32]	<.0001	1.27 [1.22, 1.32]	<.0001
Miscellaneous mental health disorders	1.14 [1.05, 1.23]	0.0012	1.12 [1.04, 1.20]	0.0028
Back pain	1.20 [1.15, 1.26]	<.0001	1.19 [1.14, 1.23]	<.0001
Neck pain	0.94 [0.88, 1.01]	0.11	0.94 [0.88, 1.00]	0.04
HIV/AIDS	1.53 [1.31, 1.78]	<.0001	1.50 [1.31, 1.72]	<.0001
Arthritis/joint pain	0.92 [0.87, 0.96]	0.0002	0.91 [0.88, 0.95]	<.0001
Headache/migraine pain	0.91 [0.83, 0.99]	0.04	0.92 [0.84, 0.99]	0.04
Use of health services[d]				
Emergency Department visit	1.21 [1.16, 1.25]	<.0001	1.23 [1.19, 1.27]	<.0001
Buprenorphine Use	6.58 [6.15, 7.05]	<.0001	6.21 [5.84, 6.60]	<.0001
Benzodiazepine Use	1.44 [1.37, 1.51]	<.0001	1.41 [1.36, 1.48]	<.0001
Muscle Relaxant use	1.02 [0.95, 1.10]	0.54	1.03 [0.97, 1.09]	0.39
Elixhauser Index	0.88 [0.87, 0.90]	<.0001	0.89 [0.87, 0.90]	<.0001

Poisson distribution with log link function is used; Model is offset using the natural log of the days of follow-up to account for varying length of exposure to opioid treatment; AIDS= Acquired immune deficiency syndrome, MCO= Managed care organization, MME= Morphine milligram equivalents; [a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b]Refers to episodes where prescription claims from primary care and other non- primary care specialty are equal; [c,d] The comorbid conditions, Elixhauser index, and use of benzodiazepines and muscle relaxants, and emergency department visits were measured during the six-month baseline period.

Table B.3 Adjusted rates for associations between prescribing specialty and misuse showing the adjusted rates for all covariates including prescribing specialty, demographic and enrollment variables, comorbid conditions, and use of other health services

	Index prescriber		*Dominant prescriber*	
Parameters	***Adjusted Rates***	***P***	***Adjusted Rates***	***P***
Dentistry	0.39 [0.36, 0.41]	<.0001	0.26 [0.25, 0.28]	<.0001
Emergency Medicine	0.78 [0.74, 0.82]	<.0001	0.41 [0.39, 0.43]	<.0001
Obstetrics/Gynecology	0.46 [0.42, 0.50]	<.0001	0.15 [0.13, 0.17]	<.0001
Pain Medicine/Anesthesiology	1.62 [1.36, 1.92]	<.0001	1.86 [1.68, 2.07]	<.0001
Physical Medicine and Rehabilitation	1.61 [1.41, 1.84]	<.0001	1.66 [1.51, 1.81]	<.0001
Podiatry	0.76 [0.62, 0.93]	0.01	0.97 [0.85, 1.11]	0.69
Psychiatry	1.00 [0.81, 1.24]	0.99	0.76 [0.61, 0.94]	0.01
Surgery	0.66 [0.61, 0.71]	<.0001	0.67 [0.63, 0.71]	<.0001
Other	0.79 [0.72, 0.86]	<.0001	0.62 [0.57, 0.67]	<.0001
Combination of other specialties [a]	N/A		0.43 [0.39, 0.48]	<.0001
Combination of primary care and other specialty [b]	N/A		0.78 [0.73, 0.83]	<.0001
Primary Care	Reference			
Demographics				
Female	0.78 [0.75, 0.82]	<.0001	0.83 [0.80, 0.86]	<.0001
Age at first episode, years	1.02 [1.01, 1.02]	<.0001	1.01 [1.01, 1.01]	<.0001
White	1.45 [1.39, 1.52]	<.0001	1.35 [1.30, 1.40]	<.0001
MCO	1.34 [1.23, 1.46]	<.0001	1.13 [1.09, 1.17]	<.0001
Urban	1.12 [1.07, 1.18]	<.0001	1.14 [1.09, 1.19]	<.0001
Eligibility Category (reference = Families with Children)				
Disabled/Chronically Ill	1.38 [1.32,1.45]	<.0001	1.37 [1.31, 1.43]	<.0001
Expansion	3.11 [2.80,3.44]	<.0001	2.90 [2.64, 3.18]	<.0001
Other	1.51 [1.41,1.63]	<.0001	1.49 [1.40, 1.58]	<.0001
MME/day (reference <20)				
20-49.9	0.94 [0.90, 0.99]	0.02	1.31 [1.26, 1.37]	<.0001
50-99.9	0.96 [0.90, 1.03]	0.24	1.22 [1.16, 1.29]	<.0001
≥100	1.29 [1.17, 1.41]	<.0001	2.07 [1.93, 2.22]	<.0001
Comorbid conditions [c]				
Alcohol abuse/dependence	1.15 [1.06, 1.25]	0.001	1.12 [1.05, 1.20]	0.002
Non-opioid drug abuse/dependence	1.28 [1.20, 1.37]	<.0001	1.26 [1.19, 1.34]	<.0001
Adjustment disorders	0.96 [0.86, 1.08]	0.50	0.98 [0.89, 1.09]	0.73

Table B.3 continued				
Anxiety disorders	1.13 [1.07, 1.20]	<.0001	1.12 [1.07, 1.18]	<.0001
Mood disorders	1.13 [1.08, 1.18]	<.0001	1.10 [1.06, 1.15]	<.0001
Miscellaneous mental health disorders	1.15 [1.04, 1.26]	0.0039	1.15 [1.06, 1.25]	0.007
Back pain	1.57 [1.50, 1.64]	<.0001	1.43 [1.38, 1.49]	<.0001
Neck pain	1.01 [0.94, 1.08]	0.87	1.01 [0.95, 1.07]	0.86
HIV/AIDS	1.16 [0.96, 1.38]	0.12	1.07 [0.91, 1.25]	0.43
Arthritis/joint pain	1.12 [1.07, 1.17]	<.0001	1.06 [1.02, 1.11]	0.002
Headache/migraine pain	1.26 [1.15, 1.37]	<.0001	1.18 [1.10, 1.28]	<.0001
Use of health services [d]				
Baseline ED visit	1.27 [1.22, 1.33]	<.0001	1.37 [1.32, 1.42]	<.0001
Buprenorphine Use	1.82 [1.69, 1.96]	<.0001	1.66 [1.56, 1.77]	<.0001
Baseline Benzodiazepine Use	1.37 [1.30, 1.45]	<.0001	1.30 [1.25, 1.37]	<.0001
Baseline Muscle Relaxant use	1.15 [1.08, 1.23]	<.0001	1.14 [1.08, 1.20]	<.0001
Elixhauser Index	0.97 [0.95, 0.99]	0.001	0.96 [0.95, 0.98]	<.0001

Poisson distribution with log link function is used; Model is offset using the natural log of the days of follow-up to account for varying length of exposure to opioid treatment; AIDS= Acquired immune deficiency syndrome, MCO= Managed care organization, MME= Morphine milligram equivalents; [a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b]Refers to episodes where prescription claims from primary care and other non- primary care specialty are equal; [c,d] The comorbid conditions, Elixhauser index, and use of benzodiazepines and muscle relaxants, and emergency department visits were measured during the six-month baseline period.

Table B.4 Adjusted rates for associations between prescribing specialty and overdose showing the adjusted rates for all covariates including prescribing specialty, demographic and enrollment variables, comorbid conditions, and use of other health services

	Index prescriber		*Dominant prescriber*	
Parameters	***Adjusted Rates***	***P***	***Adjusted Rates***	***P***
Dentistry	0.66 [0.53, 0.82]	0.0002	0.59 [0.48, 0.73]	<.0001
Emergency Medicine	0.74 [0.59, 0.91]	0.0049	0.62 [0.50, 0.77]	<.0001
Obstetrics/Gynecology	0.37 [0.25, 0.55]	<.0001	0.31 [0.20, 0.47]	<.0001
Pain medicine/Anesthesiology	2.12 [1.08, 4.14]	0.03	1.04 [0.57, 1.90]	0.90
Physical Medicine and Rehabilitation	1.84 [1.07, 3.19]	0.03	1.31 [0.84, 2.05]	0.23
Podiatry	0.94 [0.38, 2.29]	0.89	0.63 [0.28, 1.42]	0.26
Psychiatry	1.48 [0.76, 2.89]	0.25	1.19 [0.59, 2.40]	0.63
Surgery	0.64 [0.45, 0.90]	0.01	0.59 [0.44, 0.80]	0.001
Other	1.16 [0.84, 1.61]	0.36	0.85 [0.61, 1.19]	0.35
Combination of other specialties[a]	N/A		0.70 [0.48, 1.02]	0.06
Combination of primary care and other specialty[b]	N/A		0.93 [0.69, 1.25]	0.64
Primary Care	Reference		Reference	
Demographics				
Female	0.67 [0.56, 0.79]	<.0001	0.66 [0.57, 0.77]	<.0001
Age at first episode, years	1.00 [0.99, 1.00]	0.27	0.99 [0.99, 1.00]	0.13
White	2.39 [1.96, 2.91]	<.0001	2.24 [1.88, 2.66]	<.0001
MCO	1.49 [1.03, 2.14]	0.03	1.52 [1.07, 2.15]	0.02
Urban	1.18 [0.97, 1.44]	0.10	1.19 [0.99, 1.43]	0.07
Eligibility Category (reference = Families with Children)				
Disabled/Chronically Ill	1.32 [1.09, 1.61]	0.01	1.36 [1.14, 1.62]	0.0005
Expansion	2.26 [1.39, 3.67]	0.001	2.42 [1.59, 3.69]	<.0001
Other	1.86 [1.43, 2.44]	<.0001	1.76 [1.38, 2.25]	<.0001
MME/day (reference <20)			1.36 [1.14, 1.62]	0.0005
20-49.9	0.94 [0.76, 1.16]	0.54	1.12 [0.94, 1.35]	0.21
50-99.9	1.19 [0.92, 1.53]	0.19	1.34 [1.06, 1.68]	0.01
≥100	1.67 [1.18, 2.39]	0.0043	2.21 [1.65, 2.95]	<.0001
Comorbid conditions[c]				
Alcohol abuse/dependence	1.60 [1.22, 2.10]	0.0007	1.61 [1.26, 2.05]	0.0001
Non-opioid drug abuse/dependence	2.00 [1.58, 2.52]	<.0001	2.00 [1.63, 2.46]	<.0001

Table B.4 continued				
Adjustment disorders	1.44 [1.00, 2.06]	0.05	1.33 [0.95, 1.87]	0.10
Anxiety disorders	1.26 [1.02, 1.55]	0.03	1.34 [1.12, 1.62]	0.0018
Mood disorders	1.42 [1.18, 1.71]	0.0002	1.32 [1.12, 1.55]	0.0011
Miscellaneous mental health disorders	0.67 [0.43, 1.06]	0.09	0.66 [0.44, 0.99]	0.05
Back pain	1.64 [1.36, 1.99]	<.0001	1.52 [1.29, 1.80]	<.0001
Neck pain	1.03 [0.77, 1.37]	0.87	1.06 [0.83, 1.36]	0.64
HIV/AIDS	0.85 [0.35, 2.07]	0.73	0.90 [0.43, 1.91]	0.79
Arthritis/joint pain	0.88 [0.72, 1.08]	0.21	0.93 [0.78, 1.11]	0.44
Headache/migraine pain	0.83 [0.54, 1.27]	0.39	0.85 [0.59, 1.23]	0.39
Use of health services[d]				
Emergency Department visit	1.43[1.20, 1.71]	<.0001	1.42 [1.21, 1.65]	<.0001
Buprenorphine Use	1.61[1.22, 2.12]	0.0007	1.53 [1.20, 1.96]	0.0006
Benzodiazepine Use	1.69[1.38, 2.08]	<.0001	1.61 [1.34, 1.93]	<.0001
Muscle Relaxant use	0.99[0.74, 1.32]	0.93	1.15 [0.90, 1.46]	0.25
Elixhauser Index	0.98[0.92, 1.06]	0.64	0.98 [0.92, 1.05]	0.57

Poisson distribution with log link function is used; Model is offset using the natural log of the days of follow-up to account for varying length of exposure to opioid treatment; AIDS= Acquired immune deficiency syndrome, ARR = Adjusted Rate Ratio, MCO= Managed care organization, MME= Morphine milligram equivalents; [a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b]Refers to episodes where prescription claims from primary care and other non- primary care specialty are equal; [c,d] The comorbid conditions, Elixhauser index, and use of benzodiazepines and muscle relaxants, and emergency department visits were measured during the six-month baseline period.

Table B.5 Distribution of prescriber specialties for index opioid prescription– results from imputed datasets

	Imputation 1		Imputation 2		Imputation 3		Imputation 4		Imputation 5	
Dentistry	116910	26.9	116709	26.85	116851	26.89	116619	26.83	116868	26.89
Emergency Medicine	87217	20.07	87307	20.09	87251	20.08	87134	20.05	87158	20.05
Obstetrics/Gynecology	46602	10.72	46519	10.7	46596	10.72	46659	10.74	46532	10.71
Pain Medicine/Anesthesiology	2834	0.65	2866	0.66	2805	0.65	2885	0.66	2854	0.66
Physical Medicine and Rehabilitation	4232	0.97	4253	0.98	4295	0.99	4347	1.00	4278	0.98
Primary Care	121727	28.01	121863	28.04	121699	28.00	121645	27.99	121746	28.01
Podiatry	4097	0.94	4057	0.93	4048	0.93	4069	0.94	4049	0.93
Psychiatry	1692	0.39	1672	0.38	1649	0.38	1659	0.38	1738	0.4
Surgery	28859	6.64	28857	6.64	28884	6.65	29043	6.68	28840	6.64
Others	20442	4.7	20509	4.72	20534	4.72	20552	4.73	20549	4.73

Table B.6 Distribution of dominant provider specialties in an episode – results from imputed datasets

	Imputation 1		Imputation 2		Imputation 3		Imputation 4		Imputation 5	
Dentistry	105944	24.38	105757	24.33	105968	24.38	105688	24.32	105955	24.38
Emergency Medicine	65775	15.13	65873	15.16	65742	15.13	65712	15.12	65727	15.12
Obstetrics/Gynecology	58486	13.46	58477	13.45	58515	13.46	58625	13.49	58528	13.47
Pain Medicine/Anesthesiology	2180	0.5	2243	0.52	2204	0.51	2205	0.51	2130	0.49
Primary Care	110559	25.43	110515	25.43	110541	25.44	110491	25.4	110347	25.4
Physical Medicine and Rehabilitation	3304	0.76	3268	0.75	3302	0.76	3325	0.77	3350	0.77
Podiatry	3561	0.82	3564	0.82	3563	0.82	3555	0.82	3511	0.81
Psychiatry	1248	0.29	1237	0.28	1185	0.27	1239	0.29	1275	0.29
Other	15941	3.67	16059	3.7	16107	3.71	16031	3.69	16015	3.68
Surgery	25194	5.8	25198	5.8	25135	5.78	25326	5.83	25213	5.8
Combination of other specialties [a]	16323	3.76	16291	3.75	16342	3.76	16285	3.75	16350	3.76
Combination of primary care and other specialty [b]	26097	6.0	26130	6.01	26008	5.98	26130	6.01	26211	6.03

[a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b] Refers to episodes where prescription claims from primary care and other non- primary care specialty are equal

Table B.7 Adjusted rates for associations between prescribing specialty and opioid use disorder – results from imputed models

	Index prescriber		*Dominant prescriber*	
Parameters	***Adjusted Rates***	***P***	***Adjusted Rates***	***P***
Dentistry	0.91 [0.83, 0.99]	0.03	0.85 [0.81, 0.90]	<.0001
Emergency Medicine	0.94 [0.85, 1.03]	0.19	1.00 [0.95, 1.05]	0.88
Obstetrics/Gynecology	0.68 [0.57, 0.80]	<.0001	0.83 [0.78, 0.88]	<.0001
Pain medicine/Anesthesiology	1.54 [1.20, 1.97]	0.0007	1.38 [1.19, 1.60]	<.0001
Physical Medicine and Rehabilitation	1.25 [1.00, 1.57]	0.05	1.16 [1.01, 1.33]	0.03
Podiatry	0.95 [0.69, 1.31]	0.76	0.85 [0.71, 1.01]	0.07
Psychiatry	1.31 [0.91, 1.88]	0.14	1.17 [0.97, 1.42]	0.10
Surgery	0.80 [0.68, 0.94]	0.01	0.75 [0.70, 0.80]	<.0001
Other	0.96 [0.82, 1.11]	0.56	0.88 [0.80, 0.96]	0.003
Combination of other specialties[a]	N/A		0.90 [0.83, 0.98]	0.01
Combination of primary care and other specialty[b]	N/A		1.04 [0.98, 1.11]	0.16
Primary Care	Reference		Reference	
Demographics				
Female	0.63 [0.59, 0.67]	<.0001	0.59 [0.58, 0.61]	<.0001
Age at first episode, years	0.99 [0.99, 1.00]	<.0001	0.99 [0.99, 1.00]	<.0001
White	1.88 [1.76, 2.01]	<.0001	2.43 [2.35, 2.52]	<.0001
MCO	1.02 [0.89, 1.18]	0.76	2.15 [1.97, 2.34]	<.0001
Urban	1.37 [1.24, 1.50]	<.0001	1.14 [1.10, 1.19]	<.0001
Eligibility Category (reference = Families with Children)				
Disabled/Chronically Ill	1.65 [1.53, 1.78]	<.0001	1.50 [1.45, 1.55]	<.0001
Expansion	3.72 [3.10, 4.46]	<.0001	3.21 [2.98, 3.45]	<.0001
Other	1.90 [1.69, 2.14]	<.0001	1.56 [1.48, 1.65]	<.0001
MME/day (reference <20)				
20-49.9	0.98 [0.90, 1.06]	0.59	0.96 [0.92, 0.99]	0.02
50-99.9	0.97 [0.87, 1.08]	0.54	0.93 [0.89, 0.98]	0.003
≥100	1.13 [0.96, 1.34]	0.14	1.41 [1.32, 1.51]	<.0001
Comorbid conditions[c]				
Alcohol abuse/dependence	1.07 [0.96, 1.19]	0.22	1.12 [1.06, 1.18]	<.0001
Non-opioid drug abuse/dependence	3.30 [3.05, 3.58]	<.0001	3.10 [2.99, 3.22]	<.0001
Adjustment disorders	0.85 [0.70, 1.04]	0.11	0.84 [0.77, 0.91]	<.0001
Anxiety disorders	1.11 [1.02, 1.21]	0.02	1.17 [1.13, 1.22]	<.0001

Table B.7 continued				
Mood disorders	1.26 [1.17, 1.35]	<.0001	1.28 [1.24, 1.33]	<.0001
Miscellaneous mental health disorders	1.26 [1.08, 1.46]	0.003	1.08 [1.01, 1.15]	0.03
Back pain	1.14 [1.05, 1.24]	0.002	1.19 [1.14, 1.23]	<.0001
Neck pain	0.91 [0.80, 1.03]	0.14	0.93 [0.88, 0.99]	0.02
HIV/AIDS	1.55 [1.26, 1.90]	<.0001	1.53 [1.35, 1.72]	<.0001
Arthritis/joint pain	0.96 [0.88, 1.04]	0.27	0.92 [0.89, 0.96]	<.0001
Headache/migraine pain	0.97 [0.82, 1.15]	0.73	0.91 [0.84, 0.98]	0.02
Use of health services [d]				
Emergency Department visit	1.23 [1.14, 1.32]	<.0001	1.26 [1.22, 1.30]	<.0001
Buprenorphine Use	6.31 [5.53, 7.19]	<.0001	6.34 [5.99, 6.72]	<.0001
Benzodiazepine Use	1.46 [1.35, 1.59]	<.0001	1.45 [1.40, 1.51]	<.0001
Muscle Relaxant use	1.02 [0.91, 1.15]	0.72	1.05 [0.99, 1.11]	0.12
Elixhauser Index	0.89 [0.87, 0.92]	<.0001	0.89 [0.87, 0.90]	<.0001

Poisson distribution with log link function is used; Model is offset using the natural log of the days of follow-up to account for varying length of exposure to opioid treatment; AIDS= Acquired immune deficiency syndrome, MCO= Managed care organization, MME= Morphine milligram equivalents; [a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b]Refers to episodes where prescription claims from primary care and other non- primary care specialty are equal; [c,d] The comorbid conditions, Elixhauser index, and use of benzodiazepines and muscle relaxants, and emergency department visits were measured during the six-month baseline period.

Table B.8 Adjusted rates for associations between prescribing specialty and misuse - results from imputed models

	Index prescriber		*Dominant prescriber*	
Parameter	***Adjusted Rates***	***P***	***Adjusted Rates***	***P***
Dentistry	0.38 [0.33, 0.43]	<.0001	0.22 [0.21, 0.24]	<.0001
Emergency Medicine	0.69 [0.63, 0.76]	<.0001	0.34 [0.32, 0.36]	<.0001
Obstetrics/Gynecology	0.37 [0.31, 0.45]	<.0001	1.19 [1.14, 1.25]	<.0001
Pain Medicine/Anesthesiology	1.48 [1.10, 1.98]	0.01	1.79 [1.59, 2.01]	<.0001
Physical Medicine and Rehabilitation	1.54 [1.24, 1.92]	0.0001	1.49 [1.34, 1.65]	<.0001
Podiatry	1.06 [0.77, 1.47]	0.71	0.91 [0.78, 1.05]	0.20
Psychiatry	1.42 [1.02, 1.97]	0.04	0.63 [0.50, 0.81]	0.00
Surgery	0.69 [0.60, 0.80]	<.0001	0.60 [0.56, 0.65]	<.0001
Other	0.80 [0.67, 0.95]	0.01	0.55 [0.51, 0.61]	<.0001
Combination of other specialties [a]	N/A		0.24 [0.20, 0.28]	<.0001
Combination of primary care and other specialty [b]	N/A		0.47 [0.43, 0.51]	<.0001
Primary Care	Reference			
Demographics				
Female	0.81 [0.76, 0.87]	<.0001	0.69 [0.66, 0.71]	<.0001
Age at first episode, years	1.01 [1.00, 1.01]	0.01	1.01 [1.01, 1.02]	<.0001
White	1.18 [1.10, 1.26]	<.0001	1.37 [1.32, 1.42]	<.0001
MCO	1.03 [0.78, 1.34]	0.84	1.47 [1.36, 1.58]	<.0001
Urban	1.32 [1.19, 1.45]	<.0001	1.15 [1.11, 1.20]	<.0001
Eligibility Category (reference = Families with Children)				
Disabled/Chronically Ill	1.54 [1.41, 1.67]	<.0001	1.51 [1.45, 1.57]	<.0001
Expansion	3.65 [2.99, 4.45]	<.0001	3.17 [2.90, 3.47]	<.0001
Other	1.77 [1.56, 2.01]	<.0001	1.65 [1.56, 1.75]	<.0001
MME/day (reference <20)				
20-49.9	0.97 [0.89, 1.06]	0.55	1.25 [1.20, 1.30]	<.0001
50-99.9	1.01 [0.90, 1.12]	0.90	1.10 [1.05, 1.16]	0.0002
≥100	1.30 [1.11, 1.52]	0.0014	2.04 [1.91, 2.17]	<.0001
Comorbid conditions [c]				
Alcohol abuse/dependence	0.95 [0.83, 1.10]	0.51	1.11 [1.04, 1.19]	0.0014
Non-opioid drug abuse/dependence	1.26 [1.13, 1.41]	<.0001	1.26 [1.19, 1.33]	<.0001
Adjustment disorders	0.89 [0.71, 1.11]	0.29	1.01 [0.92, 1.11]	0.84
Anxiety disorders	1.13 [1.03, 1.25]	0.01	1.14 [1.09, 1.20]	<.0001
Mood disorders	1.08 [0.99, 1.17]	0.07	1.13 [1.08, 1.17]	<.0001

Table B.8 continued				
Miscellaneous mental health disorders	1.05 [0.88, 1.26]	0.59	0.87 [0.81, 0.95]	0.0007
Back pain	1.46 [1.35, 1.58]	<.0001	1.46 [1.41, 1.52]	<.0001
Neck pain	1.01 [0.90, 1.14]	0.84	1.04 [0.98, 1.10]	0.17
HIV/AIDS	1.20 [0.94, 1.54]	0.14	1.09 [0.93, 1.26]	0.28
Arthritis/joint pain	1.13 [1.04, 1.22]	0.003	1.11 [1.07, 1.16]	<.0001
Headache/migraine pain	1.19 [1.02, 1.39]	0.03	1.27 [1.19, 1.37]	<.0001
Use of health services [d]				
Emergency Department visit	1.18 [1.10, 1.28]	<.0001	1.51 [1.46, 1.56]	<.0001
Buprenorphine Use	1.72 [1.50, 1.97]	<.0001	1.78 [1.68, 1.88]	<.0001
Benzodiazepine Use	1.34 [1.23, 1.47]	<.0001	1.34 [1.28, 1.40]	<.0001
Muscle Relaxant use	1.25 [1.12, 1.39]	<.0001	1.16 [1.10, 1.22]	<.0001
Elixhauser Index	0.98 [0.95, 1.00]	0.10	0.95 [0.93, 0.96]	<.0001

Poisson distribution with log link function is used; Model is offset using the natural log of the days of follow-up to account for varying length of exposure to opioid treatment; AIDS= Acquired immune deficiency syndrome, MCO= Managed care organization, MME= Morphine milligram equivalents; [a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b] Refers to episodes where prescription claims from primary care and other non- primary care specialty are equal; [c,d] The comorbid conditions, Elixhauser index, and use of benzodiazepines and muscle relaxants, and emergency department visits were measured during the six-month baseline period.

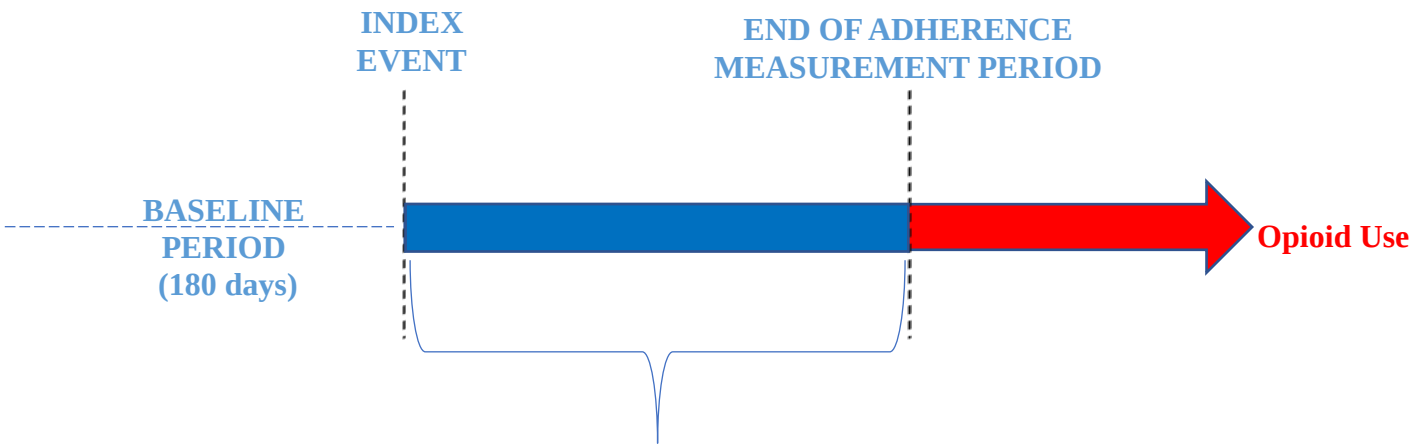
Table B.9 Adjusted rates for associations between prescribing specialty and overdose - results from imputed models

	Index prescriber		*Dominant prescriber*	
Parameter	***Adjusted Rates***	***P***	***Adjusted Rates***	***P***
Dentistry	0.66 [0.40, 1.10]	0.11	0.58 [0.47, 0.71]	<.0001
Emergency Medicine	0.83 [0.55, 1.27]	0.39	0.64 [0.51, 0.79]	<.0001
Obstetrics/Gynecology	0.11 [0.01, 1.11]	0.06	0.60 [0.46, 0.78]	0.0001
Pain Medicine/Anesthesiology	2.49 [1.05, 5.87]	0.04	1.01 [0.52, 1.96]	0.98
Physical Medicine and Rehabilitation	0.62 [0.13, 2.85]	0.52	1.13 [0.71, 1.78]	0.61
Podiatry	0.91 [0.22, 3.85]	0.90	0.46 [0.17, 1.21]	0.12
Psychiatry	1.79 [0.60, 5.36]	0.29	0.89 [0.37, 2.13]	0.79
Surgery	0.42 [0.17, 1.04]	0.06	0.52 [0.35, 0.76]	0.001
Other	1.19 [0.55, 2.61]	0.65	0.84 [0.58, 1.24]	0.38
Combination of other specialties [b]	N/A		0.65 [0.43, 0.99]	0.05
Combination of primary care and other specialty[a]	N/A		0.77 [0.54, 1.11]	0.16
Primary Care	Reference		Reference	
Demographics				
Female	0.72 [0.54, 0.98]	0.03	0.66 [0.57, 0.75]	<.0001
Age at first episode, years	1.00 [0.98, 1.01]	0.65	1.00 [0.99, 1.00]	0.17
White	3.09 [2.19, 4.38]	<.0001	2.27 [1.94, 2.67]	<.0001
MCO	0.99 [0.43, 2.29]	0.98	1.46 [1.05, 2.04]	0.03
Urban	1.05 [0.72, 1.53]	0.80	1.14 [0.95, 1.35]	0.15
Eligibility Category (reference = Families with Children)				
Disabled/Chronically Ill	1.41 [0.99, 2.01]	0.06	1.38 [1.18, 1.63]	<.0001
Expansion	2.20 [0.79, 6.12]	0.13	2.60 [1.78, 3.80]	<.0001
Other	2.16 [1.32, 3.53]	0.002	1.74 [1.38, 2.19]	<.0001
MME/day (reference <20)				
20-49.9	1.23 [0.81, 1.86]	0.33	1.07 [0.90, 1.26]	0.45
50-99.9	1.58 [0.96, 2.58]	0.07	1.28 [1.03, 1.58]	0.02
≥100	2.67 [1.44, 4.93]	0.0018	2.15 [1.64, 2.83]	<.0001
Comorbid conditions [c]				
Alcohol abuse/dependence	1.74 [1.12, 2.72]	0.01	1.52 [1.21, 1.91]	0.0004
Non-opioid drug abuse/dependence	2.25 [1.52, 3.32]	<.0001	2.07 [1.70, 2.51]	<.0001
Adjustment disorders	0.69 [0.28, 1.69]	0.41	1.26 [0.91, 1.74]	0.17
Anxiety disorders	1.35 [0.93, 1.94]	0.11	1.36 [1.14, 1.62]	0.0006
Mood disorders	1.44 [1.04, 2.00]	0.03	1.33 [1.14, 1.56]	0.0003
Miscellaneous mental health disorders	1.01 [0.47, 2.17]	0.98	0.65 [0.44, 0.95]	0.03

Table B.9 continued				
Back pain	1.34 [0.95, 1.89]	0.10	1.50 [1.28, 1.76]	<.0001
Neck pain	0.98 [0.59, 1.63]	0.94	1.10 [0.87, 1.40]	0.41
HIV/AIDS	0.36 [0.05, 2.62]	0.32	0.77 [0.36, 1.62]	0.49
Arthritis/joint pain	0.87 [0.61, 1.25]	0.46	1.01 [0.86, 1.19]	0.90
Headache/migraine pain	0.44 [0.16, 1.20]	0.11	0.84 [0.59, 1.20]	0.34
Use of health services [d]				
Emergency Department visit	1.30 [0.93, 1.81]	0.13	1.37 [1.18, 1.58]	<.0001
Buprenorphine Use	1.83 [1.13, 2.96]	0.01	1.62 [1.28, 2.04]	<.0001
Benzodiazepine Use	1.70 [1.20, 2.41]	0.0029	1.68 [1.41, 1.99]	<.0001
Muscle Relaxant use	2.12 [1.42, 3.16]	0.003	1.22 [0.97, 1.52]	0.09
Elixhauser Index	1.00 [0.90, 1.13]	0.94	0.98 [0.93, 1.04]	0.55

Poisson distribution with log link function is used; Model is offset using the natural log of the days of follow-up to account for varying length of exposure to opioid treatment; AIDS= Acquired immune deficiency syndrome, MCO= Managed care organization, MME= Morphine milligram equivalents; [a] Refers to episodes where more than one non-primary care specialty has equal prescription claims; [b] Refers to episodes where prescription claims from primary care and other non- primary care specialty are equal; [c,d] The comorbid conditions, Elixhauser index, and use of benzodiazepines and muscle relaxants, and emergency department visits were measured during the six-month baseline period.

APPENDIX C: TABLES AND FIGURES FOR CHAPTER FOUR



Note: i) Baseline period and adherence measurement period require continuous enrollment for at least 15 days for six consecutive months, ii) The blue-colored bar represents the adherence measurement period of 180 days. Enrollees with any opioid use during this period were excluded. The red-colored region represents period during which opioid use was measured

Figure C.1 Establishment of study cohort

Table C.1 Results of Cox proportional hazards models for individuals with major depressive disorder and anxiety – Exploring effect of 80% PDC threshold at one-year follow up

	MD		Anxiety	
Censoring at one-year after end of adherence measurement period				
Models	**No cancer**	**Cancer**	**No cancer**	**Cancer**
Adherence (Ref= PDC <80%)	0.92 (0.84, 1.00)	1.01 (0.90, 1.13)	**0.91 (0.81, 1.01)**	**0.90 (0.78, 1.05)**
Adherence + Demographic	0.93 (0.85, 1.01)	1.03 (0.92, 1.16)	**0.91 (0.82, 1.02)**	**0.90 (0.77, 1.05)**
Adherence + Demographic + Enrollment	0.94 (0.86, 1.04)	1.03 (0.91, 1.16)	**0.94 (0.84, 1.05)**	**0.90 (0.77, 1.05)**
Adherence + Demographic + Enrollment + Comorbid mental health and pain	0.97 (0.88, 1.07)	1.06 (0.94, 1.20)	**0.97 (0.87, 1.09)**	**0.93 (0.79, 1.08)**

Demographic covariates = Age in years, Gender, Race (White, Black or Other), Place of residence (Urban/Rural); Enrollment covariates= MCO/FFS, Eligibility categories (Disabled/Chronically Ill, Expansion, Families with Children, Others); Comorbid mental health conditions = alcohol and substance abuse disorders, adjustment disorders, other mental health conditions; Comorbid pain conditions = back pain, neck pain, arthritis/joint pain, headache/migraine; MDD = Major Depressive Disorder; PDC=Proportion of days covered; Bold refers to non-violation of proportional hazards assumption; * = $p<0.05$

Table C.2 Results of Cox proportional hazards models for individuals with major depressive disorder and anxiety – Exploring effect of multiple definitions of PDC and censoring at one-year after end of adherence measurement period

	MDD		Anxiety	
	No cancer	**Cancer**	**No cancer**	**Cancer**
Adherence variables only				
20% ≤ PDC <40%	**0.76 (0.66, 0.88)** *	**0.92 (0.75, 1.12)**	**0.85 (0.71, 1.02)**	**0.87 (0.68, 1.11)**
40% ≤ PDC <60%	**0.84 (0.72, 0.97)** *	**0.96 (0.78, 1.18)**	**0.77 (0.63, 0.94)***	**0.87 (0.67, 1.13)**
60% ≤ PDC <80%	0.77 (0.66, 0.90) *	**1.01 (0.82, 1.25)**	**0.84 (0.71, 1.05)**	0.95 (0.73, 1.23)
PDC ≥80%	0.76 (0.67, 0.87) **	**0.98 (0.82, 1.17)**	**0.78 (0.67, 0.92)***	0.83 (0.67, 1.02)
PDC<20%	Reference	Reference	Reference	Reference
Adherence + Demographic variables				
20% ≤ PDC <40%	**0.78 (0.67, 0.90) ***	**0.91 (0.75, 1.11)**	**0.87 (0.73, 1.04)**	**0.87 (0.68, 1.11)**
40% ≤ PDC <60%	**0.85 (0.73, 0.99) ***	**0.96 (0.78, 1.18)**	**0.79 (0.65, 0.96)***	**0.87 (0.67, 1.13)**
60% ≤ PDC <80%	0.79 (0.67, 0.92) *	**1.02 (0.83, 1.26)**	**0.88 (0.73, 1.07)**	0.95 (0.73, 1.23)
PDC ≥80%	0.77 (0.68, 0.89) *	**1.00 (0.84, 1.20)**	**0.80 (0.68, 0.95)***	0.82 (0.66, 1.02)
PDC<20%	Reference	Reference	Reference	Reference
Adherence + Demographic + Enrollment variables				
20% ≤ PDC <40%	**0.79 (0.69, 0.92) ****	**0.92 (0.75, 1.12)**	**0.89 (0.74, 1.06)**	**0.87 (0.68, 1.11)**
40% ≤ PDC <60%	**0.87 (0.75, 1.00)**	**0.96 (0.78, 1.18)**	**0.82 (0.67, 0.99)***	**0.87 (0.67, 1.14)**
60% ≤ PDC <80%	0.81 (0.69, 0.94) *	**1.03 (0.83, 1.27)**	**0.91 (0.75, 1.11)**	**0.95 (0.74, 1.24)**
PDC ≥80%	0.81 (0.71, 0.92) *	**1.00 (0.84, 1.20)**	**0.84 (0.72, 0.99)***	**0.83 (0.67, 1.03)**
PDC<20%	Reference	Reference	Reference	Reference
Adherent + Demographic + Enrollment + Comorbid mental health and pain				
20% ≤ PDC <40%	**0.86 (0.74, 0.99) ***	**0.93 (0.76,1.14)**	**0.99 (0.83, 1.19)**	**0.89 (0.69, 1.14)**
40% ≤ PDC <60%	**0.90 (0.78, 1.05)**	**0.97 (0.79, 1.20)**	**0.84 (0.69, 1.02)**	**0.89 (0.68, 1.15)**
60% ≤ PDC <80%	**0.91 (0.77, 1.06)**	**1.05 (0.85, 1.30)**	**0.99 (0.82, 1.23)**	**0.96 (0.74, 1.25)**
PDC ≥80%	0.88 (0.77, 1.01)	**1.04 (0.87, 1.25)**	**0.93 (0.79, 1.10)**	**0.86 (0.69, 1.08)**
PDC<20%	Reference	Reference	Reference	Reference

Demographic covariates = Age in years, Gender, Race (White, Black or Other), Place of residence (Urban/Rural); Enrollment covariates= MCO/FFS, Eligibility categories (Disabled/Chronically Ill, Expansion, Families with Children, Others); Comorbid mental health conditions = alcohol and substance abuse disorders, adjustment disorders, other mental health conditions; Comorbid pain conditions = back pain, neck pain, arthritis/joint pain, headache/migraine; MDD = Major Depressive Disorder; PDC=Proportion of days covered; Bold refers to non-violation of proportional hazards assumption; * = $p<0.05$

Table C.3 The International Classification of Diseases, Ninth Revision, Clinical Modification codes for major depressive disorders and anxiety

Type of disorder	ICD 9 codes
Major Depressive Disorders	296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 300.4, 311, V79.0
Anxiety Disorders	293.84, 300.00, 300.01, 300.02, 300.09, 300.10, 300.20, 300.21, 300.22, 300.23, 300.29, 300.3, 300.5, 300.89, 300.9, 308.0, 308.1, 308.2, 308.3, 308.4, 308.9, 309.81, 313.0, 313.1, 313.21, 313.22, 313.3, 313.82, 313.83
Source: https://www.ccwdata.org/web/guest/condition-categories	

Table C.4 The International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification codes for mental illness diagnoses that were excluded from the analysis

Type of disorder	ICD 9	ICD 10
Alzheimer's	331.0, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.20, 294.21, 294.8, 797	F01.50, F01.51, F02.80, F02.81, F03.90, F03.91, F04, G13.2, G13.8, F05, F06.1, F06.8, G30.0, G30.1, G30.8, G30.9, G31.1, G31.2, G31.01, G31.09, G91.4, G94, R41.81, R54
Schizophrenia and other psychotic disorders	293.81, 293.82, 295.00, 295.01, 295.02, 295.03, 295.04, 295.05, 295.10, 295.11, 295.12, 295.13, 295.14, 295.15, 295.20, 295.21, 295.22, 295.23, 295.24, 295.25, 295.30, 295.31, 295.32, 295.33, 295.34, 295.35, 295.40, 295.41, 295.42, 295.43, 295.44, 295.45, 295.50, 295.51, 295.52, 295.53, 295.54, 295.55, 295.60, 295.61, 295.62, 295.63, 295.64, 295.65, 295.70, 295.71, 295.72, 295.73, 295.74, 295.75, 295.80, 295.81, 295.82, 295.83, 295.84, 295.85, 295.90, 295.91, 295.92, 295.93, 295.94, 295.95, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298.0, 298.1, 298.2, 298.3, 298.4, 298.8, 298.9	F06.0, F06.2, F20.0, F20.1, F20.2, F20.3, F20.5, F20.81, F20.89, F20.9, F22, F23, F24, F25.0, F25.1, F25.8, F25.9, F28, F29, F32.3, F33.3, F44.89
Bipolar	296.00, 296.01, 296.02, 296.03, 296.04, 296.05, 296.06, 296.10, 296.11, 296.12, 296.13, 296.14, 296.15, 296.16, 296.40, 296.41, 296.42, 296.43, 296.44, 296.45, 296.46, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.7, 296.80, 296.81, 296.82, 296.89, 296.90, 296.99	F30.10, F30.11, F30.12, F30.13, F30.2, F30.3, F30.4, F30.8, F30.9, F31.0, F31.10, F31.11, F31.12, F31.13, F31.2, F31.30, F31.31, F31.32, F31.4, F31.5, F31.60, F31.61, F31.62, F31.63, F31.64, F31.70, F31.71, F31.72, F31.73, F31.74, F31.75, F31.76, F31.77, F31.78, F31.81, F31.89, F31.9, F32.8, F33.8, F34.8, F34.9, F39
Dementia	292.82, 294.8	
Parkinsons	331.82	G20.x
Source: https://www.ccwdata.org/web/guest/condition-categories		

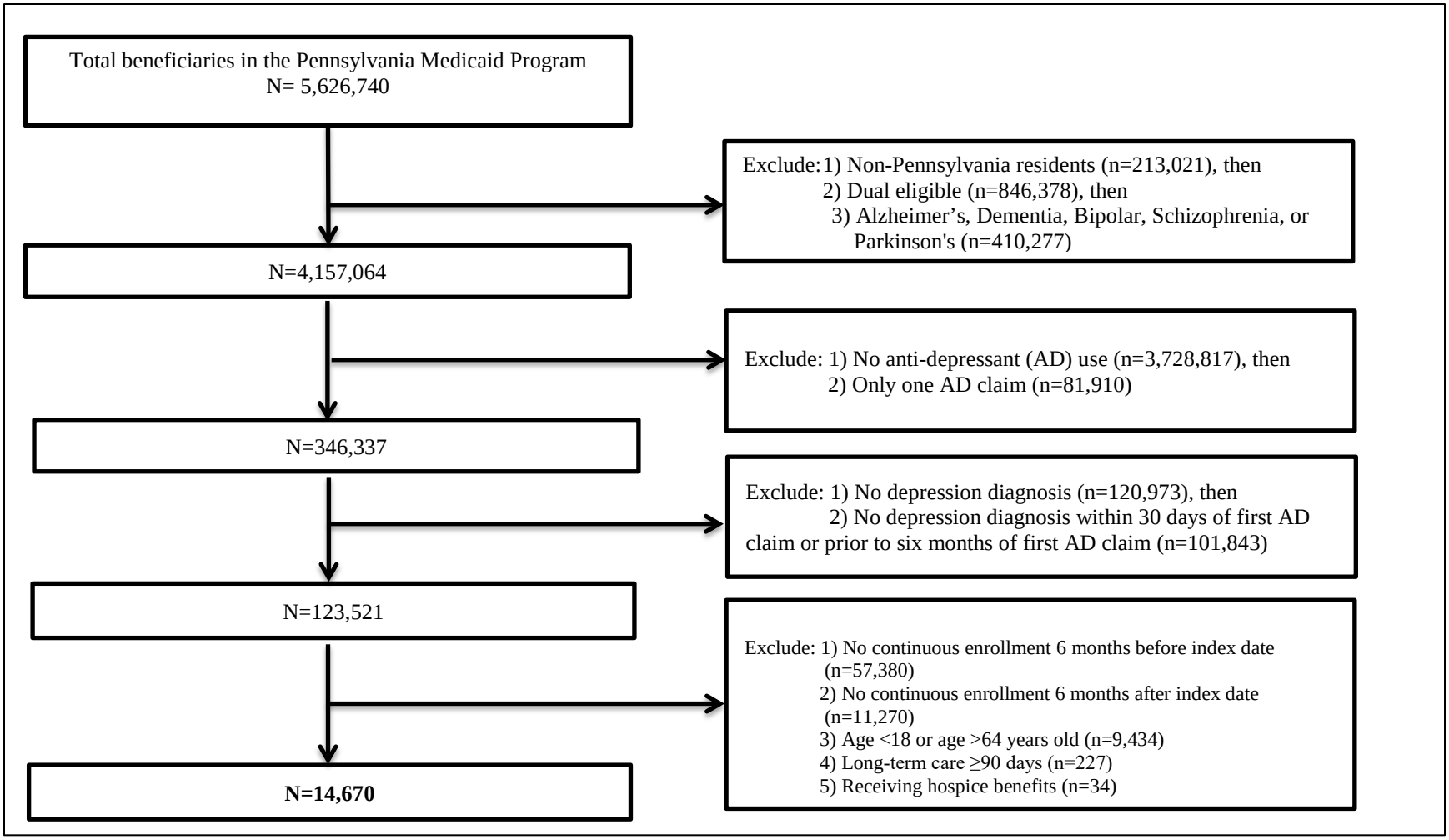


Figure C.2 Sample-size flowchart for cohort with Major Depressive Disorders

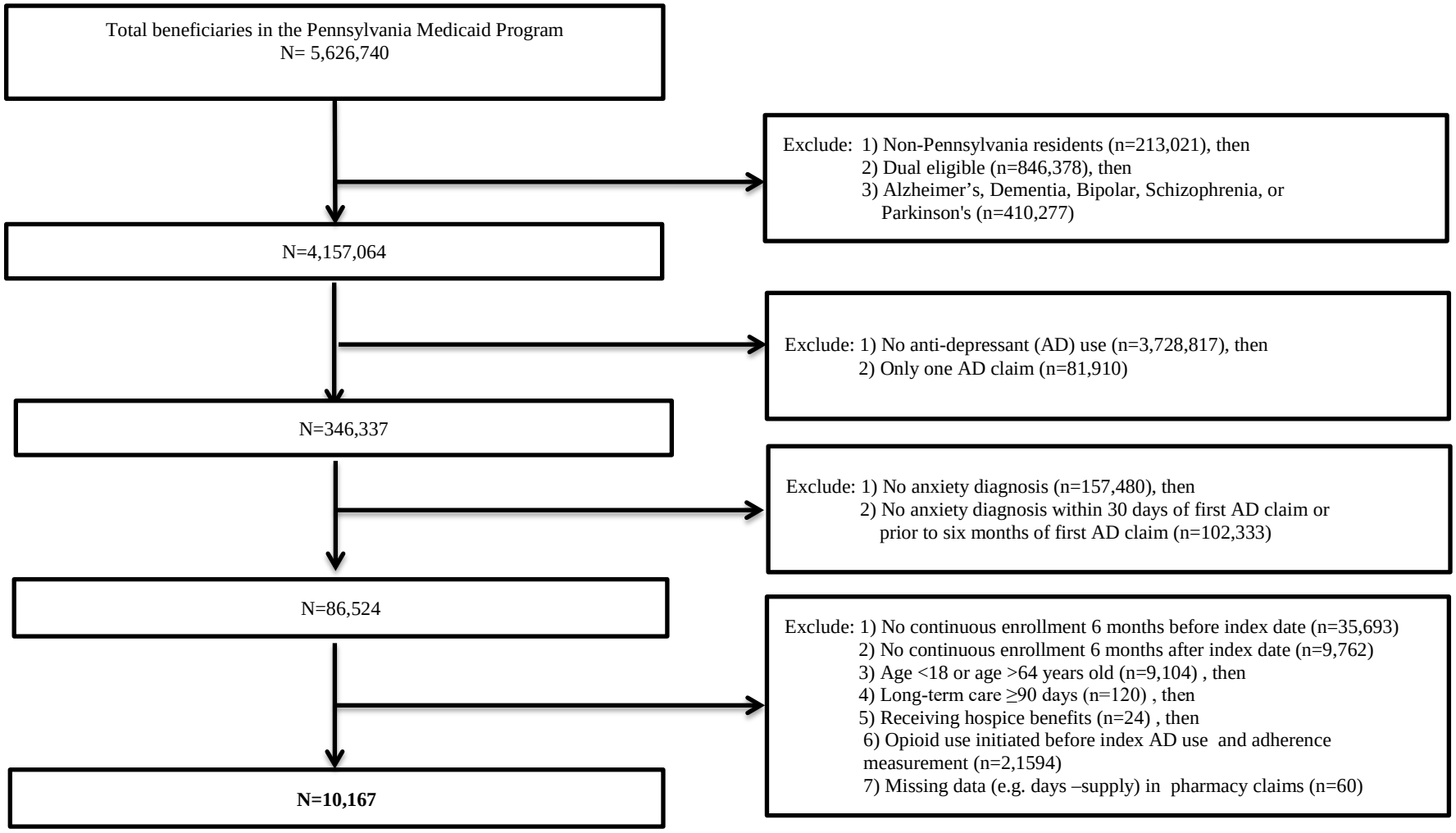


Figure C.3 Sample-size flowchart for cohort with Anxiety Disorders

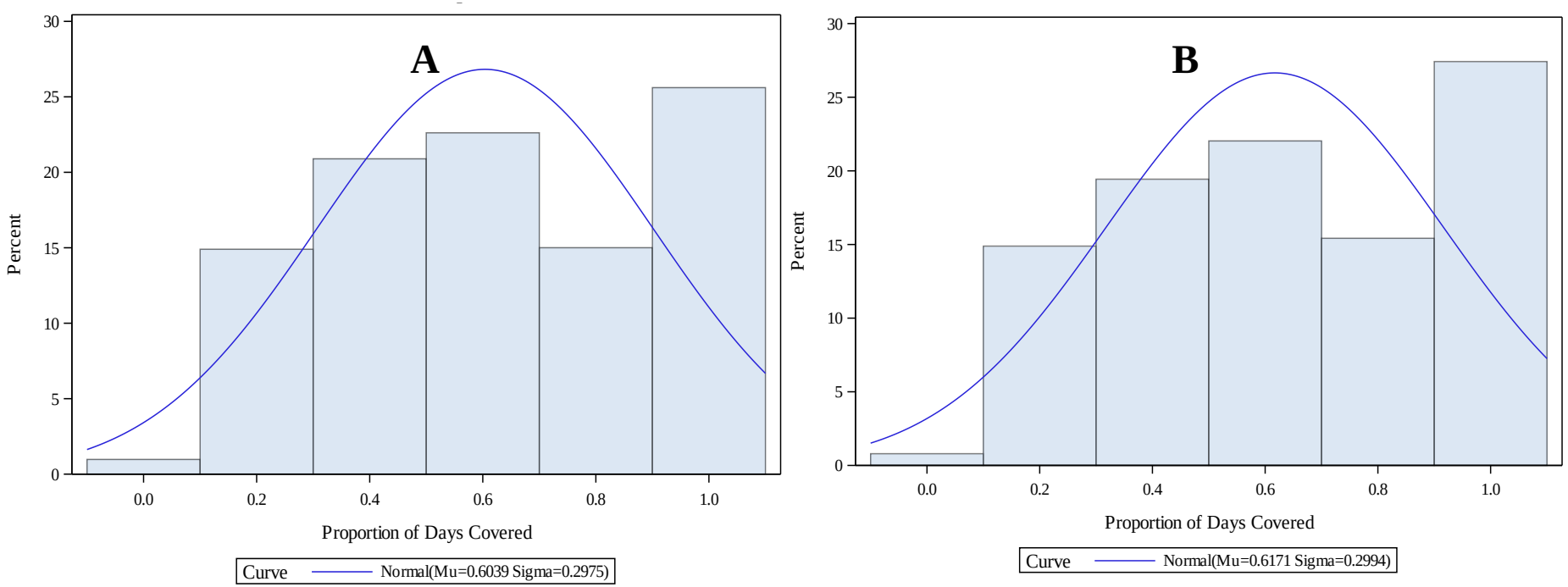


Figure C.4 Distribution of the proportion of days covered for (A) Cohort with Major Depressive Disorders, and (B) Cohort with Anxiety Disorders

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