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Economic Burden and Mortality Associated With Prescription Opioid Use

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ECONOMIC BURDEN AND MORTALITY ASSOCIATED WITH PRESCRIPTION OPIOID USE

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ABSTRACT

Prescription opioid use and misuse poses a significant public health challenge to the United States. In this dissertation we use the three-manuscript format to address some the areas of unmet research. Each manuscript has an abstract, introduction, background, methods, results, discussion, and conclusions sections.

Manuscript 1: We used a retrospective cohort design to examine the association between the patterns of initial prescription opioid use for non-cancer pain and risk of all-cause mortality among an insured opioid-naïve patient population in the U.S.

Multivariable Cox regression model was used to estimate the association of initial pattern of opioid use with all-cause mortality, adjusting for baseline covariates to control for confounding. We found that incident chronic opioid use was associated with an increased risk of all-cause mortality that persisted for up to 5 years after the initiation of opioid therapy.

Manuscript 2: We used a cross-sectional study of the Rhode Island Prescription Drug Monitoring Program data to estimate the annual statewide spending for prescription opioids in Rhode Island. A generalized linear model with gamma distribution with a log link function was used to estimate the relative differences in per-patient annual adjusted average opioid prescription cost. We found that in 2015 the annual expenditure for opioid prescriptions in Rhode Island was $44,271,827. Commercial insurance bore the majority of the cost of prescription opioid use, but cost per patient was highest among Medicare beneficiaries.

Manuscript 3: Using the 2015 Prescription Drug Monitoring Programs data for Rhode Island we examined the association between potential prescription opioid misuse and method of prescription opioid payment used. A multivariable log-binomial regression model was used to examine the risk of potential opioid misuse, controlling for sex, age group, type of opioid used, and concurrent benzodiazepine use. We found that patients on chronic opioid therapy who pay for some, but not all, opioid prescriptions in cash could be associated with potential opioid misuse only when the patient has other health insurance coverage.

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This dissertation is dedicated to GOD for HIS Amazing Grace!

PREFACE

This dissertation is written in the manuscript format, and is comprised of three manuscripts dealing with different aspects of the current prescription opioid epidemic facing the United States: risk of all-cause mortality, cost burden, and the risk of potential opioid misuse.

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CHAPTER 1

MANUSCRIPT I

Title: **Patterns of Initial Prescription Opioid Use and Risk of Mortality Among Insured Adults in the United States**

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ABSTRACT

Background: Patients with no prior exposure to opioids are often prescribed opioid analgesics for acute pain in the emergency room or office setting. Initial opioid prescription intended for short term use may result in chronic opioid use among opioid-naïve patients, increasing the risk of opioid overdose and death.

Objective: To examine the association between the patterns of initial prescription opioid use for non-cancer pain and risk of all-cause mortality among an insured opioid-naïve patient population in the U.S.

Methods: This retrospective cohort study used de-identified administrative claims database (Optum Clinformatics® Data Mart; OptumInsight, Eden Prairie, MN). Opioid prescriptions filled between January 1, 2010 and December 31, 2015 by opioid-naïve patients (in last 6 months) aged 18 years and above with no history of opioid use disorder, and not receiving cancer or palliative care were identified. All patients were required to have continuous medical and prescription coverage 6 months before and after the first opioid prescription. Based on initial pattern of opioid use (6 months after first prescription), patients were categorized either as incident daily (chronic) opioid users if they had more than 90 days' supply of opioids, or as non-daily users. Follow-up time was measured from 6 months after the index date to the end of eligibility or death, which ever came first. Multivariable Cox regression model was used to estimate the association of initial pattern of opioid use with all-cause mortality, adjusting for baseline covariates to control for confounding.

Results: A total of 4,005,001 patients were included in the study, of which 2.7% were incident daily opioid users; 54.8% were female; median age was 50 years; mean Charlson comorbidity index was 0.0 (standard deviation [sd] = 0.78); and mean daily morphine milligram equivalent (MME) was 34.10 (95% CI: 34.08 - 34.12). Among incident daily opioid users, 50% of patients were aged 65 and older and 55% had Medicare. Patients were followed for up to 6 years (median of 2.5 years) with a total of 11,294,819 person-years during which 39,417 (1%) died. Overall crude death rate was 349 deaths per 100,000 person-years; and there were 1,159 more deaths per 100,000 person-years among incident daily users than non-daily users. After adjusting for baseline covariates, patients who were incident daily users had more than twice the risk of all-cause mortality compared to non-daily users (hazard ratio [HR] = 2.57; 95% CI: 2.40 - 2.75). The hazard of death was slightly attenuated over time (HR at 5 years = 1.86; 95% CI: 1.72 - 2.02).

Conclusion: Almost 3% of opioid-naïve patients became chronic opioid users within the first 6 months of initial therapy. Incident chronic opioid use was associated with an increased risk of all-cause mortality that persisted for up to 5 years after the initiation of opioid therapy. Our findings are consistent with current Center for Disease Control and Prevention recommendation to use the lowest effective prescription opioid dose for the shortest duration among opioid-naïve patients.

INTRODUCTION

Pain is one of the most common reasons for an emergency department or outpatient office visit.[1-4] Opioid analgesics are often prescribed for acute pain in these settings because there is an established role of prescription opioid therapy in the management of moderate to severe acute pain and cancer pain.[5] However, the use of prescription opioids for chronic non-cancer remains controversial.[6-11] That notwithstanding, each year about 20% of adults in the United States are prescribed opioid analgesics for a variety of painful conditions ranging from acute injury to chronic non-cancer pain and terminal comfort measures, in part, because adequate and rapid pain relief has been used as a metric for patient satisfaction ratings.[12,13] Initial opioid therapy often intended by prescribers for short-term use often leads to unintended long-term use with adverse health outcomes including opioid misuse, opioid use disorder (OUD), overdose, and opioid-related deaths.[14-18] In recent years, deaths from drug overdose have increased dramatically, exceeding the number of deaths from motor vehicle accidents, to become the leading cause of accidental death in the United States.[19-22] The role of the initial pattern of opioid use in premature death is largely unknown.

BACKGROUND

Since 2013, mortality rates from drug overdose in the United States have frequently exceeded those from motor vehicle accidents and homicide. In 2015, drug overdose was responsible for over 50,000 deaths in the United States, with almost 63% related to opioid use - representing an age-adjusted opioid-involved death rate of 10.4 per 100,000 people.[23] More than 60% of all opioids involved in drug overdose deaths are prescribed by healthcare providers.[20,24,25] The number of deaths attributed to prescription opioid has now exceeded the total number of deaths from suicide and motor vehicle accidents combined.[26] Over the past decade, the rate of opioid-related overdose death has increased by about 200%.[23] Certain groups of opioid users are particularly vulnerable to opioid overdose, including those who seek care from multiple providers to obtain the same prescription opioid analgesic[27,28], those on high daily dosages of opioids[28-32], those with a history of mental illness[33], and Medicaid beneficiaries.[33,34] Prior studies have also established the use of long-acting opioids, especially at higher doses (≥ 50 morphine milligram equivalent [MME] per day) for chronic pain, use of ≥4 prescribers or pharmacies per year, and concurrent use of psychoactive medications including benzodiazepines and gabapentin as significant risk factors for opioid-related overdose death.[21,32,35-40] Several studies have found concurrent benzodiazepine use in 30% to 60% of opioid-related deaths.[41-43] In accordance with changes in recent opioid prescribing guidelines, the Food and Drug Administration has issued a boxed warning limiting the concurrent use of benzodiazepines with opioids.[11,44,45] Another study of opioid-naïve patients who had low-risk surgery found that the use of prescription opioids within 7 days of surgery was associated with an increased risk of long term opioid use.[46] Other populations at greater risk of harm include patients with sleep disorders, renal and liver failure, older adults, patients with mental health conditions, and patients with alcohol or other substance use disorders.[47-50]

The pattern of prescription opioid use varies from one individual patient to another depending on the indication, comorbidity, and local opioid prescribing norms. Some patients require opioid medications on a regular basis; some require it as-needed, and others take it both regularly and as needed. A recent case-control study used the Veteran Health Administration data to examine the relationship between the patterns of opioid use and health outcomes found that receiving as-needed and regularly scheduled opioid therapy was not associated with increased risk of overdose.[32] Little attention has been given to the effects of the initial pattern of incident opioid use on the risk of death from all causes among patients receiving opioid therapy for non-cancer, non-terminal care. Current guidelines for opioid use address risks associated with chronic opioid therapy, which represents only about 5% of episodes of opioid use each year in the United States and the remaining patients take prescription opioids somewhat irregularly and the risk associated with this pattern of use warrants further investigation.[51] Understanding the risk of mortality associated with the incident chronic opioid use is an important step towards decreasing opioid-related mortality. To address this gap in the evidence base, we examined the relationship between initial patterns of incident opioid use on the five-year mortality rate among opioid users without a cancer diagnosis.

METHODS

Study design and data source: This was a retrospective cohort study using de-identified administrative claims database (Optum Clinformatics® Data Mart; OptumInsight, Eden Prairie, MN). The database includes claims on health care utilization of about 35 million unique patients of all ages from geographically diverse regions of the United States who are privately insured or Medicare Advantage beneficiaries. The database provides information on member demographics and eligibility history, inpatient and outpatient medical services, outpatient pharmacy claims, and some laboratory results from January 1, 2010 to December 31, 2015. Clinical procedures and professional services are recorded using the Current Procedural Terminology (CPT) codes while associated diagnoses are recorded using the International Classification of Diseases, 9th and 10th Revisions, Clinical

Modification (ICD-9 and ICD-10) codes. Only enrollees with both a medical and prescription drug coverage are included in the database. To improve data quality and accuracy, claims submitted for payment by facilities, providers and pharmacies are usually verified, adjudicated, and adjusted prior to inclusion in the database. The dataset is linked to an existing Social Security Administration dataset which contains mortality information for all enrollees. The study protocol was approved by the University of Rhode Island Institutional Review Board.

Study population: All patients in the database who filled at least one opioid prescription were eligible for the study. Therapeutic class codes were used to identify all opioid prescriptions filled between January 1, 2010 and December 31, 2015 (Figure 1). Prescriptions with improbable or missing quantity or days' supply, and bulk containing agents were excluded. We focused on opioid prescription fills among opioid-naïve patients, defined as having no opioid prescription or OUD claim in the first observed 6 months of enrolment in the database.[52] The index date was defined as the date of the first opioid prescription among opioid-naïve patients (Figure 2). To allow for adequate ascertainment of baseline characteristics and initial pattern of prescription opioid use, we required patients to be continuously enrolled for at least 6 months before (i.e., pre-index baseline period) and 6 months after the index date (i.e., index period). Patients were excluded if they were younger than 18 years old as of the index date, or if their first opioid prescription was for a medication used to treat OUD, implying prior exposure to opioids was likely.[53] The study sample was further restricted to patients with no claims for any cancer diagnosis, or indication of palliative or hospice care. All patients were required to have a confirmed cancer diagnosis was defined as having at least two separate medical claims with a cancer diagnosis, with service dates at least 30 days apart. The cancer diagnosis codes could be in either a primary or secondary position in an inpatient or outpatient claim.[54] Hospice and palliative care were identified with ICD-9 and CPT codes. The final study sample consisted of 4,005,001 patients.

Exposure definition: The index period (6 months following the first opioid prescription claim), was used to ascertain the initial pattern of prescription opioid use. Based on the Consortium to Study Opioid use and Trends criteria,[38,55] patients were categorized either as daily (chronic) prescription opioid users if they had more than 90 non-overlapping days' supply of prescription opioids during the index period or as non-daily users otherwise. We computed the average daily morphine milligram equivalents (MME), and the number of providers and pharmacies used during the index period to fulfil opioid prescription requirements. Opioid prescription dosing information was converted to daily MME by multiplying the quantity of each prescription by the strength of the prescription, and multiplying this total by conversion factors published by the Center for Disease Control and Prevention (CDC).[56] For patients who received more than one opioid prescription on any given day, the MME of all prescriptions were added together. Based on recent CDC treatment guidelines, the average daily MME was categorized as < 50, 50-90, or >90 MME daily.[11]

Covariate information: The dataset contains information on gender (male or female), type of insurance (commercial or Medicare), type of health plan, and US states that were grouped into five census regions. Age in years was calculated as of the index opioid prescription date. Clinical characteristics that may influence the initial pattern of prescription opioid use and/or time to mortality, such as Charlson comorbidity index (a common measure of overall medical comorbidity), common pain conditions, mental health disorders, surgical procedures, pregnancy, occurrence of sprains and fractures, and substance use disorders such as alcohol, smoking, and OUD were recorded during the baseline/index period using ICD-9 and ICD-10 codes.[57,58] All clinical diagnoses were used to indicate if the patient had been diagnosed with or treated for the condition during the baseline/index period. Use of psychiatric medications such as benzodiazepines, antidepressants, antipsychotics, and gabapentin was defined as having one or more prescription claims during the index period, irrespective of whether that use overlapped with use of an opioid prescription.[38] A listing of ICD-9, ICD-10 and CPT codes used to identify various conditions is provided in Appendix A.

Outcome measurement: All-cause mortality was ascertained using mortality information from Social Security Administrations Death Index file which provided the month and year of death without information on the underlying cause of death. The date of death was imputed to be the last calendar day of each month. Observation time was measured from 6 months after the index date (i.e., the end of the index period) to the end of eligibility, or death, which ever came first. If the patient was not seen for one entire calendar year, their follow-up time was censored at the end of that calendar year. All patients were administratively censored at the end of the study (i.e., December 31, 2015).

Statistical Analysis: Descriptive statistics were computed for demographic, clinical, and prescription characteristics at baseline and presented by initial pattern of prescription opioid use. We computed overall median follow-up time and crude death rate for the study sample. Overall survival among the two the groups defined by initial patterns of incident opioid use (daily versus non-daily prescription opioid users) was compared using unadjusted and inverse-probability-weighted Kaplan-Meier survival curves.[59,60] We fit unadjusted and adjusted multivariable Cox regression model to estimate the hazard ratios (HR) with 95% confidence intervals (CI) that were used to determine the association of initial patterns of opioid use on the rate of all-cause mortality, adjusting for patient-level baseline covariates to control for confounding. Restricted quadratic splines were used to control finely and more flexibly for continuous confounders (age and average MME) allowing for a non-linear relationship with time-to-death.[61] Based on a statistical test and graphical visual inspection, the assumption of proportional hazards for initial pattern of prescription opioid use (primary exposure) was not satisfied (ρ = 11,777; χ^2=156, degree of freedom [df]=1, p-value < 0.0001), so a cross-product term between the logarithm of time (in months) and baseline exposure was included in the model. All data manipulations and statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC) and R statistical software, version 3.2.3 (R Core Team 2016). All tests of statistical significance were two-sided and performed at the 0.05 significance level.

RESULTS

A total of 4,005,001 patients were included in the study, of which 2.7% were daily opioid users; 54.8% were female; median age was 50 years; mean Charlson comorbidity index was 0.21 (standard deviation [sd] = 0.78); and mean daily morphine milligram equivalent (MME) was 34.10 (95% CI: 34.08 - 34.12). Table 1 shows baseline characteristics for the patients included in the study; overall and by incident prescription opioid exposure during the index period. The average age of patients on incident daily use was 62.2 years (sd = 15.9) compared with 49.7 (18.2) years among non-daily users. The proportion of patients ages 65 and older was higher among incident daily users (49.7%) than among the non-daily users (24.3%). Overall, the proportion of patients on daily prescription opioid use increased progressively with age while the proportion of patients among non-daily users appeared to plateau after age 25 years. More than 55% of incident daily users had Medicare compared to only about a quarter of patients in the entire cohort. The southern US census region had the largest number of patients (about 40%), followed by the West and Midwest (23% each), while the Northeast had the fewest with only 11% of the sample residing in this region.

Tobacco and alcohol were the most commonly used substances and were observed in 2.2% and 0.35% of the study cohort, respectively. For every 10,000 patients in the cohort, 4 had at least one medical claim for an overdose during the index period; 2 out of 10,000 had at least one claim for an OUD; and 1 out of 10,000 had at least one claim for an opioid overdose. Join and arthritis pain (15.2%) were the most common pain syndromes with a medical claim during the index period followed by back pain (7.5%). Almost 20% of patients had a pregnancy-related claim during the baseline period, 10% had a surgical claim, and 6% had a claim for a sprains and fractures. The proportion of patients who filled at least one antidepressant (13.4%) or a benzodiazepine (7.3%) was much higher than the proportion of claims for a mental health disorder (6%). Overall, almost 90% of patients had no comorbid physical conditions. However, 20% of patients on incident daily prescription opioid had one or more comorbid physical conditions compared to 10% among non-daily incident prescription opioid users. Similarly, on average, the number of opioid prescriptions, number of different types used, daily MME, number of providers and pharmacies involved were higher among incident daily opioid users than non-daily incident opioid users.

Patients were followed for up to 6 years (median of 2.5 years) with a total of 11,294,819 person-years during which 39,417 (1%) died (Table 2). Overall crude death rate was 349 deaths per 100,000 person-years. Among incident daily prescription opioid users, the crude incidence rate of all-cause mortality was 1,476 per 100,000 person-years compared to 317 per 100,000 person-years among non-daily users. The incidence rate difference (IRD) of 1,159 per 100,000 person-years represents the mortality rate among prescription opioid users that is attributable to a pattern of incident daily use, assuming daily users (i.e., exposed) would have had a mortality rate equal to non-daily users (i.e., unexposed) had they not been daily users. The crude rate of mortality among incident daily opioid users was 4.7 times that of the rate among incident non-daily users (crude incident rate ratio [IRR] = 4.66; 95% CI: 4.655 - 4.659). The survival probabilities of patients with incident daily and non-daily exposure to prescription opioids are shown in Figures 3 and 4. Survival was associated with the initial pattern of prescription use (p-value < 0.0001). For the duration of the follow-up, incident daily users had lower survival rates than non-daily users with this difference becoming more constant at later follow-up times. The differences persisted even after adjusting for potential confounders using inverse probability of exposure weights.

Table 3 shows the results from the unadjusted and covariate adjusted-adjusted Cox regression models. In the unadjusted model, the hazard of all-cause mortality among patients on incident daily opioid users was 4.8 times the hazard among incident non-daily users (HR = 4.79; 95% CI: 4.55 - 4.84). After adjusting for baseline demographic and clinical variables, the hazard of death among patients with incident daily prescription opioid use was 2.6 times the hazard of all-cause mortality among patients with incident non-daily prescription opioid use (HR = 2.57; 95% CI: 2.40 - 2.75). The hazard was slightly attenuated over time (HR at 5 years = 1.86; 95% CI: 1.72 - 2.02).

DISCUSSION

We found that an initial pattern of incident chronic opioid use increased risk the risk of all-cause mortality, even after adjusting for potential confounding factors measured at baseline. Almost 3% of our study population was exposed to incident daily prescription opioid use which was comparable to that found in previous studies.[62] About 27.8% of patients were exposed to at least one prescription opioid medication during a six-year period for which the data was available in the database of a commercially-insured population with Medicare Advantage customers. This is remarkably similar to a 2015 study that estimated that 92 million US adults used at least one prescription opioid medication, corresponding to about 30% of the adult population.[63] Although incident daily prescription opioid users accounted for a relatively small proportion of all prescription opioid users, it was associated with a significantly increased risk of all-cause mortality that may persist for many years after initiation of therapy. Previous studies have established that initial prescription opioids intended for short term use often lead to chronic use, and certain initial patterns of prescription opioid use have been associated with long-term use.[64] Our study shows that incident daily use is associated with increased risk of all-cause mortality among insured adult patients taking prescription opioid medications for non-cancer, non-palliative care treatment.

Pain is one of the most challenging symptoms among patients with cancer or terminal illness and moderate-to-severe pain has been reported in up to 40% of dying patients.[65] Analgesic medications including prescription opioids are often used to alleviate pain and discomfort in these settings.[66] Because we excluded all patients with any claim for cancer diagnosis or palliative care at baseline or during the index period, it is unlikely that our findings are due to the use of prescription opioids for any of these indications. The risk of all-cause mortality was shown to last far beyond the index period which is as long as the usual six-month period used to define hospice care in clinical practice.

There are several challenges to the design of a longitudinal observational drug study, including unmeasured confounding and confounding by indication, because the choice of treatment is often determined by disease severity, comorbid conditions, and physician preferences. Our analysis showed that incident prescription opioid users had more comorbid conditions and were on average, in poorer health conditions compared to non-daily prescription opioid users. After dealing with multicollinearity issues, we constructed an adjusted model designed to reduce confounding using several approaches. First, no patients had absolute contra-indications to the study medication because all patients included in the study are known to have filled at least one opioid prescription at some point during the period covered by the database. Therefore, daily and non-daily prescription users in our study population represent the same study base. We applied the same inclusion and exclusion criteria to all patients, and the exposure of interest and the outcome were measured in a similar manner. Because both groups had comparable observation times, it is unlikely that censoring was related to the initial pattern of prescription opioid use. We adjusted for measured potential confounding variables, including the use of restrictive quadratic splines for continuous variables to allow for a non-linear relationship with time-to-all-cause mortality in our model. Patients with a known history of OUD were also excluded and we adjusted for OUD and opioid overdose diagnosed during the index period because continued opioid use after an overdose is associated with a higher risk of repeated overdose and death.[67] Drug abuse, overdose, and OUD tend to occur at higher rates among long term opioid daily users.[38] After adjusting for demographic characteristics, substance use disorders, psychiatric medication use, and other medical and surgical conditions at baseline, we found that incident prescription opioid use was associated with a higher rate of mortality that persists long after treatment was initiated. Despite these challenges, to the best of our knowledge, this is one of the largest observational studies of the association between patterns of opioid use and mortality carefully designed to emulate the essential tenets of a randomized trial.[68]

Pain is a common symptom among patients seen in office and emergency room settings and prescription opioid analgesics can be beneficial in when used appropriately. There is very little evidence of long term benefits for chronic non-cancer pain or palliative care and several studies have reported significant risks associated with chronic opioid therapy.[6,7,69,70] Initial patterns of prescription opioid use are associated with long-term use which in turn is associated with increased risks of adverse health outcomes.[17,38] Prescription opioid-related deaths among patients on opioids are associated with the use of long-acting agents, use high dose therapy, concurrent use of benzodiazepines and gabapentin, and use in high risk settings such as sleep disorder, COPD, renal and liver failure, and elderly patients. Among patients ages 66 and older living in the community with chronic pulmonary disease, incident prescription use has been associated with increased risk of 30-day all-cause mortality.[71,72] A recent study reported an increased risk of infection with current prescription opioid use, especially among new users.[73] This suggests that there are several pathways to increase risk of death among patients on prescription opioids, especially new users on chronic therapy.

LIMITATIONS

The results of this study should be considered with certain study limitations in mind. First, we lacked data on socioeconomic status, and this likely limited our ability to include a sufficient set of covariates to adjust for confounding. For example, for the first time in nearly a quarter century, life expectancy decreased in the US in 2015, disproportionately affecting black men.[74,75] Racial differences in rates of opioid-related deaths have been well-documented.[76] Second, we assumed that patients were opioid-naive if they did not fill any opioid prescription during the baseline period although this may not imply that they were never exposed to opioids previously. Third, some patients may not have used their opioid prescription as recommended by the prescriber, and that any excess opioid medications from a previous prescription filled were completed before a subsequent prescription was taken.[38] Fourth, although outpatient pharmacy data reflect a complete and accurate representation of prescription opioid utilization, we did not account for prescriptions paid for in cash that may not be captured in the database. Lack of information of prescription opioid use at other health plans or prior to start of the database may have led to misclassification of some prevalent prescription users as incident user. Such misclassification was minimized by at least 6 months of enrollment with medical and pharmacy benefits prior to the index date. Fifth, ICD-9 and ICD-10 codes in administrative data may lack sensitivity and specificity in identifying certain lifestyle medical conditions such as tobacco and alcohol use.

CONCLUSIONS

A small but significant proportion (3%) of all opioid-naïve patients became incident daily prescription opioid users within the first 6 months of opioid therapy. Incident chronic opioid use was associated with a 2.6-fold increased risk of all-cause mortality that persisted for up to 5 years after the prescription opioid regimen was first started. Our findings are consistent with current CDC guidelines to use the lowest effective prescription opioid dose for the shortest duration of treatment possible, especially among opioid-naïve patients.

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Table 1. Characteristics of patients exposed to prescription opioid analgesics by initial patterns of use, 2010-2015 (N=4,005,001)

		Initial pattern of prescription opioid use	
Patients characteristics	**Overall n = 4,005,001**	**Non-daily users n=3895467**	**Daily users n=109,534**
Observation time in days, mean (SD)	1030 (503)	1030 (502)	1037 (527)
Observation time in months, mean (SD)	33.85 (16.53)	33.84 (16.50)	34.08 (17.31)
Charlson comorbidity index (95% CI)	0.21 (0.78)	0.20 (0.76)	0.47 (1.23)
Female, n (%)	2194524 (54.79)	2134152 (54.79)	60372 (55.12)[a]
Age in years, mean (SD)	50.0 (18.2)	49.7 (18.2)	62.2 (15.9)
Age group, years			
18-24	388777 (9.71)	387082 (9.94)	1695 (1.55)
25-34	562621 (14.05)	557361 (14.31)	5260 (4.80)
35-44	657303 (16.41)	648129 (16.64)	9174 (8.38)
45-54	736835 (18.40)	719801 (18.48)	17034 (15.55)
55-64	659129 (16.46)	637145 (16.36)	21984 (20.07)
65+	1000336 (24.98)	945949 (24.28)	54387 (49.65)
Insurance type, n (%)			
Commercial	3040275 (75.91)	2992684 (76.82)	47591 (43.45)
Medicare	964726 (24.09)	902783 (23.18)	61943 (56.55)
US census region, n (%)			
Midwest	932474 (23.28)	911637 (23.40)	20837 (19.02)
Northeast	456427 (11.40)	444834 (11.42)	11593 (10.58)
South	1701972 (42.50)	1656377 (42.52)	45595 (41.63)
West	914128 (22.82)	882619 (22.66)	31509 (28.77)
Substance use and misuse, n (%)			
Drug abuse	2472 (0.06)	2087 (0.05)	385 (0.35)
OUD	937 (0.02)	756 (0.02)	181 (0.17)
Overdose	1750 (0.04)	1592 (0.04)	158 (0.14)
Opioid overdose	298 (0.01)	254 (0.01)	44 (0.04)
Alcohol abuse	14195 (0.35)	13395 (0.34)	800 (0.73)
Tobacco use	88034 (2.20)	84144 (2.16)	3890 (0.55)
Cocaine	689 (0.02)	646 (0.02)	43 (0.04)
Marijuana	653 (0.02)	642 (0.02)	11 (0.01)[b]
Other substance use[c]	1574 (0.04)	1450 (0.04)	124 (0.11)
Pain-related diagnosis, n (%)			
Headaches/migraines	119384 (2.98)	115542 (2.97)	3842 (3.51)
Neck pain	134125 (3.35)	128184 (3.29)	5941 (5.42)
Back pain	298656 (7.46)	282741 (7.26)	15915 (14.53)
Abdominal pain	220595 (5.51)	214361 (5.50)	6234 (5.69)
Joint pain/arthritis	608509 (15.19)	582989 (14.97)	25520 (23.30)
Fibromyalgia/CFS	59420 (1.48)	55787 (1.43)	3633 (3.32)
Chronic pain syndromes	170959 (4.27)	157942 (4.05)	13017 (11.88)
Other pains	130927 (3.27)	125292 (3.22)	5635 (5.14)
Comorbid conditions, n (%)			
Fractures/strains	234806 (5.86)	226901 (5.82)	7905 (7.22)
Surgical diagnosis	387083 (9.66)	377179 (9.68)	9904 (9.04)
Pregnancy-related diagnosis	748729 (18.69)	722608 (18.55)	26121 (23.85)
Mental health disorders[d]	252554 (6.31)	240685 (6.18)	11869 (10.84)

Abbreviations: OUD=Opioid use disorder, SD=standard deviation, CI=confidence interval,

[a]p-value = 0.03; [b]p-value > 0.05; all other p-values < 0.0001.

[c]Includes anxiolytics, stimulants, hallucinogenic drugs, or abuse of unspecified drugs.

[d]Includes adjustment disorders, anxiety disorders, conduct disorders, cognitive disorders, mood disorders, schizophrenia and psychotic disorders, alcohol-related disorders, substance-related disorders, and miscellaneous mental health disorders.

Table 1 (cont'd)

		Initial pattern of prescription opioid use	
	Overall	Non-daily users	Daily users
Patients characteristics	n = 4,005,001	n= 3895467	n = 109,534
Use of Psychotropic medications, n (%)			
Benzodiazepines	290253 (7.25)	275774 (7.08)	14479 (13.22)
Antidepressant	536709 (13.40)	505780 (12.98)	30929 (28.24)
Antipsychotics	45406 (1.13)	41450 (1.06)	3956 (3.61)
Gabapentin	42847 (1.07)	37116 (0.95)	5731 (5.23)
Characteristics of opioid prescriptions during index period, mean (SD)			
Number of prescriptions	1.73 (1.62)	1.58 (1.18)	7.13 (4.13)
Number of prescription types	1.17 (0.44)	1.16 (0.41)	1.65 (0.83)
Number of providers involved	1.29 (0.65)	1.26 (0.60)	2.12 (1.41)
Number of pharmacies used	1.13 (0.42)	1.12 (0.38)	1.58 (0.98)
Average daily dose, MME	34.10 (17.93)	34.20 (17.43)	30.41 (30.41)
Average daily MME, n (%)			
<50	344707 (83.51)	3248793 (83.40)	95914 (87.57)
50-90	614103 (15.33)	604119 (15.51)	9984 (9.11)
>90	46191 (1.15)	42555 (1.09)	3636 (3.32)
Charlson comorbidity index, n (%)			
0	3578382 (89.35)	3490743 (89.61)	87639 (80.01)
1+	426619 (10.65)	404724 (10.39)	21895 (19.99)

Abbreviations: OUD=Opioid use disorder, SD=standard deviation, CI=confidence interval, MME=morphine milligram equivalents

[a]p-value = 0.03; [b]p-value > 0.05; all other p-values < 0.0001.

[c]Includes anxiolytics, stimulants, hallucinogenic drugs, or abuse of unspecified drugs.

[d]Includes adjustment disorders, anxiety disorders, conduct disorders, cognitive disorders, mood disorders, schizophrenia and psychotic disorders, alcohol-related disorders, substance-related disorders, and miscellaneous mental health disorders.

Table 2. Number of deaths and person-years of observation among cohort of patients initially exposed to prescription opioid daily and non-daily for non-cancer, non-palliative care conditions, 2010-2015 (N=4,005,001)

	Initial pattern of prescription opioid exposure		
	Daily users	Non-daily users	Total
Number of Deaths, n (%)	4,592(4.19)	34,825 (0.89)	39,417 (0.98)
Person-years of observation	311,000.79	10,983,818.58	11,294,819.38
Crude Mortality Rate	1476.52	317.06	348.98
Crude IRR (95% CI)	4.66 (4.655, 4.659)		
Crude RD (95% CI)[a]	1,159.47 (1159.466, 1159.467)		

Abbreviations: IRR=incidence rate ratio, IRD=incidence rate difference, CI=confidence interval
[a]Cases/100,000 person-years

Table 3. Unadjusted and adjusted hazard ratios for all-cause mortality associated with exposure to incident daily prescription opioid use versus non-daily incident prescription opioid use, 2010-2015 (N=4,005,001)

	Daily opioid users n=109,534	**Non-daily opioid users n=3,895,467**	**Overall n=4,005,001**
Deaths, n (%)	4,592 (4.19)	34,825 (0.89)	39,417 (0.98)
Person-years of observation	311,000.79	10,983,818.58	11,294,819.38
Unadjusted Hazard ratio (95% CI)	4.79 (4.55, 4.84)	Reference	…
Adjusted Hazard ratio (95% CI)[a]			
Risk at baseline	2.57 (2.40, 2.75)	Reference	….
6-months risk	2.23 (2.08-2.40)	….	….
1-year risk	2.12 (1.97, 2.28)	….	….
2-years risk	2.00 (1.86, 2.16)	….	….
3-years risk	1.94 (1.79, 2.10)	….	….
4-years risk	1.90 (1.75, 2.06)	….	….
5-years risk	1.86 (1.72, 2.02)	….	….

Abbreviations: CI=confidence interval
[a]Model adjusted for differences in age, sex, US census region, index year, Charlson comorbidity index, substance use disorders (alcohol, Smoking, opioid overdose, opioid use disorder), surgical procedure, fracture and strains, pain conditions (headache, neck and jaw pain, back pain, abdominal pain, fibromyalgia), psychiatric medications (benzodiazepines, antidepressants, gabapentin) measured at baseline and index periods and , and number of opioid providers and average daily prescription opioid dose during the index period.

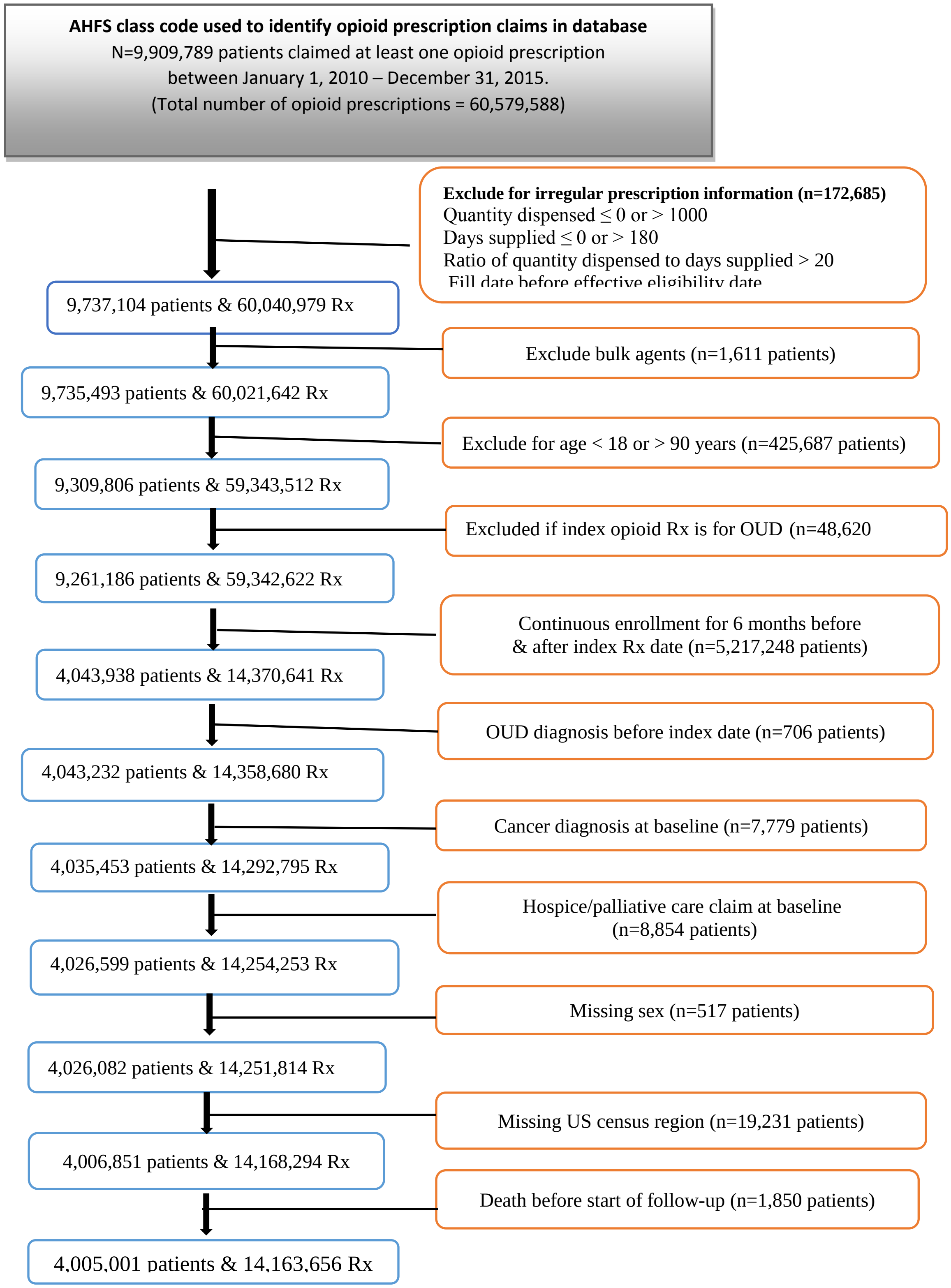

Figure 1. Study population and Sample Selection from all patients who had at least one opioid prescription, 2010-2015

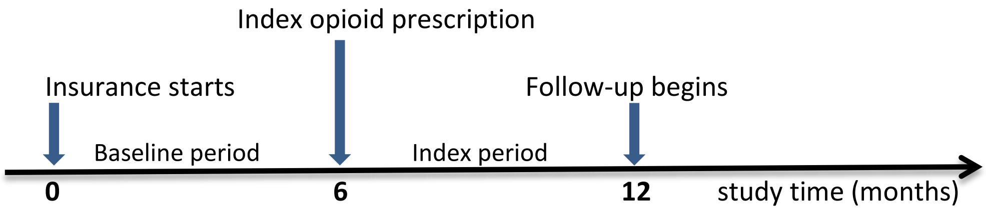

Figure 2. Study timeline for patient selection

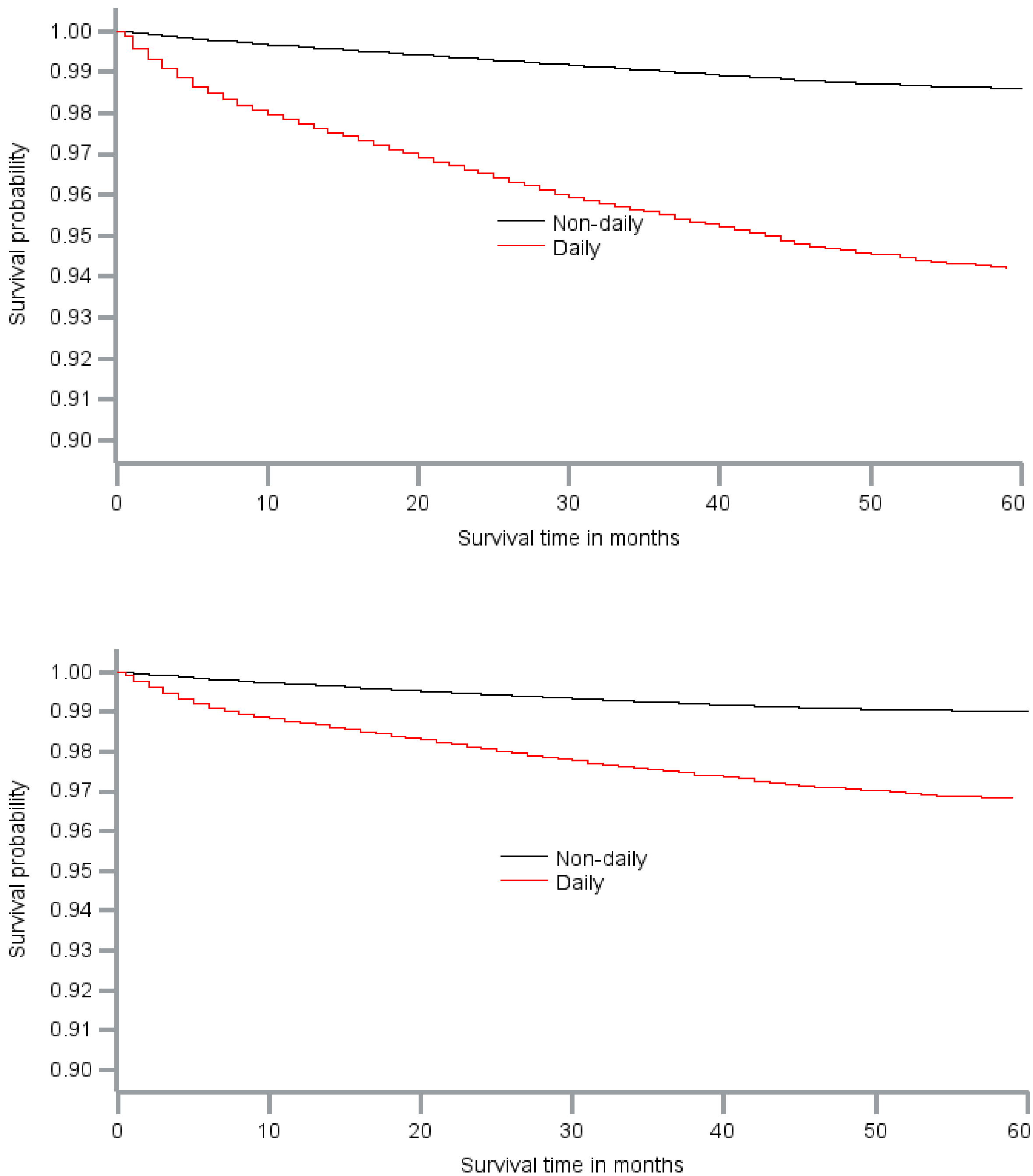

Figure 3. Unweighted (upper panel) and inverse probability of exposure weighted (lower panel) Kaplan-Meier Curves shoeing the survival experience of daily and non-daily prescription opioid users, 2010-2015.

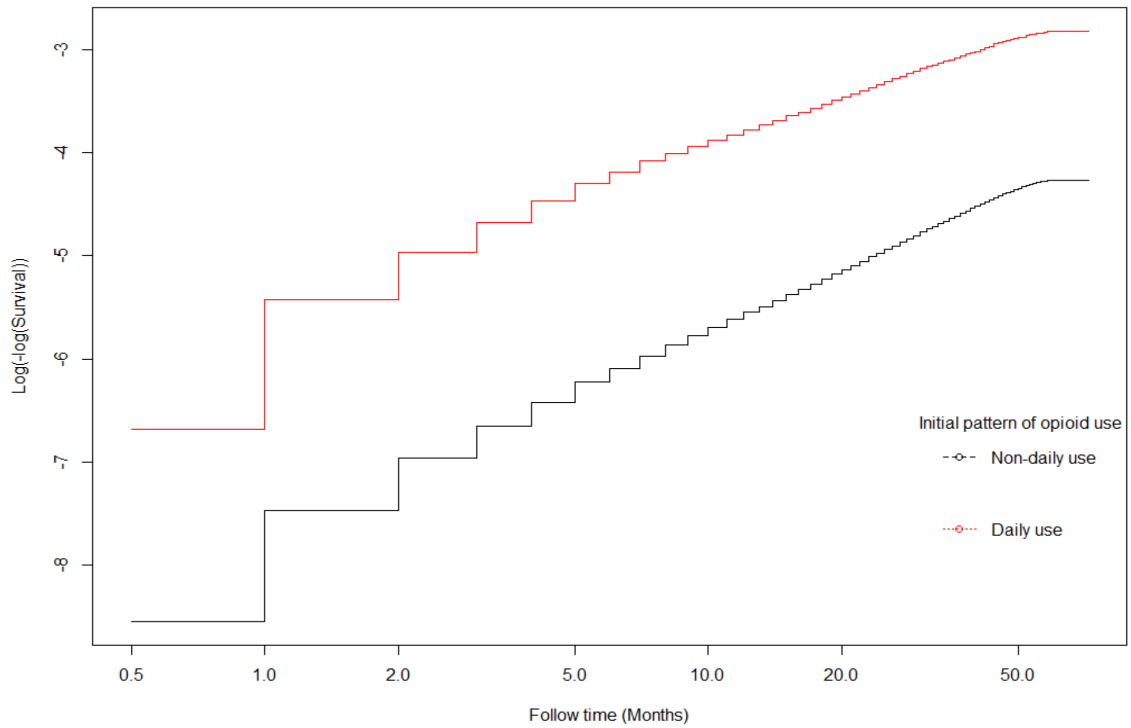

Figure 4. Log-Log of the Survival curves showing daily and non-daily users

CHAPTER 2

MANUSCRIPT II

Title: **Estimating the Direct Costs of Outpatient Opioid Prescriptions: A Retrospective Analysis of Data from the Rhode Island Prescription Drug Monitoring Program**

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ABSTRACT

BACKGROUND: Overuse and misuse of prescription opioids is associated with increased morbidity and mortality and places a significant cost burden on health systems.

OBJECTIVE: To estimate annual statewide spending for prescription opioids in Rhode Island.

METHODS: A cross-sectional study of opioids dispensed from retail pharmacies using data from the Rhode Island Prescription Drug Monitoring Program (PDMP) was performed. The study sample consisted of 651,227 opioid prescriptions dispensed to 197,062 patients between January 1, 2015, and December 31, 2015. The mean, median, and total cost of opioid use was estimated using prescription dispensings and patients as units of analysis. A generalized linear model with gamma distribution with an identity link function, and separately with a log link function, was used to estimate the absolute and relative differences in per-patient annual adjusted average opioid prescription cost, respectively, by potential predictors.

RESULTS: The estimated 2015 annual expenditure for opioid prescriptions in Rhode Island was $44,271,827. The average and median costs of an opioid prescription were $67.98 (SD $210.91) and $21.08 (quartile 1 to quartile 3 = $7.65-$47.51), respectively. Prescriptions for branded opioid products accounted for $17,380,279.05, which was approximately 39.3% of overall spending, although only 6% of all opioids dispensed were for branded drugs. On average, patients aged 45-54 years and 55-64 years had overall adjusted spending for opioids that were 1.53 (95% CI = 1.491.57) and 1.75 (95% CI = 1.71-1.80) times higher than patients aged 65 years and older, respectively. Per patient Medicaid and Medicare average annual spending for opioid prescriptions were 1.19 (95% CI = 1.16-1.22) and 2.01 (95% CI = 1.96-2.06) times higher than commercial insurance spending, respectively. Annual opioid prescription spending was 2.01 (95% CI = 1.98-2.04) and 1.50 (95% CI = 1.45-1.55) times higher among patients who also had at least 1 dispensing of a benzodiazepine or sympathomimetic stimulant, respectively. Average total spending for prescription opioids per patient increased with the average daily dosage: from 3-fold for patients using 50-90 morphine milligrams equivalent (MME) daily to 22-fold for those receiving 90 or more MME daily compared with those receiving less than 50 MME daily.

CONCLUSIONS: This study provides the first estimate of the statewide direct cost burden of prescription opioid use using PDMP data and standardized pricing benchmarks. Total annual cost increased with age up to 65 years, mean daily dose, and concurrent use of benzodiazepines or stimulants. Commercial insurance bore the majority of the cost of prescription opioid use, but cost per patient was highest among Medicare beneficiaries. In addition to reducing harms associated with opioid overuse and misuse, substantial cost savings could be realized by reducing unnecessary opioid use, especially among middle-aged adults.

SUMMARY BULLETS

What is already known about this subject

What is Already Known About This Subject:

- The overuse and misuse of prescription opioids is associated with increased morbidity and mortality, and places a significant cost burden on health systems. In 2005, White et al estimated that the total healthcare costs per patient were about 8.5 times higher among patients with a diagnosis of opioid use disorder compared to similar patients without a history of opioid use disorder[1].
- The total United States (U.S.) spending for opioid analgesic prescriptions increased substantially from $2.3 billion in 1999 to $7.4 billion in 2012.
- The total annual expense for prescription opioid utilization in the outpatient setting in the U.S. in 2012 has been estimated at approximately $9.0 billion, representing an increase of 120% from 2002.
- In 2016, the total annual expense for almost 18 million prescription drugs were filled at retail pharmacies in Rhode Island was about $1.2 billion.

What This Study Adds:

- Total annual retail expenditure for opioid analgesic prescriptions in Rhode Island for 2015 is estimate at $44,271,827.

- Total annual per-patient cost for opioid prescriptions is $17.65 higher among adults age 45-54 years, and $28.47 higher among patients of age 55-64 years as compared with those ages 65 years or older.
- Commercial insurance bears the majority of the cost of prescription opioid use but cost per patient is highest among Medicare beneficiaries.
- More than 10% of patients paid for at least one opioid prescription with cash but cash payment accounts for only 5.1% of the total annual prescription opioid expenditure.
- Among patients who also received prescriptions for benzodiazepines, annual cost for opioid dispensings was approximately twice as such as patients who did not receive benzodiazepines; while among patients who also received prescriptions for stimulants, annual cost for opioid dispensings was approximately 50% higher as compared with patients who did not receive stimulants.

INTRODUCTION AND BACKGROUND

Pain is one of the most common reasons for an outpatient office visit.[1-3] According to a 2011 Institute of Medicine report, approximately 100 million adults in the United States suffer from chronic pain each year.[4] Prescription opioid analgesics are commonly used to treat a variety of painful conditions that range from acute injury to palliative care for terminal illness. In 2012, U.S. health care providers issued over 259 million opioid prescriptions.[5] Higher rates of opioid prescribing over the past 2 to 3 decades may be attributed in part to historical changes in pain management guidelines, the Joint Commission requirements for routine pain assessment, promotion by the pharmaceutical industry, and changes in reimbursement and out-of-pocket payment for prescription opioids.[6-10]

Although use of prescription opioid analgesics is often clinically necessary, their addictive and euphoric properties easily result in misuse and often lead to opioid use disorders. In recent years, deaths from drug overdose have increased dramatically, exceeding the number of deaths from motor vehicle accidents, and have become the leading cause of accidental death in the United States.[5,11-13] In 2015 alone, drug overdose was responsible for 52,404 deaths, with 33,091 (63.2%) associated with opioids. More than 60% of opioids involved in drug overdose deaths are prescription opioids.[14,15] Benzodiazepines and opioids are often prescribed together, which has the potential risk of respiratory depression and overdose death.[16-18] The U.S. Food and Drug Administration recently issued a boxed warning limiting the concurrent use of opioids and benzodiazepines or other central nervous system depressants, adding to recent changes in opioid prescribing guidelines.[19-21]

Currently, all state legislatures, with the exception of Missouri, have implemented state-run prescription drug monitoring programs (PDMPs) that are designed to identify and track the prescribing and dispensing of controlled substances, including prescription opioids dispensed from retail pharmacies. The purpose of these PDMPs is to alert prescribers of controlled substances issued by other practitioners and to promote appropriate prescribing practices by making opioid medication history accessible to prescribers and pharmacists at the point of care delivery.[22] In most states, including Rhode Island, prescription drugs that are monitored are classified as Schedule II, III, and IV and opioid medications within Schedule V on the Drug

Enforcement Administration's (DEA) 5-tiered schedule. Drugs are assigned to 1 of these categories by the DEA based on their medicinal value and the potential for abuse and diversion.

While significant attention has been directed towards the health consequences of opioid prescribing, little has been published on the associated health care costs.[14,23-25] The annual societal cost of pain in terms of medical care and lost productivity in the United States has been estimated at $635 billion in 2010 dollars.[4] White et al. (2005) estimated that the total health care costs per patient varied from $15,884 to $18,388 among patients with opioid use disorder diagnoses compared with only $1,830-$2,210 among a similar group of patients with no documented history of such disorders.[26] Recent publications of costs related to opioid use have examined trends in expenditures using national Medicare and Medical Expenditure Panel Survey data.[23,27] Zhou et al. (2016) estimated that total U.S. spending for opioid analgesic prescriptions increased substantially from $2.3 billion in 1999 to $7.4 billion in 2012,[27] while Stagnitti et al. (2015) estimated the total expenses for outpatient prescription opioids at $9.0 billion in 2012, an increase of 120% from 2002.[28]

The effect of opioid use on statewide health systems can be quantified in terms of the direct cost of prescriptions to payers. To date, no published studies have examined state-level direct costs associated with prescription opioid dispensings from retail pharmacies across different age groups, gender, medication types, and sources of payment. In this study, data from the Rhode Island PDMP were used to estimate the distribution of the direct cost of opioid prescriptions dispensed by retail pharmacies in Rhode Island during the calendar year 2015.

The goal of this analysis was to determine the total 2015 annual expenditure for prescription opioid analgesics in Rhode Island as captured in the PDMP. The proportions of spending associated with cash payment and by public and private payers were determined. In addition, we evaluated if gender, age group, payment type, or use of benzodiazepines or stimulants were associated with the total annual prescription opioid cost per patient. Understanding these factors may help elucidate the extent of opioid use statewide and provide support for efforts by providers, public health regulators, and payers to reduce the misuse of prescription opioid analgesics.[29]

METHODS

Study Design and Data Source: A cross-sectional study was conducted to examine annual opioid use and spending by patient and by type of opioid medication dispensed using data from the 2015 Rhode Island PDMP. For this study, opioid medication included all DEA Schedule II-IV prescription medications dispensed by retail pharmacies licensed within the state.

Since June 28, 2016, Rhode Island state law requires pharmacies to monitor Schedule II-V controlled substances. Pharmacies holding a retail license in Rhode Island are legally required to electronically report all monitored controlled substances filled within 1 business day of the prescription being dispensed to the patient. This requirement includes independent pharmacies, chain pharmacies, food stores, and mass merchandisers but not substance abuse treatment programs, in-patient hospital pharmacy services, and correctional facilities. A commercial vendor links multiple prescriptions for each patient using probabilistic techniques based on the patient's name, date of birth, and street address.[30,31] Similarly, all prescriptions written by each provider and dispensed by the pharmacist are linked by unique prescriber DEA numbers.

The data provided by the Rhode Island Department of Health for our study included only de-identified patient, prescriber, and dispensing pharmacy information. Available information included patient age (in years), gender, a unique prescriber and dispensing pharmacy identifier, the National Drug Code (NDC) number, product name, strength, formulation, and therapeutic class code of each prescription, as well as the number of days supplied, metric quantity dispensed, method of payment, and date the prescription was filled. The pharmacist estimated days supply based on the quantity prescribed and the daily dosage. The payment type field was populated by the dispensing pharmacist, and a payment type of “commercial” was presumably incorrectly assigned for many older adults who were more likely enrolled in a Medicare plan. Therefore, for patients who were aged 65 years or older with a payment type of commercial, their payment type was reclassified as Medicare.

Cohort Selection: All individuals with at least 1 prescription dispensing of any Schedule II-IV controlled substance were first identified. There were 2,058,816 controlled substance prescriptions dispensed at retail pharmacies in 2015, including opioid analgesics, benzodiazepines, stimulants, skeletal muscles relaxants, and sleep aids. All prescriptions for non-opioid agents were first excluded (Figure 1); buprenorphine-containing products were excluded, since they are typically indicated for substance and opioid use disorder treatment; tramadol was also excluded because it is considered a mixed opioid-like analgesic[32,33]; and compounded formulations and bulk containers for which standardized pricing benchmarks were unavailable were excluded. Opioid medications were classified by drug type using NDC numbers. The analytic sample consisted of 651,227 opioid prescriptions dispensed to 197,062 patients from retail pharmacies in Rhode Island between January 1, 2015, and December 31, 2015. The U.S. Census Bureau estimated the population of Rhode Island to be 1,056,298 in 2015.[34] An opioid prescription dispensing was defined as any prescription drug filled at a retail pharmacy and sold to a patient or patient's agent on a particular day, whether a new or refilled prescription.

To determine the unit price of each opioid prescription, NDC numbers for opioid dispensings were first matched with the 2015 Rhode Island Medicaid Maximum Allowable Cost (MAC) listing as the default unit price for branded and generic products. For sole source (i.e., branded) products and other NDC numbers that did not match the Medicaid MAC listing, pricing data from RED BOOK Online (Truven Health Analytics, Ann Arbor, MI) was used, which provided the average wholesale price (AWP) and federal upper limit (FUL) prices during 2015. These costs were assigned using the lesser of AWP-14% or FUL. The discounting of AWP was determined in consultation with experts in the field as a conservative estimate of drug costs. Sources of payment reported included cash (private pay), commercial insurance, Medicare, Medicaid, and other (i.e., worker's compensation, Indian Health Service, the Veterans Health Administration, Tricare, and other federal sources).

We hypothesized that the total annual expenditure for opioid prescriptions was associated with the use of benzodiazepines or stimulants, use of higher daily doses of opioids, and use of multiple providers and pharmacies. This study determined if opioid prescription expenditure was associated with patient age groups, gender, or payment type. Use of benzodiazepines or stimulants was defined as the use of 1 or more prescriptions of either a benzodiazepine or a stimulant within the study year. The dosage of each prescription opioid dispensed was converted to its morphine milligram equivalent (MME) per day using NDC-based conversion factors published by the Centers for Disease Control and Prevention's National Center for Injury Prevention and Control in June 2015.[35-38] Less than 1% of opioid prescriptions did not have enough information to calculate the daily MME. Finally, a measure of potential health system abuse was defined as patients who received prescriptions for opioids from 5 or more prescribers and filled by 5 or more pharmacies within the 12-month period (called 5/5/12 criteria)—referred to as multiple provider episodes (MPE) or "doctor shopping."[39]

Statistical Analysis: The mean, median, and total costs of opioid use were estimated using opioid prescription dispensings and patients as units of analysis. All costs were retained in 2015 U.S. dollars. The last opioid prescription received during the study year was used to identify the most recently used opioid type and and to assign medication type and source of payment when patients were used as the unit of analysis. We determined overall annual spending for opioid medications and further categorized spending by age group (aged < 18, 18-24, 25-34, 35-44, 45-54, 55-64, and 65+ years); gender; medication type; and payment type. Annual cost values were non-normally distributed with a large right skew (skewness = 22.66).

With patients as the unit of analysis, a generalized linear model with gamma distribution with an identity link function, and separately with a log link function, was used to estimate the absolute and relative differences in per-patient annual adjusted average prescription opioid cost, respectively, by potential predictors.[40,41] Independent variables included in the model were age group, gender, payment type, mean daily MME per patient, use of benzodiazepines or stimulants, and conditional on the link function. The gamma family was selected, which has a constant coefficient of variation and assumes that the variance is proportional to the square of the mean.[41,42] All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC), and all statistical tests were 2-sided and performed at the 0.05 significance level. This study was approved by the institutional review board at the University of Rhode Island.

RESULTS

The study population consisted of 197,062 patients who filled a total of 651,227 opioid prescriptions in 2015. This number represents an estimated 18.7% of patients in Rhode Island who received at least 1 dispensing for an opioid medication from a retail pharmacy during 2015. Approximately 56% of patients who filled at least 1 opioid prescription were female (Table 1). About 23.9% of patients were aged 65 years and older, and 38.3% were aged 45-64 years. Based on the last opioid prescription dispensed, most patients were prescribed either hydrocodone or oxycodone (83.1%). Approximately 58.2% of patients had commercial insurance; 21.9% were covered by Medicare; and almost 10% of patients paid for their prescriptions using cash. More than 90% of patients used only 1 method of payment during the study year. A subgroup analysis of cash payment for all opioid prescriptions showed that 21,538 patients used cash payment for least 1 opioid prescription in 2015. Among them, 16,240 (75.40%) patients used only cash payment for all opioid prescriptions filled at the retail pharmacy, while 5,298 (24.60%) patients used 2 or more types of insurance payment during the same calendar year (Appendix A, available in online article).

The total 2015 annual retail expenditure for opioid prescriptions in Rhode Island was estimated at $44,271,827, which corresponded to an average spending of $3.7 million per month. The average and median costs of an opioid prescription were $67.98 (standard deviation [SD] $210.91) and $21.08 (quartile 1 to quartile 3 [Q1-Q3] = $7.65-$47.51), respectively. Both the number of opioid prescriptions dispensed and per patient annual spending increased with age but appeared to stabilize among patients aged 45 years or older (Table 2). The total annual prescription opioid spending for patients aged 45-64 years was estimated to be $26,337,403.49, which was not only proportionately higher compared with patients aged 65 years and older but also higher than spending for any other age group.

Oxycodone and hydrocodone were the most commonly dispensed opioid prescriptions, accounting for more than 82% of all prescriptions filled. The total annual expenditure for these 2 drug types was approximately $32.5 million, which accounted for 73% of all opioid prescription spending. The average cost of an oxycodone prescription was approximately $50 more than hydrocodone, reflecting a dramatically higher cost for extended-release oxycodone compared with hydrocodone products, which were mostly dispensed in generic immediate release forms. The average and median costs of a prescription of oxymorphone were $595.72 (SD $512.60) and $439.68 (Q1-Q3 = $246.94-$779.81), respectively, making it the most costly opioid prescription type among branded and generic products.

Branded opioid prescriptions were far more expensive than their generic counterparts. However, 94% of all opioid prescriptions were for a generic product, with an average price of $43.90 (SD $116.21) compared with $449.78 (SD $616.97) per branded prescription. Branded opioid prescriptions accounted for $17,380,279.05 of the yearly total, which was about 39.3% of overall spending, although only 6% of all opioids dispensed were for branded drugs.

Commercial insurance was the most common method of payment type for opioid prescriptions (51%), followed by Medicare (29.4%). Cash payment was used for 60,548 (9.3%) of all prescription opioids dispensed. We found that, on average, Medicare spent $85.31 (95% confidence interval [CI] = $84.24$86.39) per opioid prescription, which was significantly more than Medicaid and private insurance, which spent $52.15 (95% CI = $50.82-$53.48) and $65.55 (95% CI = $64.83-$66.28) per prescription, respectively. However, commercial insurance was responsible for 49.3% of the total expenditure, while Medicaid and Medicare paid for only 6.1% and 36.9%, respectively. Cash payment represented 5.1% of the annual spending.

Table 3 presents the results of a generalized linear model. Using a gamma regression model with an identity link function, gender, age group, payment type, mean daily MME per patient, use of benzodiazepines or stimulants, and MPE were statistically significant predictors of total annual expenditure. Patients aged 45-54 years and 55-64 years had overall adjusted mean spending for opioids that was $17.65 (95% CI = $15.26$20.04) and $28.47 (95% CI = $26.06-$30.88) higher,

respectively, than patients aged 65 years and older. As expected, the youngest patients had significantly lower adjusted total expenditure per patient compared with adults aged over 65 years. With regard to method of payment, overall adjusted mean costs per Medicare and Medicaid patients were \$33.20 (95% CI = \$31.05-\$35.35) and \$0.56 (95% CI = -\$0.51-\$1.63) higher, respectively, compared with commercially insured patients, while patients who used cash payments spent on average \$3.80 less than the amount charged to customers with commercial insurance.

Patients who were dispensed benzodiazepines (26.5%) or sympathomimetic stimulants (4.4%) had higher annual spending for opioid medications than those who did not receive these medications. On average, adjusted annual opioid prescription cost was \$35.99 (95% CI = \$34.45-\$37.54) higher among patients who also received at least 1 benzodiazepine dispensing, while adjusted annual opioid prescription cost was also had at least 1 dispensing for a stimulant medication. As a statistically significant predictor of annual opioid expenditure, for patients with MPE, average adjusted annual cost of opioid prescriptions per patient was increased by approximately \$863.58 (95% CI = \$689.48-\$1,037.68) compared with patients who did not meet this criteria. The adjusted annual total opioid spending per patient also increased substantially with the use of higher daily doses of opioids, since average total cost was more than \$337.73 (95% CI = \$332.84-\$342.62) greater among patients using on average more than 90 MME daily, compared with patients receiving on average of less than 50 MME daily.

Using a gamma regression model with a log link function (Table 3), there was a 69% reduction in overall adjusted average cost per patient when comparing those who were aged 18 years or younger to those aged 65 years and older. Conversely, patients aged 45-54 years and 55-64 years had overall adjusted average spending for opioids that were 1.53 (95% CI = 1.49- 1.57) and 1.75 (95% CI = 1.71-1.80) times higher, respectively, than patients aged 65 years and older. Per patient Medicaid and Medicare average adjusted annual spending for opioid prescriptions were 1.19 (95% CI = 1.16-1.22) and 2.01 (95% CI = 1.96-2.06) times higher than commercial insurance spending, respectively, while average spending per patient using cash payment was 17.4% lower than charges to commercial payers.

Patients who were dispensed benzodiazepines or a sympathomimetic stimulants had higher annual spending for opioid medications than those who were not. On average, adjusted annual opioid prescription spending was 2.01 (95% CI = 1.982.04) and 1.50 (95% CI = 1.45-1.55) times higher among patients who also had at least 1 benzodiazepine or stimulant dispensing, respectively. Average adjusted total spending for prescription opioids per patient increased with the average daily dosage: from 3-fold for patients using 50-90 MME daily to 22-fold for those receiving 90 or more MME daily compared with those receiving less than 50 MME daily. Patients with MPEs had mean adjusted annual opioid spending that was 4.34 (95% CI = 3.75-5.02) times higher than patients who did not use multiple prescribers and pharmacies.

DISCUSSION

In 2015, 197,062 patients (an estimated 18.7% of the state’s population) received at least 1 dispensing for an opioid medication from a retail pharmacy in Rhode Island. The total number of opioid prescriptions filled was 651,227, which corresponds to an average of 3.3 prescriptions per resident per year, or an estimated opioid prescribing rate of 61.65 prescriptions per 100 residents. This rate is comparable to rates estimated for other neighboring states and the rest of the country.[39,43]

The direct cost burden of prescription opioids was determined using data from a statewide PDMP, capturing controlled substance dispensings at the pharmacy level and encompassed dispensings for all providers and payment types, including cash. Thus, estimates from this study provide results that are more generalizable to the overall population, compared with analyses of a particular payer's pharmacy claims. Because PDMP programs do not include drug pricing information, this information was assimilated from other sources, providing what we believe is the first estimate of the direct annual cost burden of prescription opioid use, estimated at $44,271,827.00 for a population of approximately 1 million, in 2015 U.S. dollars. This estimate represents about 3.7% of total prescription drug sales at retail pharmacies in Rhode Island for 2016, according to a report published recently by the Kaiser Family Foundation (2017).[44] According to this report, which was based on IMS Health national prescription audit data, the total 2016 expenditure for all 18 million prescription drugs dispensed at retail pharmacies in Rhode Island was estimated at $1.2 billion. The estimate from our study does not include dispensings for tramadol, compounded products, or opioids dispensed in substance and opioid use disorder treatment centers, during inpatient hospital care, or in state correctional facilities.

In our study, the cost associated with prescription opioid use was determined in part by the intensity of use (i.e., number of dispensings and daily dosage) and the opioid product prescribed. Patients aged 45-64 years accounted for 47.14% of all opioid prescriptions dispensed and 59.49% of the total expenditure. While mean costs were highest for prescriptions for oxymorphone ($595.72), levorphanol ($560.80), and tapentadol ($492.86), dispensings for these medications accounted for only 3.7% of total overall annual cost. More than half (53.8%) of the annual cost of opioid medications for 2015 was associated with oxycodone dispensings, most of which can be attributed to higher-cost extended-release formulations, which accounted for almost 50% of the total annual expenditure even though they represented only 11% of all prescriptions. Efforts to address the cost burden of opioid overuse might target this middle-aged subgroup, with a focus on reducing the long-term use of opioids, many of which are prescribed as higher-cost extended-release formulations. Evidence for the use of opioids for chronic pain is limited amidst mounting evidence of serious dose-dependent harm.[45] Decreasing the unnecessary use of extended-release oxycodone for treatment of acute pain and the availability of a less costly generic formulation of this medication would have a dramatic effect on opioid expenditure, potentially yielding significant savings to the health care system.

Doctor-shopping behavior and the use of cash for prescription opioid payment, especially when the patient also has other types of insurance coverage, may indicate prescription opioid misuse.[46] About 21,538 (10.93%) patients paid for at least 1 opioid prescription with cash during the 2015 calendar year, and approximately 25% of these patients used at least 1 other type of insurance to pay for opioid prescriptions during the same year. The overall adjusted average prescription opioid spending by the 409 patients who met the 5/5/12 criteria was dramatically greater than that spent by patients who did not meet these criteria ($64.17 vs. $927.76, $P < 0.001$). However, higher costs associated with potential doctor shopping or use of benzodiazepines or stimulants may be an indication of poorly managed comorbid chronic conditions resulting from lack of coordinated care.

Other valid reasons for having multiple providers might include a change in primary care providers, different providers covering a patient's usual prescriber, having multiple specialists, and visits to dentists or the emergency room.[47] It is envisioned that the overuse of prescribers and pharmacies will decrease with increasing public awareness and implementation of regulations that require providers to review the PDMP before issuing a prescription for an opioid medication. However, most PDMPs are not currently integrated with electronic medical records, which make access to this information time consuming and often unfeasible.

The finding in this study that nearly 1 in 5 state residents received at least 1 opioid prescription during 2015 indicates that opioids are commonly prescribed within the state and suggests that a proportion of opioid prescribing may be clinically unnecessary. Levy et al. (2015) reported that opioids are the most commonly prescribed analgesics in the United States.48 This study, however, did not examine the clinical indications for which these opioid prescriptions were dispensed, so we could not quantify the extent and cost of inappropriate opioid prescribing. Liu et al. (2013), on the other hand, found that up to 40% of Medicaid patients receiving an opioid prescription had at least 1 marker of inappropriate prescribing, such as overlapping opioid prescriptions, overlapping opioid and benzodiazepine prescriptions, initiation of therapy with a long-acting opioid, use of long-acting opioids for acute pain, or high daily doses more than 90 MME.[24]

The Centers for Disease Control and Prevention recently published guidelines for prescribing opioids for chronic pain in the absence of cancer, palliative, or terminal care.[19] These guidelines recommend the use of non-opioids as first-line therapy for chronic pain, using opioid analgesics only when the benefits of such therapy are likely to outweigh the risks and prescribing the lowest effective dosage for the shortest number of days, when needed. Many insurers have introduced new policies to reduce inappropriate opioid prescribing, such as drug utilization review, prior authorization, quantity limitations, and pharmacy management review programs.[49,50] Trends in opioid prescribing should continue to be monitored as a measure of effectiveness of current public health interventions and narcotic stewardship programs, in order to determine if the frequency and cost burden of opioid use is diminishing.

LIMITATIONS

This study has some limitations to consider. The PDMP database does not include information describing health conditions or patient diagnoses, laboratory tests, clinician specialty, use of non-controlled prescription medications, or any other indicators of health care utilization. Since the analysis could not determine whether an opioid prescription was appropriate, we could not quantify the cost of inappropriate opioid prescribing, which limited the application of these results to improve prescribing practices.

The total cost estimate does not represent the total cost burden, since we could not estimate the cost of adverse effects or account for opioid prescriptions not filled in retail pharmacies. Furthermore, estimates from this study are a general approximation because payer reimbursement rates may vary from the methods we applied in our analysis to some degree. Also, a patient's state of residence could not be determined. However, the number of patients from neighboring states who received opioid prescriptions from Rhode Island pharmacies is likely to be offset by the number of

Rhode Island residents who filled opioid prescriptions at pharmacies in neighboring states.

The payment type variable was poorly reliable with regard to capturing Medicare as a payment source. An undetermined number of older adults were misclassified as having commercial insurance, and while we attempted to address this issue by reassigning these patients as covered by a Medicare drug plan, our ability to make inferences regarding opioid expenditure, by Medicare Advantage plans in particular, was nevertheless limited.

Finally, we recognize that the direct cost of prescriptions is merely 1 component driving health system expenses associated with pain management and opioid use in particular. Consideration of other treatment modalities, medical care, and humanistic outcomes should be included in health economic analyses that assess opioid use as facet of pain management.

CONCLUSIONS

This study provides the first estimate of a statewide direct cost burden of prescription opioid use using PDMP data and standardized pricing benchmarks. Total annual cost increased with age up to 65 years, mean daily dose, and concurrent use of benzodiazepines or stimulants. Commercial insurance bore the majority of the cost of prescription opioid use, but cost per patient was highest among Medicare beneficiaries. Almost 11% of patients used cash payment at least once during the 2015 calendar year, and cash payment accounted for about 5.1% of the total annual prescription opioid expenditure.

This analysis suggests that substantial cost savings could result from increased use of generic formulations of commonly prescribed opioid products. Greater savings and improved patient health outcomes could be realized by reducing overall opioid use, especially among middle-aged individuals.

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Table 1 Characteristics of Individuals Who Filled at Least one Opioid Prescription at a Retail Pharmacy in R.I. in 2015 (N = 197,062)

Characteristic[a]	n (% of N)
Gender[b]	110,001 (55.82)
Female	87,043 (44.17)
Male	
Age Group, Years	
less than 18	5,995 (3.04)
18-24	15,327 (7.78)
25-34	27,302 (13.85)
35-44	27,738 (14.08)
45-54	37,155 (18.85)
55-64	38,372 (19.47)
greater than 65	45,173 (22.92)
Payment Method	
Commercial Insurance	114,654 (58.18)
Medicare	43,213 (21.93)
Cash	19,476 (9.88)
Medicaid	15,767 (8.00)
Other[c]	3,952 (2.01)
Most Recent Opioid Dispensed	
Hydrocodone	90,151 (45.75)
Oxycodone	73,622 (37.36)
Codeine-based	18,409 (9.34)
Morphine	6,894 (3.50)
Hydromorphone	3,698 (1.88)
Fentanyl	1,450 (0.74)
Methadone	650 (0.33)
Tapentadol	192 (0.10)
Oxymorphone	146 (0.07)
Meperidine	64 (0.03)
Pentazocine	50 (0.03)
Butorphanol	35 (0.02)
Others[e]	1,700 (0.86)
Mean daily MME per patient[f]	
≤ 50	153,085 (77.68)
50-90	32,081 (16.28)
90+	8,536 (4.33)
Benzodiazepine use	
No	144,899 (73.53)
Yes	52,163 (26.47)
Stimulant use	
No	188,343 (95.58)
Yes	8,719 (4.42)
5/5/12 criteria	
Not met	196,653 (99.79)
met	409 (0.21)

[a]Gender, payment method, medication type and mean daily MME classified according to data captured in the last prescription dispensed in 2015.
[b]Gender was not reported for 18 patients (0.01%).
[d]Includes worker's compensation, Indian Health Services, the Veterans Health Administration, Tricare, other federal sources.
[e]Primarily opioid-containing cough products and Levorphanol (see Appendix A)
[f]MME=Morphine milligram equivalent; unable to determine MME for 3,360 (1.71%) of patients

Table 2. Opioid Prescriptions Dispensed in by R.I. Retail Pharmacies in 2015

Characteristic	Number of Prescriptions (%)	Prescription Cost ($) Mean (SD)	Median	Total	% Total Cost
Overall	651,227	67.98 (210.91)	21.08	44,271,827.00	100.00
Age group, years					
less than 18	7,889 (1.21)	20.78 (41.63)	8.54	163,902.33	0.37
18-24	22,794 (3.50)	15.45 (43.29)	7.02	352,063.77	0.80
25-34	57,597 (8.84)	34.55 (145.80)	9.36	1,990,258.63	4.50
35-44	84,085 (12.91)	61.08 (223.88)	16.47	5,135,736.95	11.60
45-54	144,608 (22.21)	81.01 (247.86)	22.95	11,714,458.06	26.46
55-64	162,352 (24.93)	90.07 (251.01)	25.32	14,622,945.43	33.03
greater than 65	171,902 (26.40)	59.87 (154.39)	22.95	10,292,461.84	23.25
Medication type					
Butorphanol	355 (0.05)	163.90 (109.88)	163.59	58,184.34	0.13
Codeine-based	37,100 (5.70)	6.86 (6.99)	4.43	254,557.96	0.57
Fentanyl	15,169 (2.33)	204.43 (552.01)	126.66	3,101,069.73	7.00
Hydrocodone	253,850 (38.98)	34.15 (54.21)	21.42	8,668,532.13	19.58
Hydromorphone	9,717 (1.47)	209.70 (554.09)	18.23	2,037,677.97	4.60
Levorphanol	9 (0.00)	560.08 (907.64)	103.12	5,040.76	0.01
Meperidine	261 (0.04)	29.20 (24.95)	19.13	7,620.44	0.02
Methadone	7,156 (1.10)	41.82 (32.23)	29.70	299,254.81	0.68
Morphine	35,462 (5.45)	108.67 (267.76)	40.22	3,853,808.20	8.70
Oxycodone	281,225 (43.18)	84.69 (235.80)	21.18	23,817,051.40	53.80
Oxymorphone	1,810 (0.28)	595.72 (512.60)	439.68	1,078,255.85	2.44
Pentazocine	341 (0.05)	173.27 (178.45)	178.75	59,084.86	0.13
Tapentadol	1,103 (0.17)	492.86 (293.16)	421.98	543,626.74	1.23
Others[a]	7,669 (1.18)	63.64 (99.66)	38.16	488,061.81	1.10
MME daily[b]					
≤ 50	430,519 (66.11)	30.28 (53.62)	14.39	13,034,889.82	29.44
50-90	135,105 (20.75)	70.26 (137.46)	28.51	9,492,612.15	21.44
90+	81,145 (12.46)	265.42 (513.27)	87.73	21,537,624.36	48.65
Generic or Brand name					
Generic	612,585 (94.07)	43.90 (116.21)	19.13	26,891,547.96	60.74
Brand name	38,642 (5.93)	449.78 (616.97)	279.43	17,380,279.05	39.26
Duration of action					
Short-acting	579,849 (89.04)	38.27 (128.72)	16.47	22,190,457.00	50.12
Long-acting	71,378 (10.96)	309.36 (453.68)	136.26	22,081,370.01	49.88
Payment type[c]					
Commercial	332,088 (50.99)	65.55 (213.46)	19.00	21,769,832.09	49.17
Medicare	191,554 (29.41)	85.31 (240.12)	28.08	16,341,749.85	36.91
Medicaid	51,490 (7.91)	52.15 (154.24)	15.13	2,685,118.58	6.07
Private pay	60,548 (9.3)	37.18 (97.84)	14.39	2,251,262.97	5.09
Other[d]	15,546 (2.39)	78.72 (234.92)	20.11	1,223,849.24	2.76

[a] Primarily opioid-containing cough products (see Appendix A)
[b] MME=Morphine milligram equivalent; unable to determine MME for 1.71% of observations
[c] If age ≥ 65 and Commercial ins. then payment type was reclassified as Medicare; Method of payment was missing for 1 prescription.
[d] Includes worker's compensation, Indian Nation, the Veterans Health Administration, Tricare, other federal sources.

Table 3: Adjusted per-Patient Total Annual Prescription Opioid Costs by Patient Demographic and Utilization Characteristics (N=197,062)

Independent variable	Mean cost per patient ($)[a] [95% CI]	Adjusted β-coeff[b]	SE	95% Conf. Interval
Intercept	64.17 (62.25, 66.10)	3.8415	0.0136	(3.8149, 3.8680)
Age group (years)				
65 +	Reference			
less than 18	-45.89 (-48.09, -43.68)	-1.1680	0.0243	(-1.2157, -1.1204)
18-24	-50.22 (-52.13, -48.31)	-1.2910	0.0173	(-1.3250, -1.2571)
25-34	-42.10 (-44.04, -40.17)	-0.7492	0.0150	(-0.7786, -0.7198)
35-44	-11.89 (-14.20, -9.59)	-0.0415	0.0149	(-0.0706, -0.0124)
45-54	17.65 (15.26, 20.04)	0.4257	0.0139	(0.3985, 0.4530)
55-64	28.47 (26.06, 30.88)	0.5621	0.0137	(0.5353, 0.5888)
Gender				
Female	Reference			
Male	5.14 (4.44, 5.84)	0.1364	0.0070	(0.1228, 0.1501)
Payment type[c]				
Commercial	Reference			
Medicaid	0.56 (-0.51, 1.63)	0.1733	0.0129	(0.1481, 0.1986)
Medicare	33.20 (31.05, 35.35)	0.6971	0.0127	(0.6722, 0.7220)
Private Pay	-3.80 (-4.69, -2.91)	-0.1917	0.0129	(-0.2170,-0.1663)
Other[d]	9.16 (5.17, 13.15)	0.2988	0.0250	(0.2498, 0.3479)
Mean daily MME per patient				
≤50	Reference			
50-90	97.91 (95.14, 100.68)	1.0756	0.0092	(1.0575, 1.0938)
>90	337.73 (332.84 , 342.62)	3.1124	0.0168	(3.0795, 3.1453)
Benzodiazepine use[e]				
No	Reference			
Yes (n = 52,163)	35.99 (34.45, 37.54)	0.6980	0.0079	(0.6825, 0.7135)
Stimulant use[f]				
No	Reference			
Yes (n = 8,719)	8.61 (6.47, 10.76)	0.4062	0.0167	(0.3735,0.4390)
5/5/12 Criteria[f]				
Not Met	Reference			
Met (n = 409)	863.58 (689.48, 037.68)	1.4672	0.0741	(1.3220, 1.6125)

[a]Mean cost per patient estimated using the identity link function;
[b]Coefficients of gamma regression and standard errors estimated using the log link function;
[c] If age ≥ 65 and Commercial Ins. then payment method was reclassified as Medicare;
[d] Includes worker's compensation, Indian Nation, the Veterans Health Administration, Tricare, other federal sources;
[e,f] Use of other benzodiazepines and stimulants defined as one of more prescriptions in a 12 month period.
[f] 5/5/12/ Criteria: Opioid prescriptions from at least 5 different pharmacies and 5 different prescribers during the 12 month period.

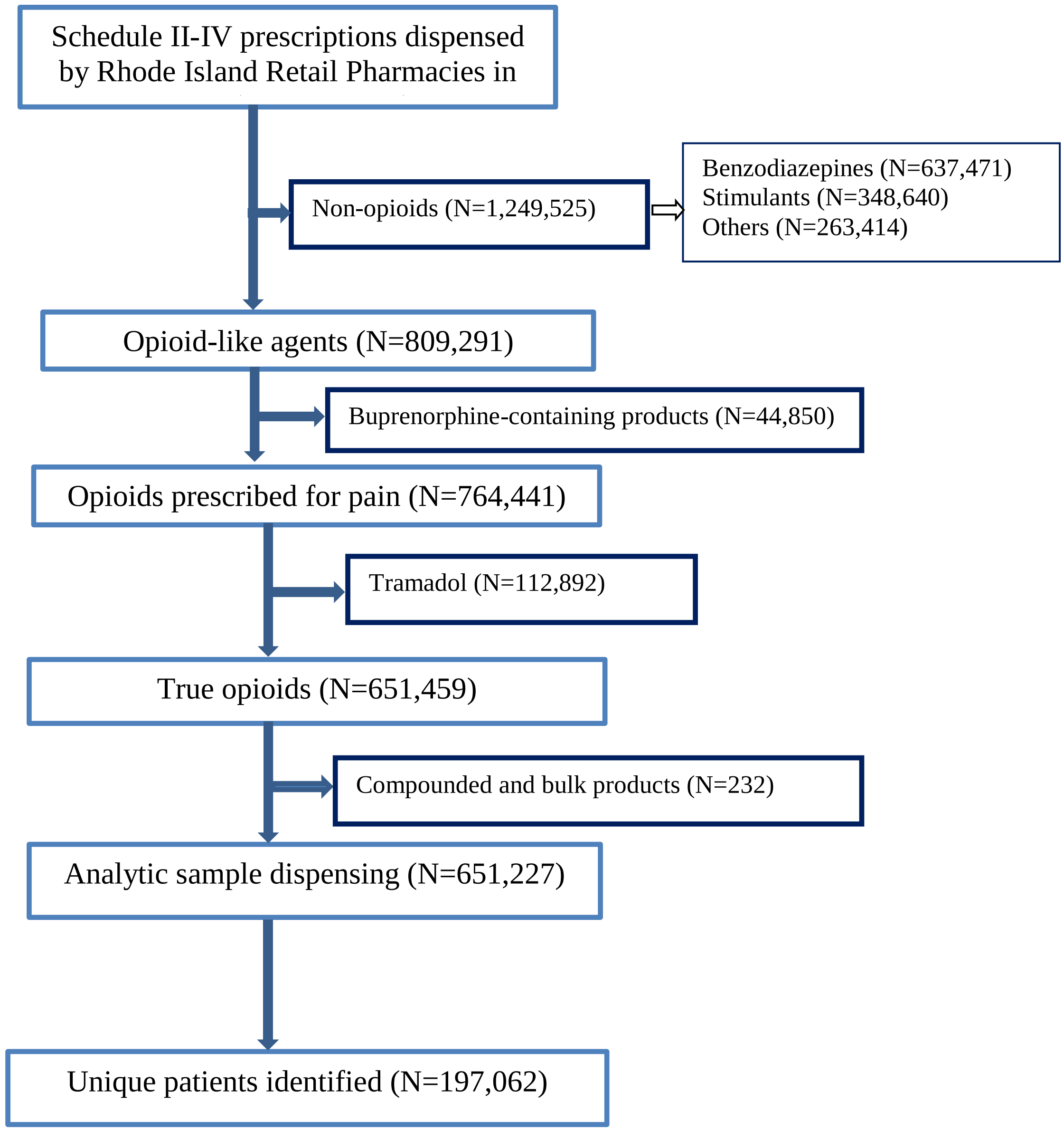

Figure 1. Sample Identification Flowchart

CHAPTER 3

MANUSCRIPT III

Title: **Assessing Association between Cash Payment and Potential Opioid Misuse among Patients on Chronic Opioid Therapy**

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ABSTRACT

Background: Prescription opioid misuse and overdose among patients on chronic opioid therapy (COT) is a serious public health problem in the United States. In response more state-run prescription drug monitoring programs (PDMP) have been implemented and strengthened. PDMP administrators and criminal investigators suggest that cash payment may be indicative of potential prescription opioid misuse (POM), but there is little systematic evidence to substantiate this claim.

Objectives: To evaluate the association of methods of payment and potential prescription opioid misuse among patients on chronic opioid therapy.

Methods: De-identified 2015 Rhode Island PDMP data was used to conduct a cross-sectional study. We restricted the study cohort to patients on COT defined as having received at least 90 days' supply during a 6-month period. The database captures information describing opioid dispensing at all R.I. retail pharmacies including sources of payment for each opioid prescription. The method of payment was categorized as no cash (insurance exclusively), cash only, or both (insurance with at least one cash payment). A modified validated opioid misuse index that combines the number of opioid prescribers and pharmacies used, and days' supply of short-acting and long-acting opioids, was used to define potential prescription opioid misuse. A multivariable log-binomial regression model was used to examine the association between cash payment and potential opioid misuse, controlling for sex, age group, type of opioid used, and concurrent benzodiazepine use. The analysis was stratified by age group (patients under 65 years vs. patients 65 and over) because the pharmacy

benefit design for many Medicare Part D drug plans includes a coverage gap where patients pay cash for a limited period of time.

Results: A total of 45,332 patients met our inclusion criteria for COT, of which 80% paid for all of their opioid prescriptions with third party insurance exclusively, 3% used only cash, and 17% had insurance and paid for at least one opioid prescription in cash. The median age was 57 years and 59% were female. Among patients under 65 years old, those who had insurance coverage and paid for at least one of their opioid prescriptions in cash were more likely to exhibit a pattern of opioid filling suggestive of prescription opioid misuse as compared to those who paid all opioid prescriptions with insurance exclusively, after controlling for potential confounding variables (adjusted risk ratio [aRR] = 1.80; 95% confidence interval [CI]: 1.73, 1.87). Among patients aged 65 years and older, the strength of the association was differed by gender. Compared with men who used only insurance to buy their opioid prescriptions (reference group), the risk of potential POM was higher among women who had insurance and used cash payment (aRR=2.19; 95% CI: 2.01 - 2.39), than among men who had insurance and also used cash payment (aRR=1.84; 95% CI: 1.62 - 2.09), than among women who used insurance exclusively (aRR=1.03; 95% CI: 0.93 - 1.15). Excess relative risk due to interaction was 0.32 on the risk ratio scale which means there is a positive modification the association between cash payment and the risk of potential prescription opioid misuse on the additive scale. In both age groups, exclusive cash payment was associated with a much lower risk of potential prescription opioid misuse.

Conclusion: While there may be legitimate reasons to pay for opioid prescriptions in cash, this study suggests that patients on COT who pay for some, but not all, opioid prescriptions in cash should raise concern for potential opioid misuse only when the patient has other health insurance coverage. The public health and clinical implications of these findings warrant further study.

INTRODUCTION

The use of chronic opioid therapy (COT) for chronic non-cancer pain has increased tremendously over the last three decades despite lack of evidence for long-term effectiveness. There is evidence that excessive opioid prescribing has contributed to the current opioid epidemic since misuse of prescribed opioids has been associated with accidental opioid overdose-related deaths.[1,2] The risk of prescription opioid misuse is the primary reason why almost all states now monitor the use of controlled substances using their prescription drug monitoring programs (PDMP). Validated criteria have been developed to help identify patterns of prescription opioid consistent with prescription opioid misuse among patients on chronic opioid therapy using administrative claims data.[3]

Limited data suggest that information on the method of payment may help detect potential prescription opioid misuse and contribute to improved opioid prescribing among physicians by identifying patients at high-risk for overdose. Almost all state PDMPs collect information on method payment, and a recent study showed that the proportion of controlled substances paid for in cash varies by about 3-fold across states.[4] High percentages of opioid prescriptions paid for in cash are generally regarded with suspicion because patients who seek prescriptions of the same controlled substances from multiple prescribers are more likely to pay for their prescriptions in cash.[5] Furthermore, the National Association of Boards of Pharmacy, PDMP administrators and law enforcement investigators believe that cash payment indicates potential prescription opioid misuse, especially when the patient has other health insurance coverage.[6] "Pill mills" also accept cash payment as a way to avoid detection.[7] The practice of concealing potential opioid misuse could have significant implications for drug utilization reviews since these evaluations are often restricted to specific health systems and could miss opioid prescriptions paid in cash. Understanding how cash payment relates to potential prescription opioid misuse may shed light on the public health magnitude of the problem and provide new ways to identify potential opioid misuse from a payer perspective.

BACKGROUND

Each year about twenty percent of adults in the United States are prescribed opioid analgesics for a variety of painful conditions ranging from acute pain due to injury to chronic cancer pain and pain occurring during terminal illness. Initial opioid therapy often intended by prescribers for short-term use sometimes leads to unintended long-term use, with adverse health outcomes including opioid misuse, overdose, and opioid-related deaths.[8-12] Prescription opioid misuse (POM) often precedes heroin use.[13] The rise in POM has been associated with a corresponding increase in opioid prescribing for therapeutic uses especially among patients with chronic pain. A recent study of controlled substance prescribing patterns in eight US states found that opioid analgesics were prescribed twice as often as stimulants or benzodiazepines.[4] A relatively small proportion of prescribers were responsible for a large proportion of prescriptions. For example, overall 10% of prescribers accounted for more than 50% of opioid prescribing and in one state 25% of opioid prescription were prescribed by 1 percent of prescribers. Prescription opioids for misuse are most commonly obtained from a family member or friend, but patients at highest risk of overdose are as likely to get them legally from a licensed clinician.[13]

There is no universally accepted definition of prescription opioid misuse (POM). It may be broadly defined as any use of a prescription opioid medication without a prescription, or in ways that are not consistent with of the recommendations of the prescriber including excessive use (higher amounts, frequency or duration), deliberate use for euphoria, diversion for illicit use, or having multiple providers prescribing overlapping prescriptions of the same medication. In this study, we focus on the excessive use of prescription opioid analgesics legally obtained from a licensed provider and filled at a retail pharmacy. A recent systematic review of seven studies highlighted differences in the way researchers have conceptualized, operationalized, and conducted validation studies.[14] Three of the studies considered POM in terms of potential or probable misuse of opioid medications acknowledging the difficulties in establishing a diagnosis of misuse from secondary sources. Several items have been used to develop algorithms to identify cases of POM including the use of ICD-9 codes, prescription records, pharmacy records, and urinary toxicology. Sullivan et al used the number of providers and pharmacies, and number of days' supply to develop an algorithm that was validated using a quantitative criterion validity study in two types of administrative claims databases, including a commercial health plan and Medicaid, with adequate support for its use.[3]

According to a recent survey, the most common reason for POM among patients on opioids is to relieve physical pain suggesting that misuse most commonly occurs among patients on COT.[15] Compared with opioid-naïve patients, the use of cash payment and POM behavior were more common among patients on COT, especially those taking schedule II opioids.[5] Several risk factors have been associated with POM among patients on COT; these include being young or middle aged adults, white race, and a history of mental health disorders (including depression or posttraumatic stress disorder), and a family or personal history substance use disorder, including tobacco use.[16-26] The risk of POM was the primary reason why states monitor controlled substances using PDMP and in recent years, there has been a growing interest in using PDMP data for epidemiologic and health services research despite absence important clinical and demographic variables.[27] One of the unique features of most PDMP is their ability to capture almost all outpatient opioid prescriptions filled at a retail pharmacy with the method of payment used by the patient irrespective of their insurance coverage.

The decision to pay for an opioid prescription with cash depends on many factors including promotional cheaper generic formulations, lack of health insurance or prescription drug coverage, the existence of a gap in prescription drug coverage especially among the elderly, or simply to minimize information made accessible to drug utilization reviewers.[28] At least 47 states collect information on the method of payment including Rhode Island. Program administrators, law enforcement investigators, and some organizations believe that cash payment suggests POM, especially when the patient has other health insurance coverage.[6,29] However, few studies have attempted to evaluation this association because most claim data sources do not capture the method of payment including cash.[30] The use of cash payment can have significant implications for drug utilization evaluation since these evaluations are often restricted to specific health systems which do not capture opioid prescriptions paid with cash. Understanding the relationship between cash payment and POM may provide policy-makers with another tool to design intervention focused on the populations most at risk of POM. The objective of this study was to evaluate the relationship between method of payment and potential POM among patients on chronic opioid therapy.

METHODS

Study design, data source, and study population: A cross-section study was conducted using the 2015 Rhode Island PDMP data, which contains de-identified records of controlled substances dispensed by all retail pharmacies in the state. These include a unique patient, prescriber, and dispensing pharmacy information, and a limited number of variables such as age (in years) and sex of the patient, National Drug Code numbers (NDC), product name, strength, formulation, and therapeutic class code of the drug, number of days' supply, metric quantity dispensed, method of payment, and the date each prescription was filled. The method of payment field populated by the dispensing pharmacist as commercial was reclassified as Medicare if the patient was aged 65 years and older since they were more likely to be enrolled in a Medicare plan. The data does not include opioid prescriptions filled during in-patient admission, incarceration, or substance abuse treatment. A detailed description of the data has been published elsewhere.[31]

All patients who filled at least one opioid prescription at a RI retail pharmacy during 2015 calendar year were eligible for inclusion in the study, regardless of the indication for the opioid medication. Schedule II-IV opioid prescriptions filled between January 1, 2015 and December 31, 2015 were identified using the National Drug Code numbers. We excluded opioid medications used for OUD treatment,[32] compounded formulations and bulk containers (for which do not have patient-level data), prescriptions with improbable data, or patients with missing sex. The time between the first and the last opioid prescription during the year was required to be at least 180 days since we were interested in POM among patients on COT. Chronic opioid therapy was defined as receiving at least 90 non-overlapping days' supply during a 6-month period.[33]

Primary exposure and covariate information: Method of payment, the primary independent variable for the analysis, was categorized as no cash (if the patients used insurance exclusively), cash only, or both (if the patient had insurance and paid for at least one opioid prescription with cash). We converted opioid prescriptions dosing information to daily milligrams of morphine equivalent by multiplying the quantity of each prescription by the strength of the prescription and multiplying this total by the CDC 2015 conversion factor[34]. For patients who received more than one opioid prescription on any given day, milligrams MME of each prescription were added together. Age (in years), gender, type of opioid and other concurrent controlled substances were captured in the database. Age was categorized as < 44, 45-54, 55-64, and 65 and above. Since some patients filled more than one type of opioid prescription during the year, the type of opioid was defined as the most commonly filled medication type, according to the number of dispensings during the year. To examine the concurrent use of benzodiazepines, each prescription's dates of use were calculated from the fill date plus the number of days supplied. Any patient with at least 90 days of overlapping dates of both a benzodiazepine and an opioid prescription in a year were considered as chronic overlapping or concurrent therapy.

Measurement of primary outcome: A modified validated opioid misuse index that combines the number of prescribers and pharmacies used, and days' supply of short-acting and long-acting opioids was used to define potential POM.[3,35] The algorithm uses the frequencies of unique providers and pharmacies utilized and counts of days' supply of long and short-acting opioids. Days supplied of short-acting opioids (91-185, 186-240, >240 days) and long-acting opioids (91-185, 186-240, >240 days) during a 6-month period, and the number of opioid prescribers (≤2, 2-4, ≥5) and the number of pharmacies used (≤2, 2-4, ≥5) during the same time period are each assigned 0, 1, or 2 points, respectively. The total score for the six months was used to classify patients as 'no misuse' (score=0) or 'possible misuse' (score=1) and 'probable misuse' (score ≥2). To create a binary outcome variable, the last two categories were combined to form a category of 'potential misuse'.

Statistical analysis: Descriptive statistics were used to compare characteristics of patients grouped by method of payment. A risk factor model was constructed with significant potential confounders included in the model to evaluate the association between method of payment and potential POM. Since risk ratio were our parameters of interest, a multivariable binomial generalized linear model with a log link functions was used to estimate the adjusted risk ratios, controlling for sex, age group, type of opioid prescription, and concurrent chronic benzodiazepine use.[36,37] Because the pharmacy benefit design for many Medicare Part D drug plans includes a coverage gap where patients pay cash for a limited period of time, the analysis was stratified by age group (patients under 65 years versus patients 65 years and over). Since the association between method of payment and potential POM was modified by sex among patients 65 years and older, relative excess risk due to interaction (RERI) was used to assess departure from additivity of 'effects' on a relative risk and risk difference scales. All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC) and all tests of statistical significance were two-sided and performed at the alpha = 0.05 significance level.

RESULTS

A total of 45,332 patients met the inclusion criteria for COT, of which 80.3% paid for all of their opioid prescriptions with a third party insurance exclusively, 3.1% used only cash, and 16.6% had insurance coverage but paid for at least one opioid prescription with cash. Table 1 shows overall and group-specific patient characteristics. The mean age of patients was 56.8 years (standard deviation [SD] =16.3) and 59.1% were female. More than 30% of patients were aged 65 years and older. On average, patients who used cash exclusively were older than patients who had insurance but the difference in age was not statistically significant. More than 55% of patients who used cash exclusively were aged 65 years and older. Patients who had insurance and paid for at least opioid prescription with cash were more likely to be in the age group 65 years and older than patients who used insurance exclusively for all opioid prescriptions (41.8% vs. 27.1%).

Most patients used commercial insurance to pay for their opioid prescriptions. Among patients who had insurance and paid for at least opioid prescription in cash, 36.7% had Medicare compared with 31.6% who also had commercial insurance. A higher proportion of patients who used cash exclusively filled fewer prescriptions and used a lower average daily MME compared with those who had insurance. The average number of opioid prescriptions among exclusive cash users was 7.82 (SD=5.39) compared with 9.92 (SD = 7.47) and 13.37 (SD = 9.97) among those who used insurance only or both cash and insurance, respectively. The highest proportions of those who filled 11 or more prescriptions and utilized on average 90 or more MME per day was among patients with insurance coverage who paid for at least one opioid prescription in cash. Furthermore, patients using cash only tended to have one or two prescribers (78.5%) and visited only one or two pharmacies (96.1%) compared with those who had some insurance coverage. Almost 40% of patients who used cash and insurance had four or more prescribers. Similarly, the highest proportion of patients on concurrent chronic benzodiazepine use (18.0%) was among those who used cash and insurance to pay for opioid prescriptions.

Table 2 shows the results of the log-binomial regression modeling the relationship between method of prescription opioid payment and potential POM. A total of 10,015 patients (22.1%) were classified as having a pattern of opioid filling consistent with potential POM. Among patients under 65 years old on COT, those who had insurance coverage and paid for at least one of their opioid prescriptions in cash were 1.8 times more likely to exhibit a pattern of prescription opioid filling suggestive of POM as compared with those who paid for all their opioid prescriptions with insurance exclusively, after controlling for potential confounding variables (RR= 1.8; 95% CI: 1.73 - 1.87). After adjusting for age group, sex, type of opioid prescription, and concurrent chronic benzodiazepine use, the use of cash exclusively among patients younger than 65 years old reduced the risk of potential POM by 52% when compared to those who had insurance and used it exclusively to purchase their opioid prescriptions (RR= 0.48; 95% CI: 0.38 - 0.61).

Among patients aged 65 years and older, the strength of the association between a dichotomous method of payment (insurance with at least one cash payment versus insurance exclusively) and potential POM differed by gender ($p = 0.0174$). The results of interaction analyses are summarized in Table 3 where men who used only third party insurance were used as the reference group for all comparisons. Compared with men who used only insurance to buy their opioid prescriptions, the risk of potential POM was higher among women who had insurance and used cash payment (aRR=2.19; 95% CI: 2.01 - 2.39), than among men who had insurance and also used cash payment (aRR=1.84; 95% CI: 1.62 - 2.09), than among women who used insurance exclusively (aRR=1.03; 95% CI: 0.93 - 1.15). After adjusting for age, sex, type of opioid medication, and concurrent benzodiazepine use, the relative excess risk due to interaction (RERI) was 0.32 on the additive and multiplicative scales. This indicates that on the additive scale, the excess relative risk of potential POM associated with being a woman aged 65 years and older with insurance who also uses cash payment is greater than the excess relative risk associated with female gender or using cash when the patient has insurance alone. On a multiplicative scale, the ratio of RRs in strata of the sex of 1.15 indicates that the estimated joint impact of both factors (female sex and use of insurance with some cash purchase) together was 15% larger than the product of the relative risk associated with each factor acting alone. Among patients aged 65 and older, exclusive cash payment was associated with a 60% lower risk of potential POM among men (aRR=0.40; 95% CI: 0.24 - 0.69) compared with exclusive use of insurance payment; among women the risk reduction associated with exclusive cash use was not statistically significant, after adjusting for potential confounders (aRR=0.48; 95% CI: 0.15 - 1.56).

DISCUSSION

We found that cash payment is associated with potential POM only when the patient has health insurance with prescription coverage. Among patients aged 65 and older, the strength of the association differed by gender; it was stronger among women than men. This is particularly concerning because in recent years the rate of overdose deaths involving opioid analgesics among women is almost double that among males.[38] Our findings are consistent with those of other studies and reports from several organizations including the Center for Disease Control and Prevention linking cash payment for controlled substances to potential opioid misuse.[5,6,29,30] A recent cross-sectional study of individuals with Veterans Health Administration payment for prescription opioid analgesics in Kentucky found that additional sources of payment for opioids, especially cash, were associated with the receipt of risky opioid regimens defined as a combination of opioid/benzodiazepine therapy or high-dose (daily MME > 90mg) opioid therapy.[39] Since a common reason for opioid misuse is persistent pain, it is likely that patients with health insurance pay for some prescriptions with cash because a refill for an opioid prescription requested too early would not be covered by their insurance or if their coverage limit is exceeded. Among patients who had insurance and paid for some opioid prescriptions with cash, 36% were Medicare beneficiary, likely reflecting gaps in prescription drug coverage among patients with Medicare Part D.

There is limited evidence that patients who seek prescriptions of the same controlled substance from multiple prescribers are more likely to pay for their prescriptions in cash.[5] We found that 17% of patients on long-term opioid therapy who had insurance coverage during the study year paid for at least one opioid prescription with cash.[28] This group of patients was more likely to see multiple providers and pharmacies than patients who use only cash or insurance. In our study, 8.1% of opioid prescriptions among patients on COT were paid for in cash. This is similar to those of a recent study using PDMP data in which five states collected information on the method of payment and the proportion of prescription opioid analgesics paid for in cash varied about from 8% to 19.5%.[4] In that study, a higher percentage of cash payment was seen in states with smaller proportions of Medicaid payment. This suggests that low Medicaid coverage may leave many people without insurance who left to pay for their opioid prescriptions with cash. Some studies have reported that providers profiteering usually accept only cash payment as a way to reduce the amount of information available to investigators to track and identify the patients and prescribers involved.[7] In our study oxycodone, hydrocodone and tramadol were the most common opioid prescriptions paid with cash. According to the CDC, oxycodone and hydrocodone constitute two of the three most common drugs involved in prescription opioid overdose deaths in the United States. A recent study found that hydromorphone, fentanyl, and methadone were more likely than other prescription opioid analgesics to be paid with cash.[30] However, cash payment was defined in that study as an opioid prescription fill identified in a PDMP data set without a corresponding matching claim in a Medicaid pharmacy claim within a few days. Our analysis uses cash payment recorded at the time the opioid prescription was dispensed and is likely to provide a more accurate estimate of the association.

Patients who paid for all their opioid prescriptions with cash were older, filled fewer opioid prescriptions, had a lower average daily dose, and spent on average less on opioid prescriptions than patients who had insurance. Cash only opioid users also saw fewer prescribers and visited fewer pharmacies. Since our operational definition of potential POM was based on days' supply (which is associated with the number of prescription) and number of prescribers and pharmacies, it is not surprising that use of cash only is associated with a lower risk of potential POM. In this sample, patients who used only cash probably lacked health insurance and could not afford to pay for expensive opioid prescriptions. Other studies have found that patients who misuse prescription opioids were more frequently uninsured, jobless, or low income adults.[15] The fact that a higher proportion of older patients paying for all opioid prescriptions with cash is surprising because almost all patients aged 65 years and older are on Medicare unless they do not have prescription drug coverage. On the contrary, patients who had health insurance with drug coverage, on average, filled more prescriptions at higher doses, saw more prescribers, visited more pharmacies, and spent more on opioid prescription (See Table 3 in Appendix C).

Estimates of the prevalence of POM among patients who are prescribed opioid analgesics vary tremendously, reflecting differences in the study populations and definitions of POM used. Twenty-two percent of patients on long-term opioid therapy on our study had a pattern of opioid filling consistent with potential POM. This is similar to other estimates of behaviors consistent with POM among patients on prescription opioids ranging from 16 to 78%.[17,20,21] The 2015 National Survey on Drug Use and Health in the United States estimated that among the 92 million adults prescribed opioid medications the previous year, 13 % reported POM while a recent primary care study of over 6,000 United States veterans found a prevalence of 5%.[15,26] These studies and ours suggest that POM is a serious public health problem in the United States. Our study suggests that use of cash payment when a patient has other health insurance coverage may be a surrogate marker of potential POM.

LIMITATIONS

Our study has some limitations. First, being a cross sectional study we could only demonstrate associations between method of payment and potential POM, not causality. We assumed that our modified validated measure of opioid misuse correctly identified patients who actually misused opioids. However, we did not have any clinical documentation or patient reported opioid use to ascertain the way prescribed opioids were used. Multiple prescribers may be part of a coordinated care within a large group practice and thus not necessarily represent risk of opioid misuse. Second, we could not account for opioid prescriptions filled in neighboring states since the data source does not provide that information. In a recent study looking at potential misuse of medications used to treat attention deficit hyperactivity disorder, patients with potential misuse behavior traveled longer distances and visited more states to fill their medications than patients without similar behaviors.[40] It is estimated that about 20% of patients who misuse opioid prescriptions get their prescriptions filled in more than one state compared to only 4% of patients with no evidence of opioid misuse.[41] Third, the method of payment may not have captured Medicare or Medicaid payment accurately. Reclassification of patients aged 65 years and older with commercial insurance as Medicare may have led to some misclassification of some methods of payment. However, such misclassification did not involve cash payment and therefore would not be expected to affect our results. Fourth, we lacked information on socioeconomic status, indications for opioid prescription, and use of illicit opioids.

CONCLUSIONS

Our study provides one of the first estimates of the relationship between cash payment and potential POM among patients on COT using a data source that directly captures the method of payment irrespective the patient's health insurance. Seventy percent of patients with insurance having drug coverage paid for at least one opioid prescription with cash. While there may be legitimate reasons to pay for opioid prescriptions with cash, this study suggests that patients on COT who pay for some, but not all, opioid prescriptions in cash should raise special concerns for potential opioid misuse only when the patient has other health insurance with drug coverage. Among patients aged 65 years and older, the strength of the association between cash payment and potential POM is stronger among women than men. Further research is needed to determine the public health relevance of these findings and whether cash payment is associated with adverse health outcomes.

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Table 1 Characteristics of patients on chronic opioid therapy by payment source in Rhode Island Prescription Drug Monitoring Program, 2015

Characteristic	Overall (N=45,332)	Cash only (N= 1,401)	Insurance only (N= 36,409)	Both (N=7,522)
Continuous variables, mean (SD)				
Number of Rx	10.43 (7.910	7.82 (5.39)	9.92 (7.47)	13.37 (9.97)
Average cost ($)	54.50 (138.18)	27.17 (55.35)	56.18 (145.17	51.46 (111.00)
Average total cost ($)	868.19 (2955.84)	302.05 (949.22)	867.59 (3036.31)	976.55 (2791.45)
Age (years)	56.80 (16.29)	61.74 (21.07)	55.98 (15.74)	59.83 (17.30)
Age group (years)				
< 44	9,897 (21.83)	250 (17.84)	8,154 (22.40)	1,493 (19.85)
45-54	9,835 (21.70)	154 (10.99)	8,365 (22.98)	1,316 (17.50)
55-64	11,822 (26.08)	224 (15.99)	10,030 (27.55)	1,568 (20.85)
65+	13,778 (30.39)	773 (55.17)	9,860 (27.08)	3,145 (41.81)
Gender				
Female	26,799 (59.12)	776 (55.39)	21,606 (59.34)	4,417 (58.72)
Male	18,533 (40.88)	625 (44.61)	14,803 (40.66)	3,105 (41.28)
Primary method of payment				1,490 (19.81)
Cash	2,891 (6.38)	1,401 (100.0)	NA	729 (9.69)
Medicaid	3,404 (7.51)	NA	2,675 (7.35)	2,762 (36.72)
Medicare	15,635 (34.49)	NA	12,873 (35.36)	2,375 (31.57)
Commercial Ins.	22,598 (49.85)	NA	20,223 (55.54)	166 (2.21)
Other	804 (1.77)	NA	638 (1.75)	
Primary opioid type used				
Hydrocodone	15,347 (33.85)	356 (25.41)	12,881 (35.38)	2,110 (28.05)
Oxycodone	15,577 (34.36)	313 (22.34)	12,188 (33.48)	3,076 (40.89)
Tramadol	8,795 (19.40)	568 (40.54)	6,802 (18.68)	1,425 (18.94)
Other	5,613 (12.38)	164 (11.71)	4,538 (12.46)	911 (12.11)
Number of opioid dispensing				
≤ 5	14,366 (31.69)	593 (42.33)	12,181 (33.46)	1,592 (21.16)
6-10	10,894 (24.03)	389 (27.77)	8,741 (24.01)	1,764 (23.45)
11+	20,072 (44.28)	419 (29.91)	15,487 (42.54)	4,166 (55.38)
Average daily MME				
≤ 50	35,370 (78.02)	1,246 (88.94)	28,728 (78.90)	5,396 (71.74)
50-90	6,482 (14.30)	106 (7.57)	5,007 (13.75)	1,369 (18.20)
90+	3,480 (7.68)	49 (3.50)	2,674 (7.34)	757 (10.06)
Number of opioid prescribers				
1	13,021 (28.72)	667 (47.61)	11,087 (30.45)	1,267 (16.84)
2	13,550 (29.89)	433 (30.91)	11,305 (31.05)	1,812 (24.09)
3	8,394 (18.52)	173 (12.35)	6,755 (18.55)	1,466 (19.49)
4+	10,367 (22.87)	128 (9.14)	7,262 (19.95)	2,977 (39.58)
Number of Pharmacies visited				
1	27,292 (60.20)	1,102 (78.66)	23,247 (63.85)	2,943 (39.13)
2	12,024 (26.52)	244 (17.42)	9,044 (24.84)	2,736 (36.37)
3	3,846 (8.48)	44 (3.14)	2,738 (7.52)	1,064 (14.15)
4+	2,170 (4.79)	11 (0.79)	1,380 (3.79)	779 (10.36)
Concurrent benzodiazepines				
No	38,053 (83.94)	1,241 (88.58)	30,641 (84.16)	6,171 (82.04)
Yes	7,279 (16.06)	160 (11.42)	5,768 (15.84)	1,351 (17.96)

Table 2 Multivariable log binomial regression models of the association between method of payment and potential POM among patients younger than 65 years old on chronic opioid therapy

Characteristic	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
Method of payment		
Insurance only	Ref.	Ref.
Cash only	0.44 (0.34, 0.56)	0.48 (0.38, 0.61)
Both	2.04 (1.95, 2.12)	1.80 (1.73, 1.87)
Age group (years)		
< 44	Ref.	Ref.
45-54	1.12 (1.07, 1.18)	1.07 (1.02, 1.12)
55-64	0.97 (0.93, 1.02)	0.96 (0.91, 1.00)
Gender		
Male	Ref.	Ref.
Female	1.01 (0.97, 1.05)	1.01 (0.97, 1.05)
Primary opioid type		
Hydrocodone	Ref.	Ref.
Oxycodone	1.86 (1.78, 1.95)	1.73 (1.65, 1.81)
Tramadol	0.86 (0.80, 0.93)	0.86 (0.80, 0.93)
Other	1.50 (1.40, 1.60)	1.46 (1.37, 1.56)
Overlapping benzodiazepine		
No	Ref.	Ref.
Yes	1.91 (1.84, 1.99)	1.74 (1.67, 1.81)

Table 3 Modification of the association between methods of payment and potential opioid misuse by gender among patients 65 years and older on chronic opioid therapy using the risk ratio scale

	Insurance exclusively		Insurance and ≥ 1 cash payment		RRs (95% CI) for payment method within strata of gender
	N with/without POM	RR (95% CI)	N with/without POM	RR (95% CI)	
Male	478/3038	1.0	287/799 (35.9)	1.84 (1.62, 2.09) p < 0.0001	1.84 (1.62, 2.09) p < 0.0001
Female	864/5480	1.03 (0.93, 1.15) p=0.1295	656/1403 (46.8)	2.19 (2.01, 2.39) p < 0.0001	2.12 (1.98, 2.27) p < 0.0001

Measure of association modification on additive scale: RERI = 0.32; $p < 0.0001$

Measure of association modification on multiplicative scale: Ratio of RRs =1.15 (95% CI: 1.08–1.22).

RRs were adjusted for age, sex type of opioid medication, and chronic concurrent benzodiazepine use.

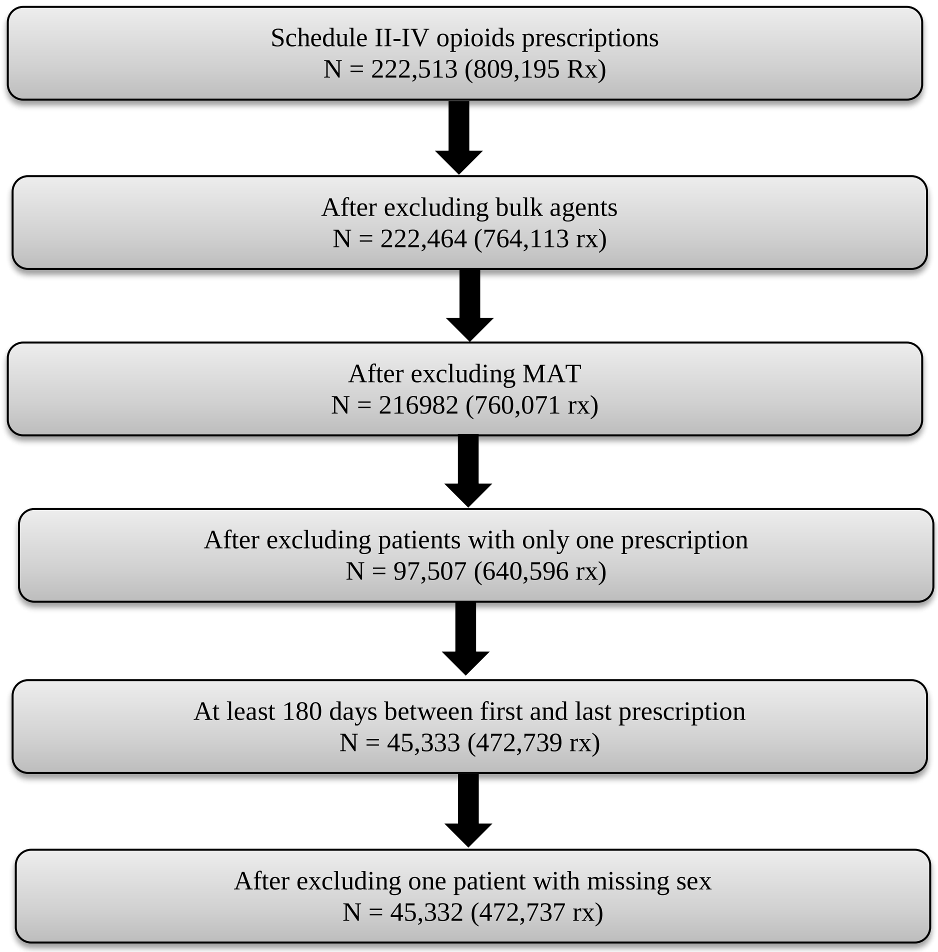

Figure 1. Flow chart for study cohort selection

CHAPTER 4

FUTURE RESEARCH WORK

In the first manuscript, we used a baseline model to evaluate the association of the initial pattern of prescription opioid use on the risk of all-cause mortality. We plan to perform additional analysis with time-varying exposure and time-varying confounding using marginal structural models. Prescription opioids use tends to vary over time and standard approaches for adjustment of confounding discussed here can be biased in the presence of time-dependent confounders that are also affected by previous prescription opioid exposure. In a situation like the one just described, marginal structural models may allow for improved adjustment of confounding.

APPENDICES

Appendix A

Table 1. Current Procedural Terminology (CPT) and International Classification of Diseases, Ninth Revision (ICD-9) codes for surgical procedures

Surgical procedures	CPT codes
Total Knee Arthroplasty	27447
Total Hip Arthroplasty	27130
Laparoscopic Cholecystectomy	47562, 47563, 47564
Open Cholecystectomy	47600, 47605, 47610
Laparoscopic Appendectomy	44970, 44979
Open Appendectomy	44950, 44960
Cesarean Section	59510, 59514, 59515
FESS	31237, 31240, 31254, 31255, 31256, 31267, 31276, 31287, 31288
Cataract Surgery	66982, 66983, 66984
TURP	52601, 52612, 52614, 52480,52630
Simple Mastectomy	19301, 19302, 19303, 19180
Carpal tunnel release	64721
Parathyroidectomy	60500
Varicose veins	37785
Hemorrhoidectomy	46221, 46945, 46946, 46250, 46260, 46257, 46258, 46261, 46262,46255
Thyroidectomy	60240
Surgical procedures	ICD-9codes
Gastric procedures	4498,4464,4495, 4438,4468,4382,4439
Incisional hernia repair	5351,5362,5359
Esophagus	4495,4466
Diaphragm	5362,5371, 5383,5372,5361,5384,5369, 5363,5375,5380
Colon	4581, 4573, 4582, 4583
Uterus	6831,6841, 6851, 6839,6849,689

FESS=Functional endoscopic sinus surgery, TURP=transurethral resection of the prostate

Table 2. Pain diagnoses

Pain disorder category	ICD-9 codes
Headache/migraines	'3840', '3502', '34000', '346', '3460', '3461', '3462', '3463', '3464', '3465', '3466', '3467' , '3468', '34600', '34601', '34602', '34603', '34610', '34611', '34612', '34613', '34620', '34621', '34622', '34623', '34630', '34631', '34632', '34633', '34640', '34641', '34642', '34643', '34650', '34651', '34652', '34653', '34660', '34661', '34662', '34663', '34670', '34671', '34672', '34673', '34680', '34681', '34682', '34683', '34690', '34691', '34692', '34693', '30781', '7840','7238','3469'
Neck/TMJD	'72231','72271','72281','72291','8390','8391','8470', '7210','7211','7220','723', '52460', '52461', '52462', '52463', '52464', '52469'
Back	'72230', '72232', '72233', '72270', '72272', '72273','72280', '72282', '72283', '72290', '72292', '72293','7371', '7373', '7384', '7385', '7392', '7393', '7394','75610', '75611', '75612', '75619', '8054', '8058', '8392', '83942', '846', '8460', '8471', '8472', '8473','8479', '75613', '7222' '724', '7213' - '7219'
Abdominal pain	'7890' '78900' '78901' '78902' '78903' '78904' '78905' '78906' '78907' '78909' '78960' '78961' '78962' '78963' '78964' '78965' '78966' '78967' '78969' '5920' '5921' '5929' '5940' '5941' '5942' '5948' '5949' '7880' 'V1301'
Joint/arthritis pain	'710', '7101', '7103', '7104','734','725','7105', '7108', '7109', '729', '7292', '7294', '7295', '7296', '737', '7378', '7379', '738', '7382', '7383','7386', '7387', '7388', '7389', '739', '7391', '7395', '7396', '7397', '7398', '7399', '711', '712', '713', '714','715','716', '717', '718', '719','726', '727', '728', '7293','7297', '7298', '7299', '730','731', '732','733', '735', '736', '7372','7374', '7381'
Fibromyalgia/CFS	'7291','78071'
Chronic pain syndrome	'3380','3382','3384','339','346','30781','7840','805','806','846','847','3502','3540','3544','3555','35571','377', '3370' - '33719', '356' - '357', '710' - '719', '720' - '724', '725 - '729', '731' - '738'
Other pain conditions	'78659', '5305','5368','7102','3883', '5951', '564','6257','617'

TMJD=Temporal-mandibular joint disorder, CFS=Chronic fatigue syndrome, CPS=chronic pain syndrome;

ICD-9= International Classification of Diseases, Ninth Revision code

Table 3. Fractures and Strains

Pain disorder category	ICD-9 codes
Fractures and strains	'81000' '81001' '81002' '81003' '81010' '81011' '81012' '81013' '81100' '81101' '81102' '81103' '81109' '81110' '81111' '81112' '81113' '81119' '81200' '81201' '81202' '81203' '81209' '81210' '81211' '81212' '81213' '81219' '81220' '81221' '81230' '81231' '81240' '81241' '81242' '81243' '81244' '81249' '81250' '81251' '81252' '81253' '81254' '81259' '81300' '81301' '81302' '81303' '81304' '81305' '81306' '81307' '81308' '81310' '81311' '81312' '81313' '81314' '81315' '81316' '81317' '81318' '81320' '81321' '81322' '81323' '81330' '81331' '81332' '81333' '81340' '81341' '81342' '81343' '81344' '81345' '81346' '81347' '81350' '81351' '81352' '81353' '81354' '81380' '81381' '81382' '81383' '81390' '81391' '81392' '81393' '81400' '81401' '81402' '81403' '81404' '81405' '81406' '81407' '81408' '81409' '81410' '81411' '81412' '81413' '81414' '81415' '81416' '81417' '81418' '81419' '81500' '81501' '81502' '81503' '81504' '81509' '81510' '81511' '81512' '81513' '81514' '81519' '81600' '81601' '81602' '81603' '81610' '81611' '81612' '81613' '8170' '8171' '8180' '8181' '8190' '8191' '9052' '82100' '82101' '82110' '82111' '82120' '82121' '82122' '82123' '82129' '82130' '82131' '82132' '82133' '82139' '8220' '8221' '82300' '82301' '82302' '82310' '82311' '82312' '82320' '82321' '82322' '82330' '82331' '82332' '82340' '82341' '82342' '82380' '82381' '82382' '82390' '82391' '82392' '8240' '8241' '8242' '8243' '8244' '8245' '8246' '8247' '8248' '8249' '8250' '8251' '82520' '82521' '82522' '82523' '82524' '82525' '82529' '82530' '82531' '82532' '82533' '82534' '82535' '82539' '8260' '8261' '8270' '8271' '9054' '80500' '80501' '80502' '80503' '80504' '80505' '80506' '80507' '80508' '80510' '80511' '80512' '80513' '80514' '80515' '80516' '80517' '80518' '8052' '8053' '8054' '8055' '8056' '8057' '8058' '8059' '80700' '80701' '80702' '80703' '80704' '80705' '80706' '80707' '80708' '80709' '80710' '80711' '80712' '80713' '80714' '80715' '80716' '80717' '80718' '80719' '8072' '8073' '8074' '8075' '8076' '8080' '8081' '8082' '8083' '80841' '80842' '80843' '80844' '80849' '80851' '80852' '80853' '80854' '80859' '8088' '8089' '8090' '8091' '8280' '8281' '8290' '8291' '9051' '9055' '8400' '8401' '802' '8403' '8404' '8405' '8406' '8407' '8408' '8409' '8410' '8411' '8412' '8413' '8418' '8419' '84200' '84201' '84202' '84209' '84210' '84211' '84212' '84213' '84219' '8430' '8431' '8438' '8439' '8440' '8441' '8442' '8443' '8448' '8449' '84500' '84501' '84502' '84503' '84509' '84510' '84511' '84512' '84513' '84519' '8460' '8461' '8462' '8463' '8468' '8469' '8470' '8471' '8472' '8473' '8474' '8479' '8480' '8481' '8482' '8483' '84840' '84841' '84842' '84849' '8485' '8488' '8489' '9057' 'V5414' 'V5415' 'V5416' 'V5424' 'V5425' 'V5426' 'V5410' 'V5411' 'V5412' 'V5420' 'V5421' 'V5422' 'V5417' 'V5419' 'V5427' 'V5429' 'V664' 'V674' 'V1352' 'V540' 'V5401' 'V5402' 'V5409' '82000' '82001' '82002''82003' '82009' '82010' '82011' '82012' '82013' '82019' '82020' '82021' '82022' '82030' '82031' '82032' '8208' '8209' '9053''V5413' 'V5423' '80000' '80001' '80002' '80003' '80004' '80005' '80006' '80009' '80050' '80051' '80052' '80053' '80054' '80055' '80056' '80059' '80100' '80101' '80102' '80103' '80104' '80105' '80106' '80109' '80150' '80151' '80152' '80153' '80154' '80155' '80226' '80227' '80228' '80229' '80230' '80231' '80232' '80233' '80234' '80235' '80300' '80301' '80302' '80303' '80304' '80305' '80306' '80309' '80350' '80351' '80352' '80353' '80354' '80355' '80356' '80359' '80400' '80401' '80402' '80403' '80404' '80405' '80406' '80409' '80450' '80451' '80452' '80453' '80454' '80455' '80456' '80459' '9050' '80236' '80237' '80238' '80239' '8024' '8025' '8026' '8027' '8028' '8029' '80156' '80159' '8020' '8021' '80220' '80221' '80222' '80223' '80224' '80225' '34939' '80600' '80601' '80602' '80603' '80604' '80605' '80606' '80607' '80618' '80608' '80609' '80610' '80611' '80612' '80613' '80614' '80615' '80616' '80617' '80619' '80620' '80621' '80622' '80623' '80624' '80625' '80626' '80627' '80628' '80629' '80630' '80631' '80632' '80633' '80634' '80635' '80636' '80637' '80638''80639' '8064' '8065' '80660' '80661' '80662' '80669' '80670' '80671' '80672' '80679' '8068' '8069' '9072' '95200' '95201' '95202' '95203' '95204' '95205''95206' '95207' '95208' '95209' '95210' '95211' '95212' '95213' '95214' '95215' '95216' '95217' '95218' '95219' '9522' '9523' '9524' '9528' '9529'

Table 4. Mental health disorders

Mental health condition	CCS codes	ICD-9
Adjustment disorders	650	3090 3091 30922 30923 30924 30928 30929 3093 3094 30982 30983 30989 3099
Anxiety disorders	651	29384 30000 30001 30002 30009 30010 30020 30021 30022 30023 30029 3003 3005 30089 3009 3080 3081 3082 3083 3084 3089 30981 3130 3131 31321 31322 3133 31382 31383
Conduct disorders	652	31200 31201 31202 31203 31210 31211 31212 31213 31220 31221 31222 31223 3124 3128 31281 31282 31289 3129 31381 31400 31401 3141 3142 3148 3149
Mood disorders	657	29383 29600 29601 29602 29603 29604 29605 29606 29610 29611 29612 29613 29614 29615 29616 29620 29621 29622 29623 29624 29625 29626 29630 29631 29632 29633 29634 29635 29636 29640 29641 29642 29643 29644 29645 29646 29650 29651 29652 29653 29654 29655 29656 29660 29661 29662 29663 29664 29665 29666 2967 29680 29681 29682 29689 29690 29699 3004 311
Schizophrenia & psychotic disorders	659	29381 29382 29500 29501 29502 29503 29504 29505 29510 29511 29512 29513 29514 29515 29520 29521 29522 29523 29524 29525 29530 29531 29532 29533 29534 29535 29540 29541 29542 29543 29544 29545 29550 29551 29552 29553 29554 29555 29560 29561 29562 29563 29564 29565 29570 29571 29572 29573 29574 29575 29580 29581 29582 29583 29584 29585 29590 29591 29592 29593 29594 29595 2970 2971 2972 2973 2978 2979 2980 2981 2982 2983 2984 2988 2989
Alcohol related disorders	660	2910 2911 2912 2913 2914 2915 2918 29181 29182 29189 2919 30300 30301 30302 30303 30390 30391 30392 30393 30500 30501 30502 30503 3575 4255 5353 53530 53531 5710 5711 5712 5713 76071 9800
Substance related disorders	661	2920 29211 29212 2922 29281 29282 29283 29284 29285 29289 2929 30400 30401 30402 30403 30410 30411 30412 30413 30420 30421 30422 30423 30430 30431 30432 30433 30440 30441 30442 30443 30450 30451 30452 30453 30460 30461 30462 30463 30470 30471 30472 30473 30480 30481 30482 30483 30490 30491 30492 30493 30520 30521 30522 30523 30530 30531 30532 30533 30540 30541 30542 30543 30550 30551 30552 30553 30560 30561 30562 30563 30570 30571 30572 30573 30580 30581 30582 30583 30590 30591 30592 30593 64830 64831 64832 64833 64834 65550 65551 65553 76072 76073 76075 7795 96500 96501 96502 96509 V6542
Miscellaneous mental health disorders	656, 658, 662, 670	31230 31231 31232 31233 31234 31235 31239 3010 30110 30111 30112 30113 30120 30121 30122 3013 3014 30150 30151 30159 3016 3017 30181 30182 30183 30184 30189 3019 E9500 E9501 E9502 E9503 E9504 E9505 E9506 E9507 E9508 E9509 E9510 E9511 E9518 E9520 E9521 E9528 E9529 E9530 E9531 E9538 E9539 E954 E9550 E9551 E9552 E9553 E9554 E9555 E9556 E9557 E9559 E956 E9570 E9571 E9572 E9579 E9580 E9581 E9582 E9583 E9584 E9585 E9586 E9587 E9588 E9589 E959 V6284 29389 2939 30011 30012 30013 30014 30015 30016 30019 3006 3007 30081 30082 3021 3022 3023 3024 30250 30251 30252 30253 3026 30270 30271 30272 30273 30274 30275 30276 30279 30281 30282 30283 30284 30285 30289 3029 3060 3061 3062 3063 3064 30650 30651 30652 30653 30659 3066 3067 3068 3069 3071 30740 30741 30742 30743 30744 30745 30746 30747 30748 30749 30750 30751 30752 30753 30754 30759 30780 30781 30789 3101 316 64840 64841 64842 64843 64844 V402 V403 V4031 V4039 V409 V673

CCS=Clinical classification system code, ICD-9=International Classification of Diseases, Ninth Revision codes

Source: Clinical Classification Software-DIAGNOSES (January 1980 through September 2015); Revised 03/24/2016

https://www.hcup-us.ahrq.gov/toolssoftware/ccs/AppendixASingleDX.txt Accessed on 1/12/2018

Table 5. List of Medical Comorbidities and ICD-9 Codes used

Condition	ICD-9 codes
Congestive Heart Failure	'39891','4254','4255','4257','4258','4259','428'
Myocardial infarction	'410' '412'
Peripheral Vascular Disease	'0930','440','441','7854','V434', '4420'-'4428', '4431'-'4439', '44770'-'44773'
Chronic Obstructive Pulmonary Disease	'4168','4169','5064','5191', '490' - '496', '500' - '505'
Diabetes Mellitus	'250 ', '2500' - '2503'
Diabetes Mellitus with complications	'3620', '2504', '2509'
Chronic Kidney Disease	'40301','40311','40391','40402','40403','40412','40413','40492','40493', '582', '583','585','586','588','V420','V451','V56'
Cardiovascular disease	'430' - '438'
Dementia	'290','2910','2911','2912','29282','2941','3310','3311','3312','33182'
Liver Disease	'07022','07023','07044','V427', '4560' - '4562', '5722' - '5728
Cirrhosis	'07032','07033','07054','5712','5714','5715','5716'
Ulcers	'531' - '534'
Rheumatoid arthritis	'7100','7101','7104','71481','725 ', ('7140' - '7142'
Paralysis	'342','3449', '3440' – '3446'
AIDS	'79571','V08', '042' - '044'

Table 6. Substance use disorders

Diagnoses	ICD-9 and ICD-10 codes
Drug abuse	'3040' '3041' '3046' '3046' '3047' '3048' '3049' '3054' '3055' '3058' 'F1120' 'F1121' 'F1320' 'F1321' 'F1920' 'F1921' 'F1310' 'F1110' 'F1910'
Overdose	'9658' '9659' '967' '9691' '9692' '9693' '9694' '9695' '9697' '9698' '9699' '9752' '9753' '9778' '9779' 'T400X1A' 'T400X2A' 'T400X3A' 'T400X4A' 'T403X1A' 'T403X2A' 'T403X3A' 'T403X4A' 'T402X1A' 'T402X2A' 'T402X3A' 'T402X4A' 'T404X1A' 'T404X2A' 'T404X3A' 'T404X4A' 'T40601A' 'T40602A' 'T40603A' 'T40604A' 'T40691A' 'T40692A' 'T40693A' 'T40694A'
Opioid overdose	'96500' '96502' '96509' 'E8501' 'E8502'
Opioid use disorder	'30400' '30401' '30402' '30403' '30470' '30471' '30472' '30473' '30550' '30551' '30552' '30553'
Tobacco	'3051' 'V1582'
Alcohol	'3050' '3039' '2652' '3030' '3039' '3050' '3575' '4255' '5353' '980x' 'V113', '2911' - '2913', '2915' - '2919', '5710' - '5713'
Marijuana	'3043''3052' '3043' '30430' '30431' '30432' '30433'
Cocaine	'3056' '3042' '30420' '30421' '30422' '30423'
Other substance use	'3053','3054','3057','3058','3059'

Appendix B.

Table 1 List of medications classified as "other" under opioid medication types in Table 1,2 &3.

Medications
Acetaminophen with codeine
Anhydrous morphine (Paregoric®)
Brompheniramine, codeine with phenylephrine
Butalbital, acetaminophen and caffeine with codeine phosphate
Butalbital, aspirin, caffeine with codeine phosphate
Carisoprodol, aspirin, and codeine phosphate
Codeine sulfate
Hydrocodone bitartrate with homatropine methylbromide
Hydrocodone with chlorpheniramine

Table 2. Use of Other Types of Insurance among 21,538 Patients Making Cash Payments for Opioid Prescriptions at Retail Pharmacies in R.I. in 2015

Insurance types used	Number of patients (%)
Cash payment for all opioid dispensings	16,240 (75.40)
Cash plus only one other type of insurance	4,835 (22.45)
Cash plus 2 other types of insurance	447 (2.08)
Cash plus 3 other types of insurance	16 (0.07)

Appendix C

Table 1 Distribution of cash payment by opioid medication type among patients on chronic opioid therapy, Rhode Island Prescription Drug Monitoring Program, 2015

Opioid medication type	Overall N=472,737	Cash payment N=38,220 (8.08)	Insurance payment N=434,517 (91.92)
Buprenorphine	1,437 (0.30)	90 (0.24)	1,347 (0.31)
Butorphanol	309 (0.07)	10 (0.03)	299 (0.07)
Fentanyl	12,992 (2.75)	922 (2.41)	12,070 (2.78)
Hydrocodone	147,245 (31.15)	8,962 (23.45)	138,283 (31.82)
Hydromorphone	6,666 (1.41)	683 (1.79)	5,983 (1.38)
Levorphanol	9 (0.00)	0 (0.00)	9 (0.00)
Meperidine	199 (0.04)	39 (0.10)	160 (0.04)
Methadone	6,575 (1.39)	799 (2.09)	5,776 (1.33)
Morphine	24,999 (5.29)	1,634 (4.28)	23,365 (5.38)
Oxycodone	175,639 (37.15)	14,462 (37.84)	161,177 (37.09)
Oxymorphone	1,650 (0.35)	68 (0.18)	1,582 (0.36)
Pentazocine	286 (0.06)	11 (0.03)	275 (0.06)
Tapentadol	880 (0.19)	42 (0.11)	838 (0.19)
Tramadol	74,843 (15.83)	9,069 (23.73)	65,774 (15.14)
Other	3,554 (0.75)	542 (1.42)	3,012 (0.69)
Codeine-based	15,454 (3.27)	887 (2.32)	14,567 (3.35)

Table 2 Listing of benzodiazepines dispensed at Rhode Island retail pharmacies, Rhode Island Prescription Drug Monitoring Program, 2015

Type of benzodiazepine	N (%)
Clonazepam	186,727 (29.29)
Alprazolam	181,412 (28.46)
Lorazepam	163,083 (25.58)
Diazepam	72,163 (11.32)
Temazepam	22,875 (3.59)
Triazolam	3,895 (0.61)
Clorazepate	3,259 (0.51)
Chlordiazepoxide	1,589 (0.25)
Oxazepam	929 (0.15)
clobazam	810 (0.13)
Flurazepam	561 (0.09)
Midazolam	85 (0.01)
Estazolam	83 (0.01)
Total	637,471

Table 3 Characteristics of patients on COT by potential POM in RI PDMP, 2015

Characteristic	Overall (N=45,332)	No misuse (N= 35,317)	Potential misuse (N= 10,015)
Continuous variables, mean (SD)			
Number of Rx	10.43 (7.910	8.06 (5.33)	18.74 (9.65)*
Average cost ($)	54.50 (138.18)	43.78 (119.10)	92.32 (185.92)
Average total cost ($)	868.19 (2955.84)	507.99 (1839.21)	2138.41 (5054.64)
Age (years)	56.80 (16.29)	57.32 (16.64)	54.96 (14.82)
Age group (years), N (%)			
< 44	9,897 (21.83)	7,552 (21.38)	2,345 (23.41)*
45-54	9,835 (21.70)	7,217 (20.43)	2,618 (26.14)
55-64	11,822 (26.08)	9,095 (25.75)	2,727 (27.23)
65+	13,778 (30.39)	11,453 (32.43)	2,325 (23.22)
Gender, N (%)			
Female	26,799 (59.12)	20,903 (59.19)	5,896 (58.87)
Male	18,533 (40.88)	14,414 (40.81)	4,119 (41.13)
Primary method of payment, N (%)			
Cash	2,891 (6.38)	2,351 (6.66)	540 (5.39)
Medicaid	3,404 (7.51)	2,483 (7.03)	921 (9.20)
Medicare	15,635 (34.49)	12,336 (34.93)	3,299 (32.94)
Commercial Ins.	22,598 (49.85)	17,549 (49.69)	5,049 (50.41)
Other	804 (1.77)	598 (1.69)	206 (2.06)
Primary opioid type used, N (%)			
Hydrocodone	15,347 (33.85)	12,807 (36.26)	2,540 (25.36)
Oxycodone	15,577 (34.36)	10,647 (30.15)	4,930 (49.23)
Tramadol	8,795 (19.40)	7,634 (21.62)	1,161 (11.59)
Other	5,613 (12.38)	4,229 (11.97)	1,384 (13.82)
Number of opioid dispensing, N (%)			
≤ 5	14,366 (31.69)	14,253 (40.36)	113 (1.13)
6-10	10,894 (24.03)	9,570 (27.10)	1,324 (13.22)
11+	20,072 (44.28)	11,494 (32.55)	8,578 (85.65)
Average daily MME, N (%)			
≤ 50	35,370 (78.02)	29,295 (82.95)	6,075 (60.66)
50-90	6,482 (14.30)	4,209 (11.92)	2,273 (22.70)
90+	3,480 (7.68)	1,813 (5.13)	1,667 (16.65)
Number of opioid prescribers, N (%)			
1	13,021 (28.72)	11,896 (33.68)	1,125 (11.23)
2	13,550 (29.89)	12,585 (35.63)	965 (9.64)
3	8,394 (18.52)	6,700 (18.97)	1,694 (16.91)
4+	10,367 (22.87)	4,136 (11.71)	6,231 (62.22)
Number of pharmacies visited, N (%)			
1	27,292 (60.20)	24,031 (68.04)	3,261 (32.56)
2	12,024 (26.52)	9,327 (26.41)	2,697 (26.93)
3	3,846 (8.48)	1,682 (4.76)	2,164 (21.61)
4+	2,170 (4.79)	277 (0.78)	1,893 (18.90)
Concurrent benzodiazepines, N (%)			
No	38,053 (83.94)	30,691 (86.90)	7,362 (73.51)
Yes	7,279 (16.06)	4,626 (13.10)	2,653 (26.49)

*All p-values were < 0.01 for bivariate analyses using X^2 test to compare the difference in covariates between no misuse and potential opioid misuse.

Abbreviations: COT=Chronic opioid therapy, PDMP=Prescription Drug Monitoring Program, Rx=prescription, MME=morphine milligram equivalent, SD=standard deviation.