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**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 state-wide spending for prescription opioids in Rhode Island.

Methods: A cross-sectional study of opioids dispensed from retail pharmacies using data from the Rhode Island (R.I.) 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 to December 31, 2015. The mean, median and total cost of opioid utilization was estimated using both 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 were used to estimate the annual adjusted average prescription opioid cost and to examine potential predictors of total annual expenditure, respectively.

Results: The estimated annual expenditure for opioid prescriptions in R.I. for 2015 was \$44,271,827. The average and median cost of an opioid prescription were \$67.98 (standard deviation [SD] \$210.91) and \$21.08 (interquartile range [IQR]: \$7.65, \$47.51), respectively. Prescriptions for branded opioid products accounted for \$17,380,279.05, which was about 39.3% of overall spending, although only 6% of all opioids dispensed were for brand-name drugs. On average, patients aged 45-54 and 55-64 years had overall adjusted spending for opioids that were 1.53 (95% confidence interval [CI]: 1.49, 1.57) and 1.75 (95% CI: 1.71, 1.80) times higher than patients age 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 one benzodiazepine or sympathomimetic stimulant dispensing, respectively. Average 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 to those receiving less than 50 MME daily.

Conclusion: This study provides the first estimate of the state-wide 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 bears the majority of the cost of prescription opioid use but

cost per patient is 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 utilization especially among middle aged adults.

SUMMARY BULLETS

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 disorder¹.
- 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.

A statement of Disclosures:

Dr. Aroke reports grants from R.I. Department of Health, during the conduct of the study.

Dr. Buchanan has nothing to disclose.

Dr. Wen has nothing to disclose.

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Dr. Kogut reports grants from R.I. Department of Health, during the conduct of the study.

Introduction

Pain is one of the most common reasons for an outpatient office visit²⁻⁴. According to a 2011 Institute of Medicine report, approximately 100 million adults in the United States suffer from chronic pain each year⁵. Prescription opioid analgesics are commonly used to treat a variety of painful conditions ranging from acute injury to palliative care in terminal illness. In 2012, healthcare providers in the United States issued over 259 million opioid prescriptions⁶. Higher rates of opioid prescribing over the past two to three 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.⁷⁻¹¹

Although the use of prescription opioid analgesics is often clinically necessary, their addictive and euphoric properties render them liable to misuse and often lead to opioid use disorders (OUDs). 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^{6,12-14}. In 2015 alone, drug overdose was responsible for 52,404 deaths, with 33,091 (63.2%) associated with an opioid. More than 60% of opioids involved in drug overdose deaths are prescription opioids^{15,16}. Benzodiazepines and opioids are often prescribed together with the potential risk of respiratory depression and overdose death¹⁷⁻¹⁹. The 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 guidelines²⁰⁻²².

Currently all states legislatures, with the exception of Missouri, have implemented a version of a state-run Prescription Drug Monitoring Program (PDMP) designed to identify and track the prescribing and dispensing of controlled substances, including prescription opioids dispensed from retail pharmacies. These PDMP aim 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.²³ In most states, including Rhode Island, prescription drugs that are classified as Schedule II, III and IV, and opioid medications within Schedule V on the Drug Enforcement Administration's (DEA) five-tiered schedule are monitored. Drugs are assigned to one 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^{15,24-26}. The annual societal cost of pain in terms of medical care and lost productivity in the U.S. has been estimated at \$635 billion, in 2010 dollars⁵. White et al (2005) estimated that the total healthcare costs per patient varied from \$15,884 to \$18,388 among patients with an opioid use disorder diagnosis compared with only \$1,830 to \$2,210 among a similar group of patients with no documented history of an opioid use disorder¹. Recent publications of cost related to opioid use have examined trends in expenditures using national Medicare data and Medical Expenditure Panel Survey (MEPS)^{24,27}. Zhou et al estimated that the 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 estimated the total expenses for outpatient prescription opioids at \$9.0 billion in 2012, an increase of 120% from 2002²⁸.

The statewide health system impact of opioid use 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 source of payment. Data from the R.I. PDMP was used to estimate the distribution of the direct cost of opioid prescriptions dispensed by retail pharmacies in R.I. during the calendar year 2015. The goal of this analysis was to determine the total annual expenditure for prescription opioid analgesics in R.I. for 2015 as captured in the PDMP. The proportions of spending associated with cash payment, and by public and private payers were determined. Finally, the study evaluated if gender, age group, payment type or use of other benzodiazepines or stimulants was 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 utilization and spending by patient and by type of opioid medication dispensed using data from the 2015 R.I. PDMP. These included all DEA Schedule II to IV prescription medications dispensed by retail pharmacies licensed within the state (A new state law that was signed on June 28, 2016 requires pharmacies to monitor Schedule II to V controlled substances). Pharmacies

holding a retail license in R.I. are legally required to electronically report all monitored controlled substances filled within one business day of the prescription being dispensed to the patient. This 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 R. I. 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), 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 the date the prescription was filled. The pharmacist estimated "days' supply" based on the quantity prescribed and the daily dosage. Patients who were 65 years of age and older and had commercial insurance documented as their method of payment were reclassified as covered by Medicare, as there was no way to distinguish individuals who were enrolled in a Medicare Advantage plan from those receiving employer-based insurance. The payment type field was populated by the dispensing pharmacist, and a payment type of "commercial" was incorrectly assigned for a majority of Medicare-eligible adults.

Cohort selection: All individuals with at least one prescription dispensing of any Schedule II to IV controlled substance was first identified. There were 2,058,816 controlled substance prescriptions dispensed at retail pharmacies in 2015. This includes 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 as they are typically indicated for substance and OUD 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 NDCs. The analytic sample consisted of 651,227 opioid prescriptions dispensed to 197,062 patients from retail pharmacies in R.I.

between January 1, 2015 to December 31, 2015. The U.S. Census Bureau estimated the population of Rhode Island to be 1,056,298 in 2015³⁴. A 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, NDCs for opioid dispensings were first matched with the 2015 R.I. Medicaid Maximum Allowable Cost (MAC) listing as the default unit price for both brand name and generic products. For sole source (i.e. branded) products and other NDCs that did not match with the Medicaid MAC listing, pricing data from the RED BOOK[®] (Truven Health Analytics, Inc.), which provided the Average Wholesale Price (AWP) and Federal Upper Limit (FUL) prices during 2015 was used. 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 others such as 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. The study determined if opioid prescription expenditure was associated with patient age groups, gender or payment type. Use of benzodiazepines or stimulants were defined as use of one 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 National Center for Injury Prevention and Control in June, 2015³⁵⁻³⁸. Finally, a measure of potential health system abuse was defined as patients who received prescriptions for an opioid from five or more prescribers filled by five or more pharmacies within the 12 month period (5/5/12 criteria), so-called multiple provider episodes (MPE) or doctor shopping³⁹.

Statistical Analysis: The mean, median and total costs of opioid utilization were estimated using both prescription dispensings and patients as units of analysis. All costs were retained in 2015 US dollars. The last prescription received during the study year was used to identify the most recently used opioid type 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 (<18, 18-24, 25-34, 35-44, 45-54, 55-64, 65+), gender, medication type, and payment type. Annual cost values were non-normally distributed with a large right skew (skewness = 22.66). Therefore, using 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 were used to estimate the annual adjusted average prescription opioid cost, and to examine potential predictors of total annual expenditure, respectively^{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 MPE. The modified Park test was used to identify and specify the appropriate distribution of the dependent variable 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 two-sided and performed at the 0.05 significance level. The study was approved by the Institutional Review Board at the University of Rhode Island.

Results

The study population consisted of 197,062 residents who filled a total of 651,227 opioid prescriptions in 2015. This represents an estimated 18.7% of residents who received at least one dispensing for an opioid medication from a retail pharmacy during 2015. Approximately 56% of patients who filled at least one opioid prescription were female (Table 1). About 23.9% were aged 65 years and older, and 38.3% were ages 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 prescription using cash. More than 90% of patients used only one 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 one 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 two or more types of insurance payment during the same calendar year (Appendix B).

The total annual retail expenditure for opioid prescriptions in R.I. for 2015 was estimated at \$44,271,827, which corresponds to an average spending of \$3.7 million per month. The

average and median cost of an opioid prescription were \$67.98 (SD \$210.91) and \$21.08 (IQR: \$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 age 45 or older (Table 2). The total annual prescription opioid spending for patients age 45-64 years was estimated to be \$26,337,403.49 and this was not only proportionately higher than for patients age 65 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 two drug types was approximately \$32.5 million, which accounts 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 (ER) oxycodone as 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 (IQR: \$246.94, \$779.81), respectively, making it the most costly opioid prescription type including brand name 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 to \$449.78 (SD \$616.97) per brand-name 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 brand-name drugs. Commercial insurance was the most common method of payment type for opioid prescriptions (51%) followed closely by Medicare (29.4%). Cash payment was used for 60,548 or 9.3% of all prescription opioids dispensed. We found that on average Medicare spent \$85.31 (95% CI: \$84.24, \$86.39) per opioid prescription, which is 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. Gender, age group, payment type, mean daily MME per patients, use of benzodiazepines or stimulants, and MPE were all statistically significant predictors of total annual expenditure. Using a gamma regression model with an identity link function, patients aged 45-54 and 55-64 years had overall adjusted mean

spending for opioids that were \$17.65 (95% CI: \$15.26, \$20.04) and \$28.47 (95% CI: \$26.06, \$30.88) higher, respectively, than patients aged 65 and older. As expected, the youngest patients had significantly lower adjusted total expenditure per patient as compared with adults over 65 years of age. With regard to the method of payment, overall adjusted mean cost 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 a benzodiazepine (26.5%) or sympathomimetic stimulants (4.4%) had higher annual spending for opioid medications than those who did not also receive dispensings for these medications. On average, annual opioid prescription cost was \$35.99 (95% CI: \$34.45, \$37.54) higher among patients who also received at least one benzodiazepine dispensing; while annual opioid prescription cost was \$8.61 (95% CI: \$6.47, \$10.76) higher among patients who also had at least one dispensing for a stimulant medication. As a most statistically significant predictor of annual opioid expenditure, for patients with MPE, average annual cost of opioid prescriptions per patient was increased by approximately \$863.58 (95% CI: \$689.48, \$1037.68) compared to patients who did not meet this criteria. The annual total opioid spending per patient also increased substantially with the use of higher daily doses of opioids, as average total cost was more than \$337.73 (95% CI: \$332.84, \$342.62) greater among patients utilizing on average more than 90 MME daily, as compared with patients receiving on average less than 50 MME daily.

Using 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 age 18 years or younger to those age 65 years and older. Conversely, patients aged 45-54 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 age 65 years and older. 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, while average spending per patient using cash payment was 17.4% lower than charges to commercial payers. Furthermore, patients who were dispensed a benzodiazepine or a sympathomimetic stimulant had higher annual spending for opioid medications than those who

were not. On average, 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 one benzodiazepine or stimulant dispensing, respectively. Average 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 to those receiving less than 50 MME daily. Finally, 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

A total of 197,062 patients - or an estimated 18.7% of the state's population received at least one dispensing for an opioid medication from a retail pharmacy in Rhode Island during 2015. 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, which 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 which provides the advantage of capturing controlled substance dispensings at the level of the pharmacy and encompasses dispensings for all providers and payment types, including cash. Thus, estimates from this study provide results that are more generalizable to the overall population, as compared with analyses of a particular payer's pharmacy claims. As 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 dollars. This represents about 3.7% of total prescription drug sale at retail pharmacies in RI for 2016 according to estimates report published recently by the Kaiser Family Foundation⁴⁴. According to the study based on IMS Health national prescription audit data, the total expenditure for all 18 million prescription drugs dispensed at retail pharmacies in R.I. in 2016 was estimated at \$1.2 billion. The estimate from this study does not include dispensings for tramadol, compounded products, or opioids dispensed in substance and OUD treatment centers, during in-patient hospital care or in state correctional facilities.

The cost associated with prescription opioid use is determined in part by both 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 ER formulations. Extended release formulations accounted for almost 50% of the total annual expenditure even though they represent only 11% of all prescriptions. Efforts to address the cost burden of opioid overuse might target this middle-aged subgroup, with focus on reducing the long term use of opioids, many of which are prescribed as higher cost ER formulations. Evidence for the use of opioids for chronic pain is very limited amidst mounting evidence of serious dose-dependent harm⁴⁵. Both decreasing the unnecessary use of oxycodone ER 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 misuse⁴⁶. About 21,538 (10.93%) patients paid at least one opioid prescription with cash during the calendar year and approximately 25% of these patients used at least one other type of insurance to pay for opioid prescriptions during the same year. The overall adjusted average prescription opioid spending for the 409 patients that met the 5/5/12 criteria was dramatically greater than patients not meeting this 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 co-morbid chronic condition resulting from lack of a usual source of care. Other valid reasons for a patient having multiple providers might include a change in the primary care provider, a different provider covering the patient's usual prescriber, having multiple specialists, and visits to a dentists or the emergency room⁴⁷. It is envisioned that the overutilization of prescribers and pharmacies will decrease with increasing public awareness and implementation of regulations requiring providers to review the PDMP prior to issuing a prescription for an opioid medication. However, most PDMPs are not currently integrated with electronic medical records making access to this information time consuming and often infeasible.

The finding in this study that nearly 1 in 5 state residents received at least one 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 have reported that opioids are the most commonly prescribed analgesics in the United States⁴⁸. This analysis did not examine the clinical indications for which these opioid prescriptions were dispensed, and thus could not quantify the extent and cost of inappropriate opioid prescribing. Liu et al found that up to 40% of Medicaid patients receiving an opioid prescription had at least one marker of inappropriate prescribing such as overlapping opioid prescriptions, overlapping opioid and benzodiazepine prescriptions, initiation of therapy with a long-acting opioid, use long-acting opioids for acute pain, or high daily doses more than 90 MME²⁶. The U.S. Centers for Disease Control and Prevention recently published guidelines for prescribing opioids for chronic pain in the absence of cancer, palliative or terminal care.²⁰ The 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, towards determining if the frequency and cost burden of opioid use is diminishing.

Limitations: 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 cannot quantify the cost of inappropriate opioid prescribing, thus limiting the application of these results to improve prescribing practices. The total cost estimate does not represent the total cost burden as 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. The patient's state of residence could not be determined. However, the number of patients from neighboring states who received opioid prescriptions from R.I. pharmacies is likely to be offset

by the number of R.I. residents who filled opioid prescriptions at pharmacies in neighboring states. Additionally, 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 is nevertheless limited. Finally, we recognize that the direct cost of prescriptions is merely one 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 assessing opioid use as facet of pain management.

Conclusion

This study provides the first estimate of the state-wide 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 calendar 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 utilization, especially among middle age individuals.

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Figure 1. Sample Identification Flowchart

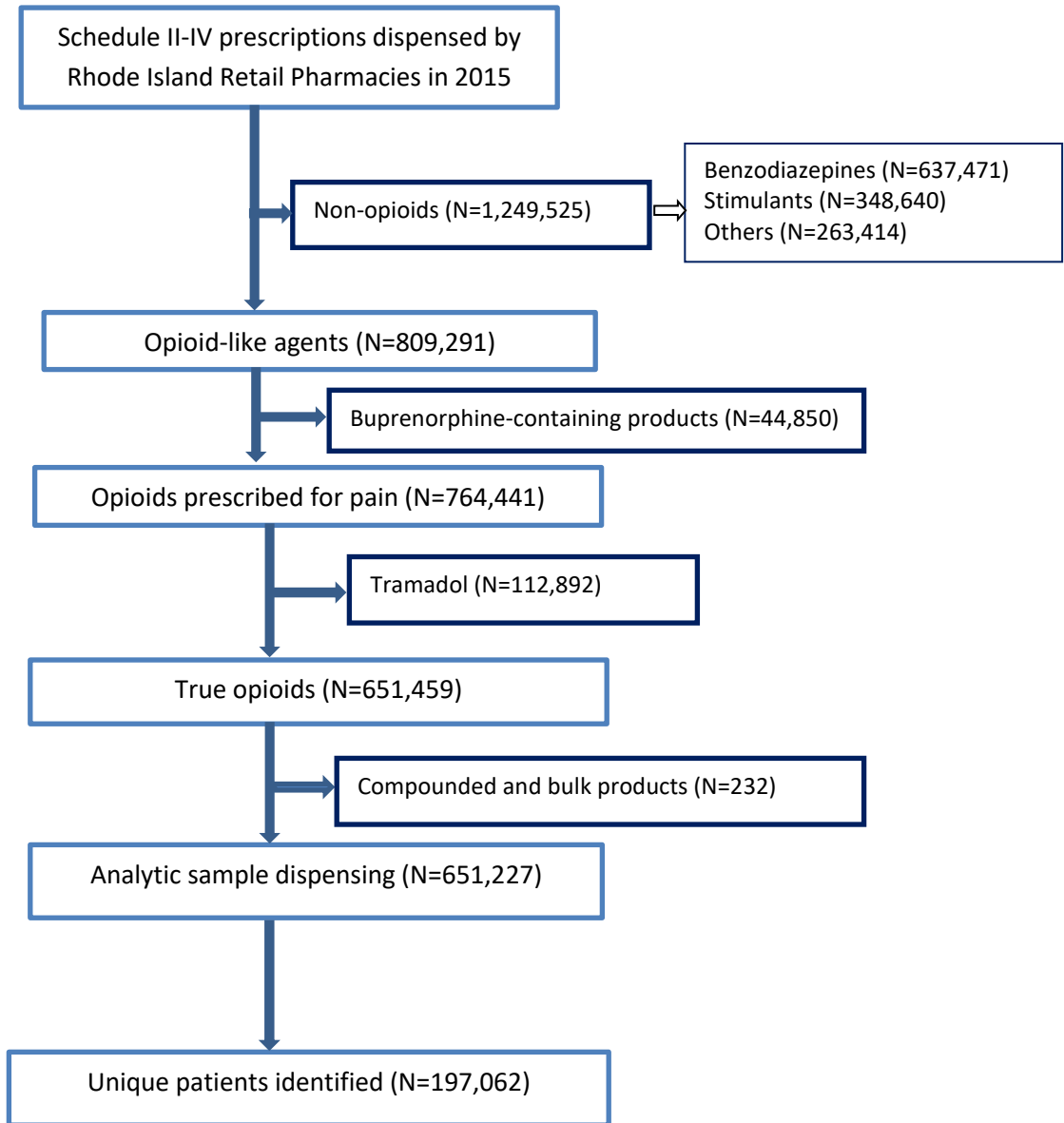


Table 1 Characteristics of Individuals Who Filled at Least one Opioid Prescription at a Retail Pharmacy in R.I. in 2015 (N = 197,062)

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)
Levorphanol	1 (0.00)
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)

^aGender, payment method, medication type and mean daily MME classified according to data captured in the last prescription dispensed in 2015.

^bGender was not reported for 18 patients (0.01%).

^cIncludes worker's compensation, Indian Health Services, the Veterans Health Administration, Tricare, other federal sources.

^ePrimarily opioid-containing cough products (see Appendix A)

^fMME=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 (\$)			% Total Cost
		Mean (SD)	Median	Total	
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

^aPrimarily opioid-containing cough products (see Appendix A)

^bMME=Morphine milligram equivalent; unable to determine MME for 1.71% of observations

^cIf 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		Adjusted β-coeffª	SE	95% Conf. Interval
	[95% CI]				
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					
	Reference				
≤50	97.91	(95.14, 100.68)	1.0756	0.0092	(1.0575, 1.0938)
50-90	337.73	(332.84, 342.62)	3.1124	0.0168	(3.0795, 3.1453)
>90					
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, 1037.68)	1.4672	0.0741	(1.3220, 1.6125)

ªMean cost per patient estimated using the identity link function;

ªCoefficients of gamma regression and standard errors estimated using the log link function;

ª If age ≥ 65 and Commercial Ins. then payment method was reclassified as Medicare;

ª Includes worker's compensation, Indian Nation, the Veterans Health Administration, Tricare, other federal sources;

ª,ª Use of other benzodiazepines and stimulants defined as one of more prescriptions in a 12 month period.

ª 5/5/12/ Criteria: Opioid prescriptions from at least 5 different pharmacies and 5 different prescribers during the 12 month period.

Appendix A.

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

Appendix B.**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)