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Association Between Initial Opioid Prescription Diagnosis Type and Subsequent Persistent Prescription Opioid Use in Rhode Island: A Population-Based Cohort Study

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Diagnosis Type and Persistent Opioid Use

Abstract

Objective: To identify initial diagnoses associated with elevated risk of prolonged prescription opioid use in a population-based retrospective study.

Methods: We included all Rhode Island residents with an initial opioid prescription dispensed between April 1, 2019 and March 31, 2020. Our primary outcome was subsequent persistent prescription opioid use, defined as at least 90 days of prescription opioid use without a gap of more than seven days starting from the fill date of the initial opioid prescription. We estimated the association between the diagnosis type on the initial opioid prescription and subsequent persistent prescription opioid use using logistic regression.

Results: Among the 87,055 patients with an initial opioid prescription, 647 (0.7%) subsequently became persistent users. Patients who become persistent users tended to receive a longer days' supply, greater quantity dispensed, but a lower MME on the initial opioid prescription. Patients prescribed an initial opioid prescription for diseases of the musculoskeletal system and connective tissue (adjusted odds ratio [aOR]: 16.1, 95% confidence internal [CI]: 9.2-28.2), diseases of the nervous system (aOR: 16.3, 95% CI: 9.2-28.9), and neoplasms (aOR: 12.1, 95% I: 6.1-23.8) had higher odds of subsequent persistent prescription opioid use after adjusting for confounders.

Conclusions: By focusing interventions and prescribing guidelines on specific types of diagnoses that carry a high risk of persistent prescription opioid use and diagnoses that would benefit equally or more from alternative management approaches, states and health care organizations may more efficiently decrease inappropriate opioid prescribing while improving the quality of patient care.

Strengths and Limitations

- This study included all opioid prescriptions dispensed to Rhode Island residents by licensed retail pharmacies for the 12-month study period which decreases selection bias and provides more generalizable results.
- This study demonstrates the utility of collecting ICD-10 codes in prescription drug monitoring programs, as this allows for consideration of the *reason* for prescriptions in population-based epidemiologic studies.
- This work provides an example that other public health jurisdictions could follow to systematically identify the diagnoses associated with all prolonged prescription opioid use.
- A high percentage (36%) of opioid initiate prescriptions with a missing diagnosis code during the analysis period.

Diagnosis Type and Persistent Opioid Use

- Identifying logical, simple, and accurate ways to collapse ICD-10 codes into meaningful groups is difficult.

Diagnosis Type and Persistent Opioid Use

Introduction

In developed countries, pain is one of the most common reasons people seek medical care and managing this pain appropriately can be clinically challenging.[1] An analysis of the National Health Interview Survey by the Centers for Disease Control and Prevention estimated that approximately 50 million Americans are burdened with chronic pain, and of those, 19.6 million have pain that frequently impacts their life or work activities.[2] While prescription opioids may be effective at relieving pain, they fail to alleviate the underlying cause of pain, and the evidence supporting their effectiveness at relieving chronic pain is controversial.[3] Additionally, prolonged prescription opioid use can cause dependence in some individuals, which may lead to addiction, overdose, and/or death.

To help define safe prescribing practices, many studies have tried to identify factors associated with prolonged opioid use following specific diagnoses or procedures, including childbirth, major surgeries, or chronic conditions.[4-6] While many studies have identified patient-level risk factors associated with persistent opioid use among those with a specific diagnosis (e.g. higher doses, history of substance abuse, anxiety, or tobacco use), none have attempted to identify initial diagnoses associated with elevated risk of prolonged opioid use overall.[5-7]

Previous regulations limiting opioid prescribing have been effective at reducing inappropriate or unsafe opioid prescribing practices.[8] Properly characterizing the underlying diagnoses and procedures that resulted in prolonged prescription opioid use could inform targeted prescribing guidelines, particularly if those underlying diagnoses and procedures can be managed effectively with non-opioid therapies. To inform these knowledge gaps, we leveraged population-based controlled substance prescribing data to estimate the association between the diagnosis type on the initial opioid prescription and subsequent persistent prescription opioid use.

Methods

Study Design and Population

We conducted a population-based retrospective cohort study utilizing data from the Rhode Island Prescription Drug Monitoring Program (PDMP). Our cohort included all Rhode Island residents with an initial opioid prescription dispensed by a retail pharmacy with a controlled substance registration between April 1, 2019 and March 31, 2020.

Diagnosis Type and Persistent Opioid Use

We identified opioid prescriptions using the American Hospital Formulary Service Pharmacologic – Therapeutic Classification Code (TCC) associated with the National Drug Code of each product in the IBM Micromedex RED BOOK, including opiate agonists (TCC 28:08.08), opiate partial agonists (TCC 28:08.12), and tramadol products (TCC 28:08.92.00.50). We excluded antitussive and antidiarrheal medications and buprenorphine products that were only FDA-approved for medication-assisted treatment for opioid use disorder as of July 30, 2020 due to our interest in opioids prescribed for pain management. We defined an initial opioid prescription as either (1) the patient's first opioid prescription or (2) an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. For patients with more than one initial opioid prescription during the analysis period, we randomly selected one initial prescription for inclusion in the analysis to maintain independence of observations.

In 2018, Rhode Island began requiring that prescribers include an ICD-10 code on all prescriptions for a controlled substance (RIDOH, 2018). In this study, our primary exposure was the diagnosis type associated with the initial opioid prescription. We classified ICD-10 codes into 20 major diagnostic groups based on ICD-10 code chapters and separately presented specific ICD-10 codes associated with at least five persistent opioid users. Our primary outcome was subsequent persistent prescription opioid use, defined *a priori* as at least 90 days of prescription opioid use without a gap of more than seven days starting from the fill date of the initial opioid prescription. We defined days of opioid use based on the fill date and days' supply for each prescription dispensed.

We excluded veterinary prescriptions based on an indicator for veterinary prescriptions, an animal name field, and the degrees listed with the prescriber's last name (i.e., DVM or VMD). Additionally, we excluded initial opioid prescriptions filled by pharmacies for which ICD-10 codes were missing for more than 80% of their dispensed opioid prescriptions due to concerns about bias among the ICD-10 codes that were entered. We defined unique patients based on the first five letters of the last name, the first three letters of the first name, and the date of birth on each prescription.

Statistical Analysis

We estimated the association between the diagnostic type of the initial opioid prescription and subsequent persistent prescription opioid use using logistic regression, adjusting for potential confounders. The diagnosis categories with fewer than five persistent opioid users were collapsed and

used as the reference group. Patients with missing diagnosis type were excluded from the model. We selected the following potential confounders *a priori*: age (continuous) and sex. Characteristics of the initial prescription (e.g., type of opioid, days' supply, quantity dispensed, daily morphine milligram equivalents [MME]) were not considered confounders because they are determined by the prescriber based on the diagnosis and, thus, are in the causal pathway between the diagnosis type and subsequent persistent opioid use.

To understand the potential impact of missing diagnostic type data, we compared the characteristics of initial opioid prescriptions with and without a diagnosis. We compared categorical variables using chi-squared tests and continuous variables using the Mann-Whitney U test.

This study was deemed exempt by the Institutional Review Board of the Rhode Island Department of Health. All analyses were conducted in SAS 9.4 (Cary, North Carolina).

Patient and Public Involvement

No patient or public involvement.

Results

Between April 1, 2019 and March 31, 2020, there were a total of 113,398 initial opioid prescriptions dispensed to 99,129 unique Rhode Island residents. Of these, 98,883 initial opioid prescriptions to 87,055 people were dispensed by pharmacies with less than 80% of initial opioid prescriptions missing an ICD-10 code. After randomly selecting one initial opioid prescription for each of the 10,294 patients with more than one during this period, there were 87,055 initial opioid prescriptions dispensed to 87,055 unique people in the final study population.

Baseline Characteristics of Initial Opioid Prescriptions

The median age of patients receiving an initial opioid prescription was 53 years (interquartile range [IQR]=36-66), and a majority (57.9%) of patients were female. Most patients paid for the initial opioid prescription with private insurance (60.3%), followed by Medicare (14.9%) and Medicaid (12.4%). The most common types of opioids prescribed on the initial prescription were oxycodone (42.2%), hydrocodone (27.9%), tramadol (14.5%), and codeine (10.9%). The median days' supply prescribed, and quantity prescribed were 4 days (IQR=3-5) and 15 units (IQR=10-20), respectively. The median

daily MME was 24.0 (IQR=18.0-30.0, **Table 1**). Most of the initial opioid prescriptions were prescribed by physicians (43.9%).

Patients with and without subsequent persistent prescription opioid use following the initial prescription were significantly different on all baseline characteristics compared, except for sex and the median MME on their initial opioid prescription. Of note, patients with versus without subsequent persistent prescription opioid use following the initial prescription were significantly older (median 60 vs. 53 years) and more likely to have paid for their initial opioid prescription with Medicare (26.1% vs. 14.8%) or cash (11.6% vs. 9.3%). Additionally, patients with versus without subsequent persistent use were more likely to have been prescribed tramadol (30.1% vs. 14.3%), hydromorphone (2.2% vs. 0.6%), or buprenorphine pain (2.8% vs. 0.1%) products; and had a longer median days' supply (10 vs. 4 days) and greater quantity dispensed (20 vs. 15 units). Finally, patients with versus without subsequent persistent use were more likely to have been prescribed their initial opioid prescription by a physician (64.6% vs. 43.8%) or an advanced nurse (19.0% vs. 13.7%) rather than a dentist (0.6% vs. 16.5%) or physician assistant (11.1% vs. 15.1%).

Overall, 32,574 patients (36.27%) were missing diagnosis code information on their initial opioid prescription. The most common diagnosis codes for the remaining 55,481 patients included diseases of the musculoskeletal system and connective tissue (n=15,525, 17.8%), diseases of the nervous system (n=8,377, 9.6%), and diseases of the digestive system (n=7,552, 8.7%; **Table 2**). Patients with and without a diagnosis differed on all characteristics compared. Notably, patients with unknown versus known diagnosis type were more likely to pay for their initial opioid prescription with cash (11.2% vs. 8.2%), to have received hydrocodone (32.6% vs. 25.2%) or codeine (15.2% vs. 8.5%) products on their initial opioid prescription, and to have received their initial opioid prescription from a dental professional (29.0% vs. 9.2%, **Table 3**).

Opioid Prescribing During the 90-Day Follow-Up Period

In the 90 days following the start of the initial opioid prescription, the daily MME increased slightly from a median of 23.3 MME (IQR=18.0-30.0) on the first day of opioids prescribed to 25.0 (IQR=18.0-30.0) on the last day of opioids prescribed. Overall, patients were prescribed a median of 5 days (IQR=3-9) of opioids total during the 90-day follow-up period.

Diagnosis Type and Persistent Opioid Use

Among the 87,055 patients with an initial opioid prescription, 647 (0.74%) subsequently used prescription opioids for at least 90 days without a gap of more than 7 days. Similarly, among the 55,481 patients with an initial opioid prescription that included a known diagnosis type, 472 (0.85%) subsequently used prescription opioids for the 90 days following their initial prescription without a gap of more than 7 days (**Table 4**). When compared to patients prescribed an initial opioid prescription in the referent group, those with diseases of the musculoskeletal system and connective tissue (adjusted odds ratio [aOR]: 16.1 95% confidence internal [CI]: 9.2-28.2), diseases of the nervous system (aOR: 16.3, 95% CI: 9.2-28.9), and neoplasms (aOR: 12.1, 95% I: 6.1-23.8) had higher odds of subsequent prescription opioid use after adjusting for age and sex, and had an elevated percentage of patients with persistent use when compared to the overall average (1.6%, 1.6%, and 1.2%, respectively, when compared to 0.8%).

When looking at the specific ICD-10 codes with at least five patients with subsequent persistent prescription opioid use, pain not elsewhere classified (123/472, 26.1%), dorsalgia (103/472, 24.3%), other joint disorders not elsewhere classified (28/472, 5.9%), and spondylosis (20/472, 4.2%) had the highest number and percentage of persistent users (**Table 5**). Notably, specific diagnoses that had a relatively high percentage of patients that went on to persistently use prescription opioids included: intraoperative and postprocedural complications and disorders of musculoskeletal system, not elsewhere classified" on their initial opioid prescription (9/89, 10.1%); rheumatoid arthritis (5/84, 6.0%); spondylosis (20/407, 4.9%); and "thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders (16/487, 3.3%).

Discussion

In the 12-month study period, nearly 10% of Rhode Island residents received at least one initial opioid prescription, of whom 0.7% went on to become persistent prescription opioid users based on our study definition. Tramadol, hydromorphone, and buprenorphine pain products were more often prescribed on the initial opioid prescription to people who became persistent prescription opioid users. Moreover, persistent users tended to receive a longer days' supply, greater quantity dispensed, but a lower MME on the initial opioid prescription. Physicians and advanced nurses more often prescribed the initial opioid prescription of patients who become persistent prescription opioid users. Overall, initial opioid prescriptions were most often prescribed for diseases of the musculoskeletal system and connective tissue, diseases of the nervous system, and diseases of the digestive system, and these diagnoses were

strongly associated with subsequent persistent prescription opioid use. Among ICD-10 codes with at least five persistent users, the percentage of patients who went on to develop persistent prescription opioid use following the initiate prescription ranged from 0.53%-10.11% by the specific ICD-10 code.

While prior work has focused on prolonged prescription opioid use following specific diagnoses or procedures, our population-based study evaluated prolonged prescription opioid use among all patients receiving initial opioid prescriptions in Rhode Island.[4-6] Despite differences in methodology, other studies estimating the frequency of persistent prescription opioid use after childbirth (1.7-2.2%), dental procedures (2.4-4.1%), elective surgeries (3.0-8.0%), or cancer treatment (8.3%) identified a substantially higher percentage of patients with persistent use compared to our study of all patients receiving initial opioid prescriptions (0.7%).[4-7,9-12] In the absence of similar population-based studies of patients receiving initial opioid prescriptions in the literature, the lower percentage of patients experiencing subsequent persistent prescription opioid use in our study could be due to the inclusion of diagnoses with a lower likelihood of persistent use, our strict definition of persistent use in this analysis, and/or a lower risk of persistent prescription opioid use in Rhode Island versus other geographic areas or in 2019-2020 compared to other time periods. While other studies often define persistent use as one or more claims for opioid prescriptions 0-90 and 90-180 days after the procedure/diagnosis, we defined persistent use as at least 90 days of prescription opioid use without a gap of more than 7 days starting from the fill date of the opioid initiate prescription.[5,7,9] We used this relatively strict definition of persistent prescription opioid in an attempt to exclude patients who intermittently used opioids and to focus our analysis on opioid prescribing patterns most likely to represent persistent use and carry the greatest risk of opioid addiction.[13]

Unfortunately, the Rhode Island PDMP only recently started collecting ICD-10 codes on controlled substance prescriptions, and as such, we do not know if the percentage of patients who developed persistent prescription opioid use following an initiate prescription has changed over time. Additionally, it is possible that the "legacy population" of long-term prescription opioid users in Rhode Island began their persistent use through different diagnoses than those reported here, particularly given changes in prescribing patterns over the past 5-10 years. The Rhode Island Department of Health, in collaboration with other sister state agencies and community-based organizations, has launched several interventions that may have reduced the persistent prescription opioid use over time, including one-on-one targeted

prescriber education on responsible prescribing, appropriate regulation regarding prescribing, and provider reimbursement for the use of non-opioid pain management strategies.[14-16]

A primary benefit of categorizing diagnosis type through ICD-10 codes in this population-based study is the ability to systematically review opioid prescribing patterns among patients with different diseases or sources of pain. Previous studies have shown the dangers of inappropriate prescribing, but effectively targeting interventions and prescribing guidelines to minimize risk of persistent opioid use while appropriately managing pain is challenging.[17] Our study identified a few diagnosis types on initial opioid prescriptions that are associated with greater odds of subsequent persistent prescription opioid use in Rhode Island, which allows our state to prioritize interventions that target specific practice areas. For instance, we found that diseases of the musculoskeletal system and connective tissue were highly associated with subsequent persistent prescription opioid use. Given that many patients with musculoskeletal pain can improve over time independent of treatment, prior work has suggested that non-pharmacological treatments be utilized first (e.g., physical therapy, acupuncture, massages), followed by or with anti-inflammatory medications, and if patients are still experiencing pain, prescription opioids.[18,19] Importantly, as the pathophysiology of musculoskeletal diseases is inflammatory, a prescription opioid to block pain is not clinically appropriate, and if pharmacological therapy is necessary, anti-inflammatory medications may be more efficacious than opioids.[20] By focusing interventions and prescribing guidelines on specific types of diagnoses that carry a high risk of persistent opioid use and benefit equally or more for alternative management approaches, states and health care organizations may efficiently decrease inappropriate opioid prescribing while improving the quality of patient care.

This study can serve as an example for other states looking to undertake a similar analysis of new persistent prescription opioid use in their population and highlights the added value of collecting ICD-10 codes associated with prescriptions in PDMPs. Replicating this study in other regions could inform the standard of care for pain management and hopefully lead to safer prescribing patterns.

A major strength of this study is the inclusion of all opioid prescriptions dispensed to Rhode Island residents by licensed retail pharmacies for the 12-month study period through the Rhode Island PDMP. The use of a large, population-based study decreases selection bias and provides more generalizable results, although we are not able to identify specific subpopulations with unique risk profiles using this

approach. Additionally, our restrictive definition of persistent prescription opioid use likely minimized the inclusion of intermittent prescription opioid users in this group, improving the specificity of our outcome. Finally, this study demonstrates the utility of collecting ICD-10 codes in PDMPs, as this allows for consideration of the *reason* for prescriptions in population-based epidemiologic studies. This highlights for us the advantage to increase ICD 10 reporting. As reporting increases, this dataset provides a way to systematically identify the diagnoses associated with all opioid prescriptions dispensed to Rhode Island residents.

Despite the advantages of having ICD-10 codes in the Rhode Island PDMP, the largest limitation of this study was the high percentage (36%) of opioid initiate prescriptions with a missing diagnosis code during the analysis period. Unfortunately, we are not able to determine whether the prescriber neglected to provide an ICD-10 code on the prescription, or the pharmacy neglected to include the ICD-10 code when reporting to the PDMP. Although initial opioid prescriptions with and without ICD-10 codes were significantly different on all characteristics compared, our sample size was large, and the most meaningful difference was that prescriptions missing ICD-10 codes were more often written by dental professionals. It may be useful to support dental professionals in the reporting of ICD-10 codes, including sharing the results of these types of studies, to improve the completeness of reporting. Additionally, this analysis is limited to opioids dispensed by retail pharmacies and does not include those dispensed at hospitals or by Veterans Affairs, which may modify our results. Finally, due to variation in the specificity of ICD-10 codes, identifying logical, simple, and accurate ways to collapse them into meaningful groups is difficult. Improved systematic methods for categorizing ICD-10 codes into clinically meaningful groups would be useful for future epidemiologic studies.

Conclusions

Despite nearly 10% of Rhode Island residents receiving an initial opioid prescription in the 12-month study period, only 0.7% went on to become persistent prescription opioid users based on our study definition. Diseases of the musculoskeletal system and connective tissue, diseases of the nervous system, and neoplasms carried a high risk of subsequent persistent opioid use. For diagnoses in these groups that would benefit equally or more from alternative management approaches, we can create targeted interventions and prescribing guidelines to efficiently decrease inappropriate opioid prescribing while improving the quality of patient care.

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Competing Interests

None declared.

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Table 1. Baseline Characteristics of Rhode Island Residents Dispensed Initial Opioid Prescriptions, April 1, 2019 – March 31, 2020*

Characteristic	Overall N=87,055 n (%)†	Subsequent Persistent Prescription Opioid Use		P-value¶
		Yes N=647 n (%)†	No N=86,408 n (%)†	
Patient				
Age	53 (36-66)‡	60 (52-71)‡	53 (36-66)‡	<0.0001α
Sex				
Female	50,399 (57.89)	393 (60.74)	50,006 (57.87)	0.3336
Male	36,652 (42.10)	254 (39.26)	36,398 (42.12)	
Unknown	<5	0 (0.00)	<5	
Payment method				
Private insurance	52,491 (60.30)	288 (44.51)	52,203 (60.41)	<0.0001
Medicare	12,948 (14.87)	169 (26.12)	12,779 (14.79)	
Medicaid	10,829 (12.44)	84 (12.98)	10,745 (12.44)	
Cash	8,079 (9.29)	75 (11.59)	8,004 (9.26)	
Workers' compensation	433 (0.50)	<5	429 (0.05)	
Unknown	2,275 (2.61)	27 (4.17)	2,248 (2.60)	
Prescription				
Opioid type				
Oxycodone	37,631 (42.23)	244 (37.71)	37,387 (43.27)	<0.0001
Hydrocodone	24,261 (27.87)	130 (20.09)	24,131 (27.93)	
Tramadol	12,590 (14.46)	195 (30.14)	12,395 (14.34)	
Codeine	9,525 (10.94)	16 (2.47)	9,509 (11.00)	
Morphine	2,327 (2.67)	19 (2.94)	2,308 (2.67)	
Hydromorphone	494 (0.57)	14 (2.16)	480 (0.56)	
Buprenorphine (pain)§	91 (0.10)	18 (2.78)	73 (0.08)	
Methadone	42 (0.05)	<5	39 (0.05)	
Fentanyl	28 (0.03)	<5	25 (0.03)	
Tapentadol	27 (0.03)	<5	23 (0.03)	
Opium	22 (0.03)	0 (0.00)	22 (0.03)	
Oxymorphone	6 (0.01)	<5	5 (0.01)	
Butorphanol	<5	0 (0.00)	<5	
Pentazocine	<5	0 (0.00)	<5	
Dihydrocodeine	<5	0 (0.00)	<5	
Meperidine	<5	0 (0.00)	<5	
Initial Opioid Prescription				
Days' supply	4 (3-5)‡	10 (6-30)‡	4 (3-5)‡	<0.0001α
Quantity prescribed	15 (10-20)‡	20 (20-84)‡	15 (10-20)‡	<0.0001α
Median daily MME	24.0 (18.0-30.0)‡	22.5 (15.0-45.0)‡	24.0 (18.0-30.0)‡	0.2606α
90-day follow-up period				
Total days prescribed	5 (3-9)‡	86 (81-89)‡	5 (3-8)‡	<0.0001α
Initial MME	23.3 (18.0-30.0)‡	20.0 (10.0-30.0)‡	23.3 (18.0-30.0)‡	<0.0001α
Final MME	25.0 (18.0-30.0)‡	22.5 (15.0-46.1)‡	25.0 (18.0-30.0)‡	0.0179α
Prescriber type				
Physician	38,240 (43.93)	418 (64.61)	37,822 (43.77)	<0.0001
Advanced nurse	11,973 (13.75)	123 (19.01)	11,850 (13.71)	
Physician assistant	13,077 (15.02)	72 (11.13)	13,005 (15.05)	
Dental professional	14,262 (16.38)	4 (0.62)	14,258 (16.50)	
Unknown	9,503 (10.92)	30 (4.64)	9,473 (10.96)	

*Initial opioid prescriptions defined as either the patient's first opioid prescription or an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. For patients with more than 1 opioid initiate prescription during this period, we randomly selected one for inclusion in this analysis. † Unless otherwise specified. ‡ Median (IQR). § This analysis excluded buprenorphine products only FDA-approved for medication-assisted treatment of opioid use disorder. ¶ Chi-squared test unless otherwise specified. αMann Whitney U test.

Diagnosis Type and Persistent Opioid Use

Table 2. Diagnosis Type on Initial Opioid Prescriptions Dispensed to Rhode Island Residents, April 1, 2019 – March 31, 2020*

Diagnosis Type	Overall	Subsequent Persistent Prescription Opioid Use	
		Yes	No
	N=87,055 n (%)	N=647 n (%)	N=86,408 n (%)
Unknown	31,574 (36.27)	175 (27.05)	31,399 (36.34)
Diseases of the musculoskeletal system and connective tissue	15,525 (17.83)	253 (39.10)	15,272 (17.67)
Diseases of the nervous system	8,377 (9.62)	133 (20.56)	8,244 (9.54)
Diseases of the digestive system	7,552 (8.67)	<5	7,549 (8.74)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	7,133 (8.19)	28 (4.33)	7,105 (8.22)
Factors influencing health status and contact with health services	3,833 (4.40)	10 (1.55)	3,823 (4.42)
Injury, poisoning and certain other consequences of external causes	3,290 (3.78)	5 (0.77)	3,285 (3.80)
Diseases of the genitourinary system	2,974 (3.42)	<5	2,972 (3.44)
Neoplasms	1,960 (2.25)	25 (3.86)	1,935 (2.24)
Pregnancy, childbirth and the puerperium	1,246 (1.43)	0 (0.00)	1,246 (1.44)
Diseases of the respiratory system	811 (0.93)	<5	808 (0.94)
Diseases of the skin and subcutaneous tissue	756 (0.87)	5 (0.77)	751 (0.87)
Diseases of the circulatory system	479 (0.55)	<5	478 (0.55)
Certain infectious and parasitic diseases	416 (0.48)	<5	415 (0.48)
Diseases of the eye and adnexa	277 (0.32)	0 (0.00)	277 (0.32)
Mental and behavioral disorders	272 (0.31)	<5	270 (0.31)
Endocrine, nutritional and metabolic diseases	267 (0.31)	0 (0.00)	267 (0.31)
Congenital malformations, deformations and chromosomal abnormalities	145 (0.17)	0 (0.00)	145 (0.17)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	85 (0.10)	<5	84 (0.10)
External causes of morbidity and mortality	82 (0.09)	0 (0.00)	82 (0.09)
Certain conditions originating in the perinatal period	<5	0 (0.00)	<5

*Initial opioid initiate prescriptions were defined as either the patient's first opioid prescription or an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. For patients with more than one initial opioid prescription during this period, we randomly selected one for inclusion in this analysis.

Diagnosis Type and Persistent Opioid Use

Table 3. Characteristics Associated with Unknown Diagnosis Type on Opioid Initiate Prescriptions Dispensed to Rhode Island Residents, April 1, 2019 – March 31, 2020*

Characteristic	Known Diagnosis Type N=55,481 n (%)†	Unknown Diagnosis Type N=31,574 n (%)†	P-value¶
Patient			
Age	54 (37-66)‡	52 (34-65)‡	<0.0001α
Sex			
Female	33,007 (59.49)	17,392 (55.08)	<0.0001
Male	22,474 (40.51)	14,178 (44.90)	
Unknown	0 (0.0)	<5	
Payment method			
Private insurance	33,777 (60.88)	18,714 (59.27)	<0.0001
Medicare	8,358 (15.06)	4,590 (14.54)	
Medicaid	6,861 (12.37)	3,968 (12.57)	
Cash	4,552 (8.20)	3,527 (11.17)	
Workers' compensation	241 (0.43)	192 (0.61)	
Unknown	1,692 (3.05)	583 (1.85)	
Prescription			
Opioid type			
Oxycodone	26,422 (47.62)	11,209 (35.50)	<0.0001
Hydrocodone	13,955 (25.15)	10,306 (32.64)	
Tramadol	8,417 (15.17)	4,173 (13.22)	
Codeine	4,719 (8.51)	4,806 (15.22)	
Morphine	1,483 (2.67)	844 (2.67)	
Hydromorphone	314 (0.57)	180 (0.57)	
Buprenorphine (pain)§	70 (0.13)	21 (0.07)	
Methadone	32 (0.06)	10 (0.03)	
Fentanyl	25 (0.05)	<5	
Tapentadol	16 (0.03)	11 (0.03)	
Opium	18 (0.03)	<5	
Oxymorphone	<5	<5	
Butorphanol	<5	<5	
Pentazocine	0 (0.00)	<5	
Dihydrocodeine	<5	0 (0.00)	
Meperidine	<5	<5	
Persistent Opioid Use			
Yes	472 (0.85)	55,009 (99.15)	<0.0001
No	175 (0.55)	31,399 (99.45)	
Initial Opioid Prescription			
Days' supply	5 (3-5)‡	4 (3-5)‡	<0.0001α
Quantity prescribed	18 (10-20)‡	15 (10-20)‡	<0.0001α
Daily MME	25.0 (18.8-30.0)‡	22.5 (18.0-30.0)‡	<0.0001α
90-day follow-up period			
Total days prescribed	5 (3-5)‡	5 (3-7)‡	<0.0001α
Initial MME	25.0 (18.8-30.0)‡	22.5 (18.0-30.0)‡	<0.0001α
Final MME	25.0 (18.8-30.0)‡	22.5 (18.0-30.0)‡	<0.0001α
Prescriber type			
Physician	26,083 (47.01)	12,157 (38.50)	<0.0001
Physician assistant	8,954 (16.14)	4,123 (13.06)	
Advanced nurse	8,458 (15.24)	3,515 (11.13)	
Dental professional	5,101 (9.19)	9,161 (29.01)	
Unknown	6,885 (12.41)	2,618 (8.29)	

*Opioid initiate prescriptions were defined as either the patient's first opioid prescription or an opioid prescription that started at least60 days after the patient's previous opioid prescription ended. For patients with more than one opioid initiate prescription during this period, we randomly selected one for inclusion in this analysis. † Unless otherwise

Diagnosis Type and Persistent Opioid Use

specified. ‡ Median (IQR). § This analysis excluded buprenorphine products only FDA-approved for medication-assisted treatment of opioid use disorder. ¶ Chi-squared test unless otherwise specified. [α]Mann Whitney U test.

Diagnosis Type and Persistent Opioid Use

Table 4. Association Between the Diagnosis Type on the Initial Opioid Prescription and Subsequent Persistent Prescription Opioid Use among Rhode Island Residents, April 1, 2019 – March 31, 2020*†

Diagnosis Type	Subsequent Persistent Prescription Opioid Use		Adjusted OR (95% CI)‡
	No N=55,019 n (row %)	Yes N=472 n (row %)	
Diseases of the musculoskeletal system and connective tissue	15,272 (98.37)	253 (1.63)	**16.07 (9.18-28.18)**
Diseases of the nervous system	8,244 (98.41)	133 (1.59)	**16.34 (9.22-28.95)**
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	7,105 (99.61)	28 (0.39)	**4.16 (2.15-8.05)**
Factors influencing health status and contact with health services	3,823 (99.74)	10 (0.26)	**2.68 (1.17-6.12)**
Injury, poisoning and certain other consequences of external causes	3,285 (99.85)	5 (0.15)	1.58 (0.56-4.43)
Neoplasms	1,935 (98.72)	25 (1.28)	**12.08 (6.14-23.75)**
Diseases of the skin and subcutaneous tissue	751 (99.34)	5 (0.66)	**7.46 (2.65-20.98)**
Other§	14,594 (99.91)	13 (0.09)	Ref.

* Opioid initiate prescriptions defined as either the patient's first opioid prescription or an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. For patients with more than one opioid initiate prescription during this period, we randomly selected one for inclusion in this analysis.

† Persistent prescription opioid use defined as defined *a priori* as ≥90 days of opioid use without a gap of more than seven days starting from the fill date of the opioid initiate prescription.

‡ Adjusted for potential confounders selected *a priori*: age (continuous) and sex.

§ Other includes all initial opioid prescriptions for: diseases of the digestive system, diseases of the genitourinary system, pregnancy, childbirth and the puerperium, diseases of the respiratory system, diseases of the circulatory system, certain infectious and parasitic diseases, diseases of the eye and adnexa, mental and behavioral disorders Endocrine, nutritional and metabolic diseases, congenital malformations, deformations and chromosomal abnormalities, diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, external causes of morbidity and mortality, certain conditions originating in the perinatal period.

Diagnosis Type and Persistent Opioid Use

Table 5. ICD-10 Codes on Initial Opioid Initiate Prescriptions with the Highest Number of Subsequent Persistent Prescription Opioid Users, Rhode Island Residents - April 1, 2019 – March 31, 2020*

Diagnosis	Subsequent Persistent Prescription Opioid Use	
	Yes N=472 n (row %)	No N=22,498 n (row %)
Pain, not elsewhere classified (G89)	123 (1.86)	6,483 (98.14)
Dorsalgia (M54)	103 (2.11)	4,790 (97.89)
Other joint disorder, not elsewhere classified (M25)	28 (1.42)	1,946 (98.58)
Spondylosis (M47)	20 (4.91)	387 (95.09)
Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders (M51)	16 (3.29)	471 (96.71)
Other and unspecified soft tissue disorders, not elsewhere classified (M79)	11 (1.04)	1,048 (98.96)
Osteoarthritis of knee (M17)	11 (1.33)	819 (98.67)
Other and unspecified osteoarthritis (M19)	9 (2.19)	402 (97.81)
Intraoperative and postprocedural complications and disorders of musculoskeletal system, not elsewhere classified (M96)	9 (10.11)	80 (89.89)
Other spondylopathies (M48)	8 (1.54)	510 (98.46)
Abdominal and pelvic pain (R10)	6 (0.53)	1,125 (99.47)
Polyosteoarthritis (M15)	6 (2.93)	199 (97.07)
Other rheumatoid arthritis (M06)	5 (5.95)	79 (94.05)
All other ICD-10 codes?	100 (0.31)	32,511 (99.69)

* Opioid initiate prescriptions were defined as either the patient's first opioid prescription or an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. For patients with more than one opioid initiate prescription during this period, we randomly selected one for inclusion in this analysis.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	4-5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5-6

Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	4-5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5-6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5-6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a
Statistical methods	#12c	Explain how missing data were addressed	6
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a
Statistical methods	#12e	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and	6

		unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	6
Participants	#13c	Consider use of a flow diagram	
n/a			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	6-7
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
n/a			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
n/a			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-8
Main results	#16b	Report category boundaries when continuous variables were	15-20

		categorized	
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
19			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	#18	Summarise key results with reference to study objectives	8-11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	11
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	8-11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	8-11
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

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Association Between Initial Opioid Prescription Diagnosis Type and Subsequent Chronic Prescription Opioid Use in Rhode Island: A Population-Based Cohort Study

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Diagnosis Type and Chronic Opioid Use

Abstract

Objective: To identify initial diagnoses associated with elevated risk of chronic prescription opioid use.

Design: Population-based, retrospective cohort study.

Setting: State of Rhode Island.

Participants: Rhode Island residents with an initial opioid prescription dispensed between April 1, 2019, and March 31, 2020.

Primary Outcome Measure: Subsequent chronic prescription opioid use, defined as receiving 60 or more days' supply of opioids in the 90 days following an initial opioid prescription.

Results: Among the 87,055 patients with an initial opioid prescription, 3,199 (3.7%) subsequently became chronic users. Patients who become chronic users tended to receive a longer days' supply, greater quantity dispensed, but a lower morphine milligram equivalents on the initial opioid prescription. Patients prescribed an initial opioid prescription for diseases of the musculoskeletal system and connective tissue (adjusted odds ratio [aOR]: 5.9, 95% confidence internal [CI]: 4.7-7.6), diseases of the nervous system (aOR: 6.3, 95% CI: 4.9-8.0), and neoplasms (aOR: 5.6, 95% CI: 4.2-7.5) had higher odds of subsequent chronic prescription opioid use, compared to a referent group that included all diagnosis types with fewer than 15 chronic opioid users, after adjusting for confounders.

Conclusions: By focusing interventions and prescribing guidelines on specific types of diagnoses that carry a high risk of chronic prescription opioid use and diagnoses that would benefit equally or more from alternative management approaches, states and health care organizations may more efficiently decrease inappropriate opioid prescribing while improving the quality of patient care.

Strengths and Limitations

- This study included all Rhode Island residents with an initial opioid prescription dispensed by a licensed retail pharmacy during the 12-month study period, which decreases selection bias and provides more generalizable results.
- A high percentage (36%) of initial opioid prescriptions had a missing diagnosis code during the analysis period, which may bias our results.
- Identifying logical, simple, and accurate ways to collapse ICD-10 codes into meaningful groups is difficult.

Diagnosis Type and Chronic Opioid Use

Introduction

In developed countries, pain is one of the most common reasons people seek medical care and managing this pain appropriately can be clinically challenging.[1] An analysis of the National Health Interview Survey by the Centers for Disease Control and Prevention estimated that approximately 50 million Americans are burdened with chronic pain, and of those, 19.6 million have pain that frequently impacts their life or work activities.[2] While prescription opioids may be effective at relieving pain, they fail to alleviate the underlying cause of pain, and the evidence supporting their effectiveness at relieving chronic pain is controversial.[3] Additionally, chronic prescription opioid use can cause dependence in some individuals, which may lead to addiction, overdose, and/or death.

To help define safe prescribing practices, many studies have tried to identify factors associated with prolonged opioid use following specific diagnoses or procedures, including childbirth, major surgeries, or chronic conditions.[4-6] While many studies have identified patient-level risk factors associated with chronic opioid use among those with a specific diagnosis (e.g., higher doses, history of substance abuse, anxiety, or tobacco use), none have attempted to identify initial diagnoses associated with elevated risk of chronic opioid use overall.[5-7]

Previous regulations limiting opioid prescribing have been effective at reducing inappropriate or unsafe opioid prescribing practices.[8] Properly characterizing the underlying diagnoses and procedures that resulted in chronic prescription opioid use could inform targeted prescribing guidelines, particularly if those underlying diagnoses and procedures can be managed effectively with non-opioid therapies. To inform these knowledge gaps, we leveraged population-based controlled substance prescribing data to estimate the association between the diagnosis type on the initial opioid prescription and subsequent chronic prescription opioid use.

Methods

Study Design and Population

We conducted a population-based retrospective cohort study utilizing data from the Rhode Island Prescription Drug Monitoring Program (PDMP). Our cohort included all Rhode Island residents with an initial opioid prescription dispensed by a retail pharmacy with a controlled substance registration between April 1, 2019 and March 31, 2020.

Diagnosis Type and Chronic Opioid Use

We identified opioid prescriptions using the American Hospital Formulary Service Pharmacologic – Therapeutic Classification Code (TCC) associated with the National Drug Code of each product in the IBM Micromedex RED BOOK, including opiate agonists (TCC 28:08.08), opiate partial agonists (TCC 28:08.12), and tramadol products (TCC 28:08.92.00.50). We excluded antitussive and antidiarrheal medications and buprenorphine products that were only FDA-approved for medication-assisted treatment for opioid use disorder as of July 30, 2020 due to our interest in opioids prescribed for pain management. We defined an initial opioid prescription as either (1) the patient's first opioid prescription or (2) an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. When defining initial opioid prescriptions, we utilized prescriptions filled on/after January 1, 2019 to ensure there was a "look-back" of at least 90 days for all patients. For patients with more than one initial opioid prescription during the analysis period, we randomly selected one initial prescription for inclusion in the analysis to maintain independence of observations.

In 2018, Rhode Island began requiring prescribers to include the primary ICD-10 code on all prescriptions for a controlled substance.[9] In this study, our primary exposure was the diagnosis type associated with the primary ICD-10 code on the initial opioid prescription. We classified ICD-10 codes into 20 major diagnostic groups based on ICD-10 code chapters and separately presented specific ICD-10 codes associated with at least 15 chronic opioid users. Our primary outcome was subsequent chronic prescription opioid use, defined as ≥60 days' supply of opioids dispensed in the 90 days following the fill date of an individual's initial opioid prescription (including the days' supply of the initial prescription).[10] When monitoring subsequent chronic opioid prescription use, we utilized prescription data through July 1, 2020 to ensure at least 90 days of follow-up following the initial opioid prescription for all patients.

We excluded veterinary prescriptions based on an indicator for veterinary prescriptions, an animal name field, and the degrees listed with the prescriber's last name (i.e., DVM or VMD). Additionally, we excluded initial opioid prescriptions filled by pharmacies for which ICD-10 codes were missing for more than 80% of their dispensed opioid prescriptions due to concerns about bias among the ICD-10 codes that were entered. We defined unique patients based on the first five letters of the last name, the first three letters of the first name, and the date of birth on each prescription.

Statistical Analysis

Diagnosis Type and Chronic Opioid Use

We estimated the association between the diagnosis type on the initial opioid prescription and subsequent chronic prescription opioid use using logistic regression, adjusting for potential confounders. The diagnosis categories with fewer than 15 chronic opioid users were collapsed and used as the reference group. Patients with missing diagnosis type were excluded from the model. We selected the following potential confounders *a priori*: age (continuous) and sex. Characteristics of the initial prescription (e.g., type of opioid, days' supply, quantity dispensed, daily morphine milligram equivalents [MME]) were not considered confounders because they are determined by the prescriber based on the diagnosis and, thus, are in the causal pathway between the diagnosis type and subsequent chronic opioid use. While other sociodemographic and clinical factors likely impact chronic opioid use (e.g., socioeconomic status), these variables are not recorded in the Rhode Island PDMP database. To understand the potential impact of missing diagnosis category information, we compared the characteristics of initial opioid prescriptions with and without a diagnosis.

This study was deemed exempt by the Institutional Review Board of the Rhode Island Department of Health (IRB approval number: 2019-30). All analyses were conducted in SAS 9.4 (Cary, North Carolina).

Patient and Public Involvement

No patient or public involvement.

Results

Between April 1, 2019 and March 31, 2020, there were a total of 113,398 initial opioid prescriptions dispensed to 99,129 unique Rhode Island residents. Of these, 98,883 initial opioid prescriptions to 87,055 unique people were dispensed by pharmacies with less than 80% of initial opioid prescriptions missing an ICD-10 code. After randomly selecting one initial opioid prescription for each of the 10,294 patients with more than one during this period, there were 87,055 initial opioid prescriptions dispensed to 87,055 unique people in the final study population.

Baseline Characteristics of Initial Opioid Prescriptions

The median age of patients receiving an initial opioid prescription was 53 years (interquartile range [IQR]=36-66), and a majority (57.9%) of patients were female. Most patients paid for the initial opioid prescription with private insurance (60.3%), followed by Medicare (14.9%) and Medicaid (12.4%). The

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most common types of opioids prescribed on the initial prescription were oxycodone (42.2%), hydrocodone (27.9%), tramadol (14.5%), and codeine (10.9%). The median days' supply prescribed, and quantity prescribed were 4 days (IQR=3-5) and 15 units (IQR=10-20), respectively. The median daily MME was 22.5 (IQR=18.0-30.0, **Table 1**). Most of the initial opioid prescriptions were prescribed by physicians (43.9%).

Patients with and without subsequent chronic prescription opioid use following the initial prescription differed on all baseline characteristics compared, except for sex and the median MME on their initial opioid prescription. Of note, patients with versus without subsequent chronic prescription opioid use following the initial prescription tended to be older (median 63 vs. 53 years), more likely to have paid for their initial opioid prescription with Medicare (27.5% vs. 14.4%), and less likely to have paid with private insurance (44.3% vs 60.9%). Additionally, patients with versus without subsequent chronic use were somewhat more likely to have been prescribed tramadol (34.0% vs. 13.7%), hydromorphone (1.3% vs. 0.5%), or buprenorphine pain (1.9% vs. 0.0%) products; and had a longer median days' supply (10 vs. 4 days) and greater quantity dispensed (20 vs. 15 units). Finally, patients with versus without subsequent chronic use were somewhat more likely to have been prescribed their initial opioid prescription by a physician (65.8% vs. 43.1%) or an advanced nurse (16.9% vs. 13.6%) rather than a dentist (0.7% vs. 17.0%) or physician assistant (11.6% vs. 15.2%).

Overall, 32,574 patients (36.27%) were missing diagnosis code information on their initial opioid prescription. The most common diagnosis codes for the remaining 55,481 patients included diseases of the musculoskeletal system and connective tissue (n=15,525, 17.8%), diseases of the nervous system (n=8,377, 9.6%), and diseases of the digestive system (n=7,552, 8.7%; **Table 2**). Notably, patients with unknown versus known diagnosis type were somewhat more likely to pay for their initial opioid prescription with cash (11.2% vs. 8.2%), to have received hydrocodone (32.6% vs. 25.2%) or codeine (15.2% vs. 8.5%) products on their initial opioid prescription, and to have received their initial opioid prescription from a dental professional (29.0% vs. 9.2%, **Table 3**).

Opioid Prescribing During the 90-Day Follow-Up Period

In the 90 days following the start of the initial opioid prescription, the daily MME increased slightly from a median of 23.3 MME (IQR=18.0-30.0) on the first day of opioids prescribed to 25.0 (IQR=18.0-

30.0) on the last day of opioids prescribed. Overall, patients were prescribed a median of 5 days (IQR=3-9) of opioids total during the 90-day follow-up period.

Among the 87,055 patients with an initial opioid prescription, 3,199 (3.7%) subsequently had chronic prescription opioid use per our definition. Similarly, among the 55,481 patients with an initial opioid prescription that included a known diagnosis type, 2,305 (4.2%) subsequently had chronic prescription opioid use (**Table 4**). When compared to patients prescribed an initial opioid prescription in the referent group (i.e., all diagnosis categories with fewer than 15 chronic opioid users), those with diseases of the musculoskeletal system and connective tissue (adjusted odds ratio [aOR]: 5.9 95% confidence internal [CI]: 4.7-7.6), diseases of the nervous system (aOR: 6.3, 95% CI: 4.9-8.0), and neoplasms (aOR: 5.6, 95% I: 4.2-7.5) had higher odds of subsequent chronic prescription opioid use after adjusting for age and sex, and had an elevated percentage of patients with chronic use when compared to the overall average (7.5%, 7.2%, and 7.6%, respectively, when compared to 1.0%).

When looking at the specific ICD-10 codes with at least 15 patients with subsequent chronic prescription opioid use, pain not elsewhere classified (G89; 592/2,305, 25.7%), dorsalgia (M54; 477/2,305, 20.7%), pain, unspecified (R52; 95/2,305, 4.1%), and other joint disorders not elsewhere classified (M25; 94/2,305, 4.1%) had the highest number of chronic users (**Table 5**). Notably, specific diagnoses that had a relatively high percentage of patients that progressed to chronic use following the initial opioid prescription included: intraoperative and postprocedural complications and disorders of musculoskeletal system, not elsewhere classified (31/89, 34.8%); polyosteoarthritis (38/205, 18.5%); rheumatoid arthritis (15/84, 17.9%); and spondylosis (69/407, 17.0%).

Discussion

In the 12-month study period, nearly 10% of Rhode Island residents received at least one initial opioid prescription, of whom 3.7% went on to become chronic prescription opioid users based on our study definition. Tramadol, hydromorphone, and buprenorphine pain products were more often prescribed on the initial opioid prescription to people who became chronic prescription opioid users. Moreover, chronic users tended to receive a longer days' supply, greater quantity dispensed, but a lower MME on the initial opioid prescription. Physicians and advanced nurses more often prescribed the initial opioid prescription of patients who become chronic prescription opioid users. Overall, initial opioid prescriptions were most often prescribed for diseases of the musculoskeletal system and connective

tissue, diseases of the nervous system, and diseases of the digestive system, and these diagnoses were strongly associated with subsequent chronic prescription opioid use. Among ICD-10 codes with at least 15 chronic users, the percentage of patients who went on to develop chronic prescription opioid use following the initial prescription ranged from 1.9-34.8% by the specific ICD-10 code.

While prior work has focused on chronic prescription opioid use following specific diagnoses or procedures, our population-based study evaluated chronic prescription opioid use among all patients receiving initial opioid prescriptions in Rhode Island.[4-6] Despite differences in methodology, other studies estimating the frequency of chronic prescription opioid use after childbirth (1.7-2.2%), dental procedures (2.4-4.1%), elective surgeries (3.0-8.0%), or cancer treatment (8.3%) identified a similar percentage of patients with chronic use compared to our study of all patients receiving initial opioid prescriptions (3.67%).[4-7,11-14] In the absence of similar population-based studies, these comparisons suggest that the percentage of patients experiencing subsequent chronic prescription opioid use in our study was generally similar to what might be expected based on prior work. While other studies often define chronic use as one or more claims for opioid prescriptions 0-90 and 90-180 days after the procedure/diagnosis, we defined chronic use as at least 60 days' supply of opioids dispensed in the 90 days following the fill date of an individual's initial opioid prescription (including the days' supply of the initial prescription).[5,7,9,10] We used this relatively strict definition of chronic prescription opioid in an attempt to exclude patients who intermittently used opioids and to focus our analysis on opioid prescribing patterns most likely to represent chronic use and carry the greatest risk of opioid addiction.[15]

Unfortunately, the Rhode Island PDMP only recently started collecting ICD-10 codes on controlled substance prescriptions, and as such, we do not know if the percentage of patients who developed chronic prescription opioid use following an initial prescription has changed over time. Additionally, it is possible that the "legacy population" of long-term prescription opioid users in Rhode Island began their chronic use through different diagnoses than those reported here, particularly given changes in prescribing patterns over the past 5-10 years. The Rhode Island Department of Health, in collaboration with other sister state agencies and community-based organizations, has launched several interventions that may have reduced the chronic prescription opioid use over time, including one-on-one targeted prescriber education on responsible prescribing, appropriate regulation regarding prescribing, and provider reimbursement for the use of non-opioid pain management strategies.[9,16,17]

Diagnosis Type and Chronic Opioid Use

A primary benefit of categorizing diagnosis type through ICD-10 codes in this population-based study is the ability to systematically review opioid prescribing patterns among patients with different diseases or sources of pain. Previous studies have shown the dangers of inappropriate prescribing, but effectively targeting interventions and prescribing guidelines to minimize risk of chronic opioid use while appropriately managing pain is challenging.[18] Our study identified a few diagnosis types on initial opioid prescriptions that are associated with greater odds of subsequent chronic prescription opioid use in Rhode Island, which allows our state to prioritize interventions that target specific practice areas. For instance, we found that diseases of the musculoskeletal system and connective tissue were highly associated with subsequent chronic prescription opioid use, and initial opioid prescriptions with ICD-10 codes for polyosteoarthritis, rheumatoid arthritis, spondylosis, and intraoperative/postprocedural complications and disorders of the musculoskeletal system had a particularly high percentage of patients develop chronic use after initiation. Given that many patients with musculoskeletal pain can improve over time independent of treatment, prior work has suggested that non-pharmacological treatments be utilized first (e.g., physical therapy, acupuncture, massages), followed by or with anti-inflammatory medications, and if patients are still experiencing pain, prescription opioids.[19,20] Importantly, as the pathophysiology of musculoskeletal diseases is inflammatory, a prescription opioid to block pain is not clinically appropriate, and if pharmacological therapy is necessary, anti-inflammatory medications may be more efficacious than opioids.[21] This is true for diagnoses of polyosteoarthritis, rheumatoid arthritis, and spondylosis, which are generally inflammatory in nature, and depending on the diagnosis standard treatment guidelines recommend treatment with non-steroidal anti-inflammatory drugs, corticosteroids, muscle relaxants, steroids, disease-modifying antirheumatic drugs, biologics, anti-seizure medications, warming therapy, exercise, and/or antidepressants rather than opioid pain management.[22] By focusing interventions and prescribing guidelines on specific types of diagnoses that carry a high risk of chronic opioid use and benefit equally or more for alternative management approaches, states and health care organizations may efficiently decrease inappropriate opioid prescribing while improving the quality of patient care. Our study suggests that interventions focused on appropriate management of musculoskeletal conditions, including polyosteoarthritis, rheumatoid arthritis, and spondylosis, may be particularly beneficial given the overall association with chronic use and the high percentage of patients who develop chronic use after an initial opioid prescription for one of these diagnoses.

This study can serve as an example for other states looking to undertake a similar analysis of new chronic prescription opioid use in their population and highlights the added value of collecting ICD-10 codes associated with prescriptions in PDMPs. Replicating this study in other regions could inform the standard of care for pain management and hopefully lead to safer prescribing patterns.

A major strength of this study is the inclusion of all opioid prescriptions dispensed to Rhode Island residents by licensed retail pharmacies for the 12-month study period through the Rhode Island PDMP. The use of a large, population-based study decreases selection bias and provides more generalizable results, although we are not able to identify specific subpopulations with unique risk profiles using this approach. Additionally, our restrictive definition of chronic prescription opioid use likely minimized the inclusion of intermittent prescription opioid users in this group, improving the specificity of our outcome. Finally, this study demonstrates the utility of collecting ICD-10 codes in PDMPs, as this allows for consideration of the *reason* for prescriptions in population-based epidemiologic studies. This highlights for us the advantage of increasing ICD-10 reporting. As reporting increases, this dataset provides a way to systematically identify the diagnoses associated with all opioid prescriptions dispensed to Rhode Island residents.

Despite the advantages of having ICD-10 codes in the Rhode Island PDMP, the largest limitation of this study was the high percentage (36%) of opioid initiate prescriptions with a missing diagnosis code during the analysis period. Unfortunately, we are not able to determine whether the prescriber neglected to provide an ICD-10 code on the prescription, or the pharmacy neglected to include the ICD-10 code when reporting to the PDMP. Although initial opioid prescriptions with and without ICD-10 codes were significantly different on all characteristics compared, our sample size was large, and the most meaningful difference was that prescriptions missing ICD-10 codes were more often written by dental professionals. It may be useful to support dental professionals in the reporting of ICD-10 codes, including sharing the results of these types of studies, to improve the completeness of reporting. Additionally, this analysis is limited to opioids dispensed by retail pharmacies and does not include those dispensed at hospitals or by Veterans Affairs, which may modify our results. Finally, due to variation in the specificity of ICD-10 codes, identifying logical, simple, and accurate ways to collapse them into meaningful groups is difficult. Improved systematic methods for categorizing ICD-10 codes into clinically meaningful groups would be useful for future epidemiologic studies.

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Conclusions

Despite nearly 10% of Rhode Island residents receiving an initial opioid prescription in the 12-month study period, 3.7% went on to become chronic prescription opioid users based on our study definition. Diseases of the musculoskeletal system and connective tissue, diseases of the nervous system, and neoplasms carried a high risk of subsequent chronic opioid use. For diagnoses in these groups that would benefit equally or more from alternative management approaches, we can create targeted interventions and prescribing guidelines to efficiently decrease inappropriate opioid prescribing while improving the quality of patient care.

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Contribution Statement

B.D.H., L.C.C., A.B., and H.W. - substantial contributions to the conception of the work, the acquisition, analysis, and interpretation of data, drafting the work and revising it critically for important intellectual content and gave final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LB, ND, CO, JB, SVB, JM - Substantial contributions to the conception of the work, revising it critically for important intellectual content, and gave final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing Interests

None declared.

Data Availability Statement

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Data from the Rhode Island Prescription Drug Monitoring Program can be obtained by submitting a request to the Drug Overdose Surveillance Program at the Rhode Island Department of Health. Please visit: https://ridoh-overdose-surveillance-rihealth.hub.arcgis.com/.

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Diagnosis Type and Chronic Opioid Use

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Table 1. Baseline Characteristics of Rhode Island Residents Dispensed Initial Opioid Prescriptions, April 1, 2019 – March 31, 2020*

Characteristic	Overall N=87,055 n (%)†	Subsequent Chronic Prescription Opioid Use**	
		Yes N=3,199 n (%)†	No N=83,856 n (%)†
Patient			
Age	53 (36-66)‡	63 (53-73)‡	53 (36-65)‡
Sex			
Female	50,399 (57.89)	1,850 (57.83)	48,549 (57.90)
Male	36,652 (42.10)	1,349 (42.17)	35,303 (42.10)
Unknown	<5	0 (0.00)	<5
Payment method			
Private insurance	52,491 (60.30)	1,416 (44.26)	51,075 (60.91)
Medicare	12,948 (14.87)	881 (27.54)	12,067 (14.39)
Medicaid	10,829 (12.44)	343 (10.72)	10,486 (12.50)
Cash	8,079 (9.29)	389 (12.16)	7,690 (9.17)
Workers' compensation	433 (0.50)	22 (0.69)	411 (0.49)
Unknown	2,275 (2.61)	148 (4.63)	2,127 (2.54)
Prescription			
Opioid type			
Oxycodone	37,631 (42.23)	1,072 (33.51)	36,559 (43.60)
Hydrocodone	24,261 (27.87)	628 (19.63)	23,633 (28.18)
Tramadol	12,590 (14.46)	1,089 (34.04)	11,501 (13.72)
Codeine	9,525 (10.94)	135 (4.22)	9,390 (11.20)
Morphine	2,327 (2.67)	110 (3.44)	2,217 (2.64)
Hydromorphone	494 (0.57)	40 (1.25)	454 (0.54)
Buprenorphine (pain)§	91 (0.10)	61 (1.91)	30 (0.04)
Methadone	42 (0.05)	27 (0.84)	15 (0.02)
Fentanyl	28 (0.03)	19 (0.59)	9 (0.01)
Tapentadol	27 (0.03)	8 (0.25)	19 (0.02)
Opium	22 (0.03)	5 (0.16)	17 (0.02)
Oxymorphone	6 (0.01)	<5	5 (0.01)
Butorphanol	<5	<5	<5
Pentazocine	<5	0 (0.00)	<5
Dihydrocodeine	<5	<5	0 (0.00)
Meperidine	<5	<5	<5
Initial Opioid Prescription			
Days' supply	4 (3-5)‡	10 (5-30)‡	4 (3-5)‡
Quantity prescribed	15 (10-20)‡	20 (20-60)‡	15 (10-20)‡
MME	22.5 (18.0-30.0)‡	20 (10.0-30.0)‡	24.0 (18.8-30.0)‡
90-day follow-up period			
Total days dispensed	5 (3-9)‡	85 (66-100)‡	5 (3-8)‡
Initial MME	23.3 (18.0-30.0)‡	20.0 (10.0-30.0)‡	25.0 (18.8-30.0)‡
Final MME	25.0 (18.0-30.0)‡	20.0 (10.0-40.0)‡	25.0 (18.8-30.0)‡
Prescriber type			
Physician	38,240 (43.93)	2,105 (65.80)	36,135 (43.09)
Advanced nurse	11,973 (13.75)	541 (16.91)	11,432 (13.63)
Physician assistant	13,077 (15.02)	372 (11.63)	12,705 (15.15)
Dental professional	14,262 (16.38)	22 (0.69)	14,240 (16.98)
Unknown	9,503 (10.92)	159 (4.97)	9,344 (11.14)

*Initial opioid prescriptions defined as either the patient's first opioid prescription or an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. For patients with more than one initial opioid prescription during this period, we randomly selected one for inclusion in this analysis. † Unless otherwise specified. ‡ Median (IQR). § This analysis excluded buprenorphine products only FDA-approved for medication-assisted treatment of opioid use disorder. **Chronic prescription opioid use defined as ≥60 days' supply of opioids dispensed in the 90 days following the fill date of an individual's initial opioid prescription (including the days' supply of the initial prescription).

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Table 2. Diagnosis Type on Initial Opioid Prescriptions Dispensed to Rhode Island Residents, April 1, 2019 – March 31, 2020*

Diagnosis Type	Overall	Subsequent Chronic Prescription Opioid Use	
		Yes	No
	N=87,055 n (%)	N=3,199 n (%)	N=83,856 n (%)
Unknown	31,574 (36.27)	894 (27.95)	30,680 (36.59)
Diseases of the musculoskeletal system and connective tissue	15,525 (17.83)	1,157 (36.17)	14,368 (17.13)
Diseases of the nervous system	8,377 (9.62)	601 (18.79)	7,776 (9.27)
Diseases of the digestive system	7,552 (8.67)	34 (1.06)	7,518 (8.97)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	7,133 (8.19)	158 (4.94)	6,975 (8.32)
Factors influencing health status and contact with health services	3,833 (4.40)	63 (1.97)	3,770 (4.50)
Injury, poisoning and certain other consequences of external causes	3,290 (3.78)	55 (1.72)	3,235 (3.86)
Diseases of the genitourinary system	2,974 (3.42)	12 (0.38)	2,962 (3.53)
Neoplasms	1,960 (2.25)	148 (4.63)	1,812 (2.16)
Pregnancy, childbirth and the puerperium	1,246 (1.43)	<5	1,244 (1.48)
Diseases of the respiratory system	811 (0.93)	12 (0.38)	799 (0.95)
Diseases of the skin and subcutaneous tissue	756 (0.87)	15 (0.47)	741 (0.88)
Diseases of the circulatory system	479 (0.55)	16 (0.50)	463 (0.55)
Certain infectious and parasitic diseases	416 (0.48)	5 (0.16)	411 (0.49)
Diseases of the eye and adnexa	277 (0.32)	<5	275 (0.33)
Mental and behavioral disorders	272 (0.31)	9 (0.28)	263 (0.31)
Endocrine, nutritional and metabolic diseases	267 (0.31)	6 (0.19)	261 (0.31)
Congenital malformations, deformations and chromosomal abnormalities	145 (0.17)	5 (0.16)	140 (0.17)
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	85 (0.10)	<5	81 (0.10)
External causes of morbidity and mortality	82 (0.09)	<5	81 (0.09)
Certain conditions originating in the perinatal period	<5	0 (0.00)	<5

*Initial opioid prescriptions were defined as either the patient's first opioid prescription or an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. For patients with more than one initial opioid prescription during this period, we randomly selected one for inclusion in this analysis.

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Table 3. Characteristics Associated with Unknown Diagnosis Type on Initial Opioid Prescriptions Dispensed to Rhode Island Residents, April 1, 2019 – March 31, 2020*

Characteristic	Known Diagnosis Type N=55,481 n (%)†	Unknown Diagnosis Type N=31,574 n (%)†
Patient		
Age	54 (37-66)‡	52 (34-65)‡
Sex		
Female	33,007 (59.49)	17,392 (55.08)
Male	22,474 (40.51)	14,178 (44.90)
Unknown	0 (0.0)	<5
Payment method		
Private insurance	33,777 (60.88)	18,714 (59.27)
Medicare	8,358 (15.06)	4,590 (14.54)
Medicaid	6,861 (12.37)	3,968 (12.57)
Cash	4,552 (8.20)	3,527 (11.17)
Workers' compensation	241 (0.43)	192 (0.61)
Unknown	1,692 (3.05)	583 (1.85)
Prescription		
Opioid type		
Oxycodone	26,422 (47.62)	11,209 (35.50)
Hydrocodone	13,955 (25.15)	10,306 (32.64)
Tramadol	8,417 (15.17)	4,173 (13.22)
Codeine	4,719 (8.51)	4,806 (15.22)
Morphine	1,483 (2.67)	844 (2.67)
Hydromorphone	314 (0.57)	180 (0.57)
Buprenorphine (pain)§	70 (0.13)	21 (0.07)
Methadone	32 (0.06)	10 (0.03)
Fentanyl	25 (0.05)	<5
Tapentadol	16 (0.03)	11 (0.03)
Opium	18 (0.03)	<5
Oxymorphone	<5	<5
Butorphanol	<5	<5
Pentazocine	0 (0.00)	<5
Dihydrocodeine	<5	0 (0.00)
Meperidine	<5	<5
Chronic Opioid Use		
Yes	472 (0.85)	175 (0.55)
No	55,009 (99.15)	31,399 (99.45)
Initial Opioid Prescription		
Days' supply	5 (3-5)‡	4 (3-5)‡
Quantity prescribed	18 (10-20)‡	15 (10-20)‡
Daily MME	25.0 (18.8-30.0)‡	22.5 (18.0-30.0)‡
90-day follow-up period		
Total days prescribed	5 (3-5)‡	5 (3-7)‡
Initial MME	25.0 (18.8-30.0)‡	22.5 (18.0-30.0)‡
Final MME	25.0 (18.8-30.0)‡	22.5 (18.0-30.0)‡
Prescriber type		
Physician	26,083 (47.01)	12,157 (38.50)
Physician assistant	8,954 (16.14)	4,123 (13.06)
Advanced nurse	8,458 (15.24)	3,515 (11.13)
Dental professional	5,101 (9.19)	9,161 (29.01)
Unknown	6,885 (12.41)	2,618 (8.29)

*Initial opioid prescriptions were defined as either the patient's first opioid prescription or an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. For patients with more than one initial opioid prescription during this period, we randomly selected one for inclusion in this analysis. † Unless otherwise

Diagnosis Type and Chronic Opioid Use

specified. ‡ Median (IQR). § This analysis excluded buprenorphine products only FDA-approved for medication-assisted treatment of opioid use disorder.

Diagnosis Type and Chronic Opioid Use

Table 4. Association Between the Diagnosis Type on the Initial Opioid Prescription and Subsequent Chronic Prescription Opioid Use among Rhode Island Residents, April 1, 2019 – March 31, 2020*†

Diagnosis Type	Subsequent Chronic Prescription Opioid Use		Adjusted OR (95% CI)‡
	No N=53,176 n (row %)	Yes N=2,305 n (row %)	
Diseases of the musculoskeletal system and connective tissue	14,368 (92.55)	1,157 (7.45)	**5.94 (4.68-7.56)**
Diseases of the nervous system	7,776 (92.83)	601 (7.17)	**6.26 (4.90-8.01)**
Diseases of the digestive system	7,518 (99.55)	34 (0.45)	**0.43 (0.29-0.65)**
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	6,975 (97.78)	158 (2.22)	**1.96 (1.48-2.60)**
Factors influencing health status and contact with health services	3,770 (98.36)	55 (1.67)	1.34 (0.96-1.89)
Injury, poisoning and certain other consequences of external causes	3,235 (98.33)	55 (1.67)	1.38 (0.97-1.96)
Neoplasms	1,812 (92.45)	148 (7.55)	**5.60 (4.20-7.47)**
Diseases of the circulatory system	463 (96.66)	16 (3.34)	**2.05 (1.18-3.57)**
Other§	7,259 (99.00)	73 (1.00)	Ref.

* Initial opioid prescriptions defined as either the patient's first opioid prescription or an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. For patients with more than one initial opioid prescription during this period, we randomly selected one for inclusion in this analysis.

† Chronic prescription opioid use defined as ≥60 days' supply of opioids dispensed in the 90 days following the fill date of an individual's initial opioid prescription (including the days' supply of the initial prescription).

‡ Adjusted for potential confounders selected *a priori*: age (continuous) and sex.

§ Other includes all initial opioid prescriptions for diagnosis types with 15 or less chronic users, including: certain conditions originating in the perinatal period, certain infectious and parasitic diseases, congenital malformations, deformations and chromosomal abnormalities, diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism, diseases of the eye and adnexa, external causes of morbidity and mortality, pregnancy, childbirth and the puerperium, mental and behavioral disorders, endocrine, nutritional and metabolic diseases, diseases of the skin and subcutaneous tissue, diseases of the respiratory system, and diseases of the genitourinary system.

Diagnosis Type and Chronic Opioid Use

Table 5. ICD-10 Codes on Initial Opioid Prescriptions with the Highest Number of Subsequent Chronic Prescription Opioid Users, Rhode Island Residents - April 1, 2019 – March 31, 2020*

Diagnosis	Subsequent Chronic Prescription Opioid Use	
	Yes N=2,305 n (row %)	No N=53,176 n (row %)
Pain, not elsewhere classified (G89)	592 (7.86)	6,087 (92.14)
Dorsalgia (M54)	477 (9.75)	4,416 (90.25)
Pain, unspecified (R52)	95 (2.27)	4,081 (97.73)
Other joint disorder, not elsewhere classified (M25)	94 (4.76)	1,880 (95.24)
Spondylosis (M47)	69 (16.95)	338 (83.05)
Thoracic, thoracolumbar, and lumbosacral intervertebral disc disorders (M51)	67 (13.76)	420 (86.24)
Osteoarthritis of knee (M17)	59 (7.11)	771 (92.89)
Other and unspecified soft tissue disorders, not elsewhere classified (M79)	58 (5.48)	1,001 (94.52)
Other and unspecified osteoarthritis (M19)	50 (12.17)	361 (87.83)
Other spondylopathies (M48)	42 (8.11)	476 (91.89)
Polyosteoarthritis (M15)	38 (18.54)	167 (81.46)
Intraoperative and postprocedural complications and disorders of musculoskeletal system, not elsewhere classified (M96)	31 (34.83)	58 (65.17)
Abdominal and pelvic pain (R10)	23 (2.03)	1,108 (97.97)
Oseoarthritis of hip (M16)	22 (5.46)	381 (94.54)
Malignant neoplasm of bronchus and lung (C34)	22 (14.29)	132 (85.71)
Presence of other functional implants (Z96)	17 (3.83)	427 (96.17)
Other deforming dorsopathies (M43)	15 (8.77)	156 (91.23)
Other rheumatoid arthritis (M06)	15 (17.86)	69 (82.14)
All other ICD-10 codes	592 (1.88)	30,847 (98.12)

* Initial opioid prescriptions were defined as either the patient's first opioid prescription or an opioid prescription that started at least 60 days after the patient's previous opioid prescription ended. For patients with more than one initial opioid prescription during this period, we randomly selected one for inclusion in this analysis.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary	2

		of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	4-5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	4
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	5-6

Bias	#9	Describe any efforts to address potential sources of bias	6
Study size	#10	Explain how the study size was arrived at	4-5
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	5-6
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	5-6
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a
Statistical methods	#12c	Explain how missing data were addressed	6
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a
Statistical methods	#12e	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and	6

		unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	6
Participants	#13c	Consider use of a flow diagram	
n/a			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	6-7
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
n/a			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
n/a			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-8
Main results	#16b	Report category boundaries when continuous variables were	15-20

		categorized	
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
19			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	#18	Summarise key results with reference to study objectives	8-11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	11
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	8-11
Generalisability	#21	Discuss the generalisability (external validity) of the study results	8-11
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12