Predictors of Chronic Opioid Use in Non-Cancer Patients : Practice Implications from a Retrospective Cohort Study

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Competing interest:

- Audrey Béliveau has no conflict of interest
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Abstract

Background: Chronic opioid use contributes to Canada's current opioid epidemic and is linked to overdose and death. We aimed to identify predictors of chronic opioid use, to help inform practice change patterns that might curtail new or chronic use.

Methods: Using Quebec administrative claims databases, a cohort study was conducted in non-cancer outpatients age ≥18 years who initiated an opioid between 01 January 2012 and 31 December 2016. We defined chronic use as ≥90 consecutive or ≥120 cumulative days over a 12-month follow-up. Multivariate logistic regression evaluated opioid prescription practices, sociodemographics, medical history, and previous prescription drug use as potential predictors of chronic opioid use. The area under the curve (AUC) of the receiver operating characteristic curve was used to assess the predictive performance of each model.

Results: Of 124,492 new opioid users, 4,172 (3.4%) transitioned to chronic use. Chronic users accounted for half the opioids dispensed. Development of chronic use was associated with acetaminophen/codeine baseline use for ≥90 days (OR=6.18, 95%CI 4.90 – 7.80), long-acting opioids at treatment initiation (OR= 5.93, 95%CI 5.22 – 6.73), initial dispensing duration ≥30 days (OR=4.24, 95%CI 3.82 – 4.70) and chronic pain conditions (OR=2.41, 95%CI: 2.16 – 2.69). Other associated factors were initial prescription by a general practitioner, women age ≥75, multiple concomitant opioids, and acetaminophen for ≥90 days. The strongest predictors of chronic use were initial dispensing ≥30 days and chronic pain diagnosis (AUC=0.76).

Interpretation: We identified factors associated with chronic opioid use that may help plan strategies to curtail harmful opioid use.

Introduction

Although opioids provide pain relief, well-known harms of prolonged use include addiction, misuse, abuse and accidental overdose, including death (1-5). Over time, Canada has seen a steady rise in opioid users, prescriptions and resulting harms (6), a phenomenon referred to by Health Canada and others as an opioid epidemic (7). A systematic review of interventions and policies on appropriate opioid prescribing reveal that most interventions are effective in decreasing the rate of opioid prescriptions but have limited impact on opioid-related harms (8). A recent US study showed that the amount of opioids prescribed in milligram morphine equivalent (MME) per person decreased between 2010 and 2017 (9). However, the duration of each filled opioid prescription increased steadily over time, reaching an average of 18 days per filled prescription in 2017, with 42% patients receiving ≥30 days.

Patients exposed to longer durations of opioid use appear to be at higher risk for opioid misuse and other opioid-related harms (10, 11). Strategies to identify and/or prevent unnecessary chronic opioid use, as well as close monitoring of those under chronic therapy may help mitigate adverse effects. Our study aimed to identify associated factors and predict which patients are at risk for transitioning to chronic opioid use in order to inform practice change at the point of care.

Methods

Design, Setting and Population

We conducted a retrospective cohort study of non-cancer adults (age ≥18 years) initiating an opioid treatment in the outpatient setting. New use was defined as the absence of opioid dispensing in the previous 12 months. Patients entered the cohort at the time of opioid initiation (index date). We studied the opioids covered by the public drug plan of Quebec between 01 January 2012 and 31 December 2016: morphine, codeine, fentanyl, hydromorphone, oxycodone, meperidine, butorphanol and pentazocine. We excluded methadone because of its indication for the treatment of abuse, as well as codeine/acetaminophen because of its availability over-the-counter. Each patient included was followed for 12 months after opioid initiation in order to assess chronic use (up to 31 December 2017). The study was approved by the Ethics Committee of Université de Montréal.

Data sources

We used three linked administrative claims databases (RAMQ): beneficiary, prescription drug claims, and medical services claims. The Quebec public drug plan covers approximately 3.5 million (43% coverage), including seniors (≥65 years), welfare recipients, and residents who do not have access to a private drug plan and their dependents. The beneficiary database contains demographics (age group, sex), region (urban, semi-urban, rural), co-pay (as proxy for socioeconomic status, SES), and coverage periods. The prescription claims database records dispensings of prescribed drugs covered by the public drug plan (excluding in-hospital and over-the-counter medications). Each claim records the

date of dispensing, drug and number of units dispensed, dose per unit, prescription duration, prescriber's identification number and specialty. There is no information on indication. The physician claims database records all medical services billed on a fee-for-service in inpatient, outpatient, or emergency room (ER) settings. Each claim includes: service date, type (examination, procedure, etc.), physician's identification number and specialty, location of service, and diagnostic code (ICD-9). The beneficiary, prescription, and physician claims databases can be linked using the patient's anonymized health insurance number.

Study sample

We obtained a random sample of 125,000 new opioid users (maximum allowed by RAMQ) who met additional eligibility criteria: 1) At least 12 months of continuous enrolment in the public drug plan before and after opioid initiation, 2) absence of a physician billing diagnostic code for cancer throughout the study period, 3) absence of previous methadone dispensing. Because the prescription database does not cover inpatient dispensing, we excluded individuals who were hospitalized or institutionalized for ≥70% follow-up.

Analysis

For each patient, we determined the total duration of opioid use by summing up the number of days with an active prescription within the 12-month follow-up. In the presence of overlap between different opioids, we considered that the treatments were taken concomitantly during the period of overlap. To account for hospitalizations or institutionalizations, we assumed that a patient who had an active prescription before and after discharge remained exposed throughout admission. Conversely, if no opioid was

dispensed after discharge, we considered that the opioid was discontinued. We categorized patients into chronic and non-chronic users using the definition most frequently found in the literature (12-16): ≥90 consecutive days or ≥120 cumulative days during a 12-month follow-up.

We collected the following information on index opioid dispensing: product, concomitant opioid dispensings, mode of action (short- or long-acting), dispensing duration (<15 days, 15-29 days, ≥30 days) and, prescriber's specialty. We converted the initial daily dose in MME using published conversion factors (17), and used the following categories: <30, 30-49, 50-89, ≥90 MME/day. If more than one opioid prescription were filled at index date, the initial daily dose was the sum of MME of each prescription. We estimated opioid dosage intensity by dividing the total MME by total duration of use (MME/day) excluding the number of days of hospitalization, since MME could not be calculated during this period. We also determined the number of different opioid products used during follow-up.

We assessed patient sociodemographics: age group (18-44; 45-54; 55-64; 65-74; 75-84; ≥85), sex, region (urban, semi-urban, rural), and level of co-pay (<65 years, welfare recipients, low income ≥65 years, medium income ≥65 years, high income ≥65 years). We determined the general health status through the Charlson Comorbidity Index (CCI), which is based on the diagnoses recorded in physician claims (18) .

Since indication is not recorded in the RAMQ drug claims database, we used ICD-9 codes recorded in physician claims as potential indications and created the following mutually exclusive categories: 1) Medical services for surgical procedures or diagnosis related to accident, fracture or surgery in the 30 days prior to index date or, an initial opioid prescription written by a dentist; 2) Diagnoses associated with chronic pain in the 12 months prior to index date (arthritis, spinal stenosis, fibromyalgia, osteoporosis, deformation of the spine, neuropathy, limb pain, neck pain); 3) Diagnoses of other types of pain in the 12 months prior; 4) Hospitalization within seven days before index date to account for any other in-hospital procedure not billed on a fee-for-service.

We identified claims with diagnoses of known risk factors for opioid abuse such as psychiatric disorder (mood disorder, schizophrenia, anxiety, other), substance abuse, dementia, prior dispensing of benzodiazepines, antipsychotics, antidepressants used in pain (tricyclic, venlafaxine, duloxetine, paroxetine, fluoxetine), non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, acetaminophen/codeine and gabapentinoids.

To compare the characteristics of chronic and non-chronic opioid users we used mean and standard deviation (SD) for continuous variables, and frequencies for categorical variables. We identified factors associated with chronic opioid use through a multivariate logistic regression analysis, which included an interaction term between age and sex. In order to identify leverage points for the development of targeted interventions at the point of care, we developed a parsimonious predictive model. We used the area under the curve (AUC)

of the receiver operating characteristic (ROC) curve to determine the predictive performance of the model (19). An AUC ≥0.7 was considered to be a good predictive performance (20). We conducted all statistical analysis using SAS version 9.4.

Results

Population

The cohort included 124,492 eligible new users of opioids of whom, 4,172 (3.4%) became chronic users. Chronic users accounted for 51.1% of MMEs dispensed (Table 1). The mean duration of opioid use was 242.7 days for chronic users and the mean treatment intensity 41.5 MME/day. In non-chronic users, mean duration of use was 10.9 days and treatment intensity 36.3 MME/day. The majority of patients were dispensed only one opioid product during follow-up, although 10.1% of chronic users used three or more.

Prescription characteristics

Hydromorphone was the most frequently dispensed at initiation regardless of usage group, with concomitant use of more than one opioid more likely to occur among chronic users (Table 2). At initiation, a long-acting opioid was dispensed to almost one quarter of chronic users compared to 1.3% of non-chronic users, with differences being most important for long-acting transdermal fentanyl. More than one quarter of chronic users filled an initial opioid prescription of ≥30 days, compared to 2.8% in non-chronic users. A daily dose of ≥90 MME was also more frequent in chronic versus non-chronic users. General practitioners (GPs) represented the majority of prescribers and wrote initial prescriptions

of the longest duration, whereas surgeons and urologists prescribed the highest mean dose at initiation (Table 3).

User characteristics

Compared to non-chronic users, chronic users were older and more likely to be female (Table 4). Hospitalization prior to opioid initiation, psychiatric diagnoses, dementia and substance abuse were more frequent among chronic users. The use of psychotropic drugs (benzodiazepines, antipsychotics, antidepressants), analgesics or gabapentinoids was also notably higher among chronic users. A quarter of chronic and 15.0% of non-chronic users had an unknown potential indication for the opioid dispensed.

Predictors of chronic use

Compared with patients age 18-44 years, men≥ 85 years (odds ratio, OR=1.90), women aged 75-84 years (OR=1.99) and women age ≥85 years (OR=2.14) were most likely to become chronic users (Table 5). Patients living in a semi-urban or rural area and those with poorer health status were also more likely to transition to chronic use. Compared with morphine, patients initiating an opioid treatment with hydromorphone or oxycodone were 1.2 times more likely to become chronic users. Conversely, codeine was associated with a lower probability (OR=0.60). Patients having received multiple opioids concomitantly at treatment initiation were twice as likely to become chronic users. Dispensing of a long-acting opioid at treatment initiation, compared to short-acting, was the strongest risk factor for chronic opioid use (OR=6.02) followed by an initial dispensing of ≥30 days (OR=4.22). Patients prescribed opioids by a specialist, whether a surgeon, gynecologist,

emergency physician, urologist or dentist, were less likely to become chronic users than patients prescribed opioids by a GP. Patients with an unknown potential indication were 2.5 times more likely to become chronic users, followed by patients with a diagnosis associated with chronic pain (OR=2.41).

A predictive model that included all covariates was associated with an AUC of 0.87 (Figure 1). An initial dispensing duration ≥ 30 days and a diagnosis associated with chronic pain were the strongest predictors of chronic opioid use. Together, these two variables predicted chronic use with an AUC of 0.76. Although long-acting opioids had the highest OR in the multivariate analysis, this variable did not have the greatest effect on the AUC.

Interpretation

In this non-cancer community-dwelling adult population, 3.4% of opioid initiators became chronic users. Age and sex were found to be associated with chronic use, especially in women aged ≥75 years, even after controlling for the presence of chronic conditions associated with pain. Factors strongly associated with chronic use were long-acting opioids at initiation, a first filled opioid prescription of ≥30 days and use of acetaminophen/codeine for ≥90 days in the preceding 12 months. Scripts written by GPs provided on average a week's duration of opioids and most frequently led to chronic use. Even though the *CDC guideline for prescribing opioids for chronic pain* advises against initiating therapy with a long-acting opioid because of a greater risk of overdose (21), 24.0% of chronic users in our study population received a long-acting opioid at index date. Furthermore, of chronic users, 6.3% appeared to initiate treatment with transdermal fentanyl. These results are likely not

explained by an under-ascertainment of previous opioid usage as we accounted for recent hospitalizations. A parsimonious model that included an incident prescription ≥30 days and a diagnosis of chronic pain was associated with an AUC of 0.74, which exceeded the usual threshold of 0.7 for good performance.

Similar estimates of chronic use were obtained in the US (3.3%) (22), Australia (2.6%) (23), Germany (1.3%) (24) and Norway (3.0%) (25). Our estimate was, however, lower than those derived from the National Prescription Drug Utilization Information System (NPDUIS), which ranged between 9.9 to 17.7% across Canadian provinces (26). Differences in the definition of chronic use likely led to divergent results. In our study, chronic users accounted for 51.1% of MMEs dispensed to the cohort, which is lower than the 87% found in British Columbia for the years 2005-2012 (14) but consistent with those obtained in other studies (27-30). Predictors of chronic opioid use were also found in previous studies, such as conditions associated with chronic pain (27), history of substance abuse, dementia (16), prior use of psychotropic drugs or analgesics (23, 29, 31), hydromorphone or oxycodone at initiation, concomitant opioids and initial daily dose ≥90MMEs, consistent with a study showing that the risk of chronic use increased with a higher dose of opioids at initiation (30). Patients receiving ≥90MMEs at index date had mostly initiated opioid with short-acting hydromorphone or oxycodone and were not hospitalized prior the index date. While we were able to identify potential indications for 76.3% of the cohort, there were still 24.1% of chronic and 15.0% of non-chronic users whose indication remained unknown. A recent Ontario study, also conducted using administrative claims data, found a similar 12% proportion of patients with no clear

indication (32). Compared with other studies, our study was conducted in the general population as opposed to sub-populations such as patients with traumatic injuries (33), patients with hip arthroscopy (16, 34) or musculoskeletal disorder (35, 36). To our knowledge, the development of a predictive model for chronic use was attempted in only one other study in which long-acting opioid and use of tramadol were the leading predictors (29).

Patients who receive a first opioid fill ≥ 30 days and a chronic pain diagnosis are at risk of preventable overdose, since the strongest predictors of chronic opioids use are easily identifiable at the point of care. One strategy might be for pharmacists to dispense opioids for shorter periods (e.g., 7-14 days) for the first 1-2 months, in patients with a clear indication. We also found that opioids are often prescribed to patients with multiple comorbidities, which increases the risk of interactions with sedative hypnotics, NSAIDs or gabapentinoids. Pharmacists should suggest alternatives such as topical analgesics and other agents (37), but these formulations are not covered by the Quebec public drug plan. The subgroup of patients with no identified potential indication were more likely to become chronic users and should therefore be examined further.

Our study had several limitations. The RAMQ drug claims database does not record inpatient medication use; it is possible that some opioid exposures were missed. We mitigated this limitation by considering opioid dispensing prior to and after admission to account for continuous use during hospitalization periods. Finally, some opiates identified

as predictors of opioid use, such as tramadol (27, 29) were not examined because they were not covered by the public drug plan during the study period.

In conclusion, our findings indicate that patients at risk of becoming chronic opioid users can be identified at the point of care by pharmacists based on an initial opioid dispensing of ≥30 days and a pre-existing chronic pain diagnosis. This could help inform strategies to help curtail chronic opioid use.

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Table 1: Patterns of opioid use during the 12-month follow-up in chronic and non-chronic users

	Chronic users N=4 172 (3.4%)	Non-chronic users N=120 492 (96.6%)
Total duration (days)		
Mean (SD)	242.7 (86.6)	10.9 (15.3)
Median	235	5
Min - Max	90 – 365	1 – 119
Treatment intensity (MME/day)		
Mean (SD)	41.5 (57.4)	36.3 (23.2)
Median	29.2	30.0
Min - Max	0.7 – 1 761.2	0.2 – 990.0
Number of different opioids, n (%)		
1	2,412 (57.8)	105,266 (88.4)
2	1,338 (32.1)	12,933 (10.7)
≥3	422 (10.1)	1,060 (0.9)
Min - Max	1 – 5	1 – 5

MME= Milligram Morphine Equivalent

Table 2: Characteristics of the initial opioid dispensing in chronic and non-chronic opioid users

	Chronic users N=4,172 n (%)	Non-chronic users N=120,492 n (%)	Difference in Proportion % [95%CI]
Opioid dispensed at index date			
Morphine	1,132 (27.1)	39,051 (32.4)	-5.3 [3.9 – 6.6]
Codeine	347 (8.3)	10,630 (8.8)	-0.5 [0.0 – 1.3]
Hydromorphone	1,507 (36.2)	47,729 (39.6)	-3.6 [2.0 – 5.0]
Oxycodone	797 (19.1)	21,121 (17.5)	+1.6 [0.4 – 2.8]
Butorphanol	1 (0.0)	3 (0.0)	0.0 [0.0 – 0.1]
Fentanyl	264 (6.3)	235 (0.2)	+6.1 [5.4 – 6.9]
Meperidine	33 (0.8)	1,514 (1.3)	-0.5 [0.1 – 0.7]
Pentazocin	1 (0.0)	16 (0.0)	0.0 [0.0 – 0.1]
Concomitant products at index date	90 (2.2)	193 (0.2)	+2.0 [1.6 – 2.5]
Concomitant products during index dispensing	141 (3.4)	1,252 (1.0)	+2.3 [1.8 – 3.0]
Mode of action			
Short-acting	3,169 (76.0)	118,885 (98.7)	-22.7 [21.4 – 24.0]
Long-acting	1,003 (24.0)	1,607 (1.3)	+22.7 [21.4 – 24.0]
Initial dose (MME/day)			
<30	2,299 (55.1)	49,381 (41.0)	+14.1 [12.6 – 15.7]
30-49	1,071 (25.7)	40,304 (33.5)	-7.8 [6.4 – 9.1]
50-89	563 (13.5)	26,526 (22.0)	-8.5 [7.4 – 9.6]
≥90	239 (5.7)	4,281 (3.6)	+2.2 [1.5 – 2.9]
Initial duration (days)			
<15	2,456 (58.9)	112,104 (93.0)	-34.2 [32.7 – 35.7]
15-29	584 (14.0)	5,065 (4.2)	+9.8 [8.8 – 10.9]
≥30	1,132 (27.1)	3,323 (2.8)	+24.4 [23.0 – 25.8]
Prescriber's specialty			
General practitioner	3,567 (85.5)	82,913 (68.8)	+16.7 [15.6 – 17.8]
Surgeon	177 (4.2)	23,742 (19.7)	-15.5 [14.8 – 16.1]
Gynecologist	2 (0.1)	2,014 (1.7)	-1.6 [1.5 – 1.7]
Emergency physician	47 (1.1)	2,927 (2.4)	-1.3 [0.9 – 1.6]
Urologist	6 (0.1)	1,802 (1.5)	-1.4 [1.2 – 1.5]
Dentist	1 (0.0)	1,573 (1.3)	-1.3 [1.2 – 1.4]
Other*	352 (8.4)	4,886 (4.1)	+4.4 [3.6 – 5.3]
Unknown	20 (0.5)	635 (0.5)	0.0 [0.0 – 0.2]

*Other specialties included: immunologist, pathologist, anesthesiologist, cardiologist, dermatologist, gastroenterologist, hematologist, pneumonologist, internist, physiatrist, neurologist, ophthalmologist, otolaryngologist, psychiatrist, nuclear medicine specialist, nephrologist, endocrinologist, rheumatologist and geriatrician.

Table 3: Mean dose (MME/day) and duration (days) at index date by prescriber specialty in all users

	Dose (MME/day) Mean (SD)	Duration (days) Mean (SD)	Prescription ≥30 days at index date (%)
Prescriber specialty			
General practitioner	33.3 (24.2)	6.6 (6.7)	3,675 (82.5)
Surgeon	47.6 (28.0)	5.4 (4.3)	240 (5.4)
Gynecologist	33.7 (17.6)	3.8 (3.2)	11 (0.25)
Emergency physician	38.9 (22.2)	5.0 (3.9)	27 (0.6)
Urologist	42.9 (23.8)	3.9 (3.0)	8 (0.18)
Dentist	38.1 (24.4)	3.8 (2.5)	5 (0.11)
Other*	35.5 (26.1)	8.3 (8.7)	452 (10.2)
Unknown	40.6 (28.8)	6.9 (8.5)	37 (0.83)

*Other specialties included: immunologist, pathologist, anesthesiologist, cardiologist, dermatologist, gastroenterologist, hematologist, pneumonologist, internist, physiatrist, neurologist, ophthalmologist, otolaryngologist, psychiatrist, nuclear medicine specialist, nephrologist, endocrinologist, rheumatologist and geriatrician.

Table 4: Characteristics of chronic and non-chronic opioid users

	Chronic users N=4 172 n (%)	Non-chronic users N=120 492 n (%)	Difference in proportion % [95%CI]
Age group (years)			
18-44	459 (11.0)	35,000 (29.2)	-18.2 [17.0 – 19.0]
45-54	568 (13.6)	16,688 (13.9)	-0.3 [0.0 – 1.3]
55-64	752 (18.0)	20,681 (17.2)	+0.8 [0.0 – 2.1]
65-74	851 (20.4)	27,085 (22.5)	-2.1 [0.8 – 3.3]
75-84	852 (20.4)	15,077 (12.5)	+7.9 [6.7 – 9.2]
≥85	690 (16.5)	5,961 (5.0)	+11.5 [10.5 – 12.8]
Gender			
Male	1,627 (39.0)	53,517 (44.4)	-5.4 [3.9 – 6.9]
Female	2,545 (61.0)	66,975 (55.6)	+5.4 [3.9 – 6.9]
Region of residence			
Urban	1,275 (30.6)	39,419 (32.7)	-2.2 [0.7 – 3.6]
Semi-urban	1,695 (40.6)	47,768 (39.6)	+1.0 [0.0 – 2.5]
Rural	1,178 (28.2)	32,902 (27.3)	+0.9 [0.0 – 2.3]
Unknown	24 (0.6)	403 (0.3)	+0.2 [0.1 – 0.5]
Socio-economic status			
Beneficiary of drug program (<65 years)	853 (20.5)	52,374 (43.5)	-23.0 [21.7 – 24.3]
Welfare Recipient	942 (22.6)	20,351 (16.9)	+5.7 [4.4 – 7.0]
Low Income (≥65 years)	261 (6.3)	3,585 (3.0)	+3.3 [2.6 – 4.1]
Medium Income (≥ 65 years)	1,297 (31.1)	21,159 (17.6)	+13.5 [12.1 – 15.0]
High Income (≥ 65 years)	819 (19.6)	23,023 (19.1)	+0.5 [0.0 – 1.8]
Charlson Comorbidity index			
0	2,423 (58.1)	89,623 (74.4)	-16.3 [14.8 – 17.8]
1	1,199 (28.7)	23,107 (19.2)	+9.6 [8.2 – 11.0]
≥2	550 (13.2)	7,762 (6.4)	+6.7 [5.7 – 7.8]
Hospitalization before opioid initiation	777 (18.6)	26,543 (22.0)	-3.4 [2.2 – 4.6]
Potential indications for opioid initiation			
Accident, fracture or surgery	497 (11.9)	37,546 (31.2)	-19.3 [18.2 – 20.2]
Diagnosis associated with chronic pain	1,977 (47.4)	28,886 (24.0)	+23.4 [21.9 – 25.0]
Other diagnosis associated with pain	383 (9.2)	17,054 (14.2)	-5.0 [4.0 – 5.8]
Hospital visit for unknown diagnosis	310 (7.4)	18,909 (15.7)	-8.3 [7.4 – 9.1]
Unknown potential indication	1,005 (24.1)	18,097 (15.0)	+9.1 [7.8 – 10.4]
Risk factors for opioid abuse			
Psychiatric disorder			
Mood disorder	236 (5.7)	3,976 (3.3)	+2.4 [1.7 – 3.1]
Schizophrenia	192 (4.6)	3,116 (2.6)	+2.0 [1.4 – 2.7]
Anxiety disorder	283 (6.8)	3,683 (3.1)	+3.7 [3.0 – 4.5]
Other psychiatric disorder	486 (11.7)	6,127 (5.1)	+6.6 [5.6 – 7.6]

Dementia	292 (7.0)	2,148 (1.8)	+5.2 [4.5 – 6.0]
Substance abuse	113 (2.7)	1,783 (1.5)	+1.2 [0.7 – 1.8]
Psychotropic drug dispensing in 12 months before index date			
Benzodiazepines	1,958 (46.9)	27,495 (22.8)	+24.1 [22.6 – 25.7]
Antipsychotics	774 (18.6)	9,426 (7.8)	+10.7 [9.6 – 12.0]
Antidepressants	988 (23.7)	13,729 (11.4)	+12.3 [11.0 – 13.6]
NSAIDs			
Short-term (<90 days)	943 (22.6)	25,664 (21.3)	+1.3 [0.0 – 2.6]
Long-term (≥90 days)	745 (17.9)	6,835 (5.7)	+12.2 [110 – 13.4]
Acetaminophen			
Short-term (<90 days)	550 (13.2)	8,968 (7.4)	+5.7 [4.7 – 6.8]
Long-term (≥90 days)	983 (23.6)	7,191 (6.0)	+17.6 [16.3 – 18.9]
Acetaminophen/codeine combination			
Short-term (<90 days)	452 (10.8)	7,164 (6.0)	+4.9 [4.0 – 5.9]
Long-term (≥90 days)	164 (3.9)	335 (0.3)	+3.7 [3.1 – 4.3]
Gabapentinoid			
Short-term (<90 days)	330 (7.9)	2,990 (2.5)	+5.4 [4.6 – 6.3]
Long-term (≥90 days)	622 (14.9)	4,219 (3.5)	+11.4 [10.4 – 12.5]

Table 5: Multivariate logistic regression of the association between patient and treatment characteristics and chronic opioid use

Characteristic	Crude Odds Ratio	95% CI	Adjusted Odds Ratio	95% CI
Men				
18-44 years	Reference		Reference	
45-54 years	2.10	(1.78 – 2.47)	1.44	(1.21 – 1.72)
55-64 years	2.25	(1.92 – 2.64)	1.38	(1.16 – 1.64)
65-74 years	1.59	(1.35 – 1.86)	1.12	(0.94 – 1.34)
75-84 years	2.26	(1.88 – 2.71)	1.27	(1.03 – 1.55)
≥85 years	4.17	(3.28 – 5.32)	1.90	(1.44 – 2.49)
Women				
18-44 years	Reference		Reference	
45-54 years	1.54	(1.20 – 1.98)	1.12	(0.85 – 1.47)
55-64 years	1.55	(1.22 – 1.97)	1.31	(1.01 – 1.69)
65-74 years	2.26	(1.79 – 2.85)	1.56	(1.21 – 2.00)
75-84 years	3.01	(2.36 – 3.86)	1.99	(1.53 – 2.60)
≥85 years	3.16	(2.36 – 4.24)	2.14	(1.55 – 2.95)
Region of residence				
Urban	Reference		Reference	
Semi-urban	1.10	(1.02 – 1.18)	1.18	(1.08 – 1.28)
Rural	1.11	(1.02 – 1.20)	1.23	(1.13 – 1.35)
Charlson Comorbidity index				
0	Reference		Reference	
1	1.92	(1.79 – 2.06)	1.23	(1.14 – 1.34)
>2	2.62	(2.38 – 2.87)	1.42	(1.27 – 1.59)
Opioid dispensed at index date				
Morphine	Reference		Reference	
Codeine	1.13	(1.00 – 1.27)	0.60	(0.52 – 0.69)

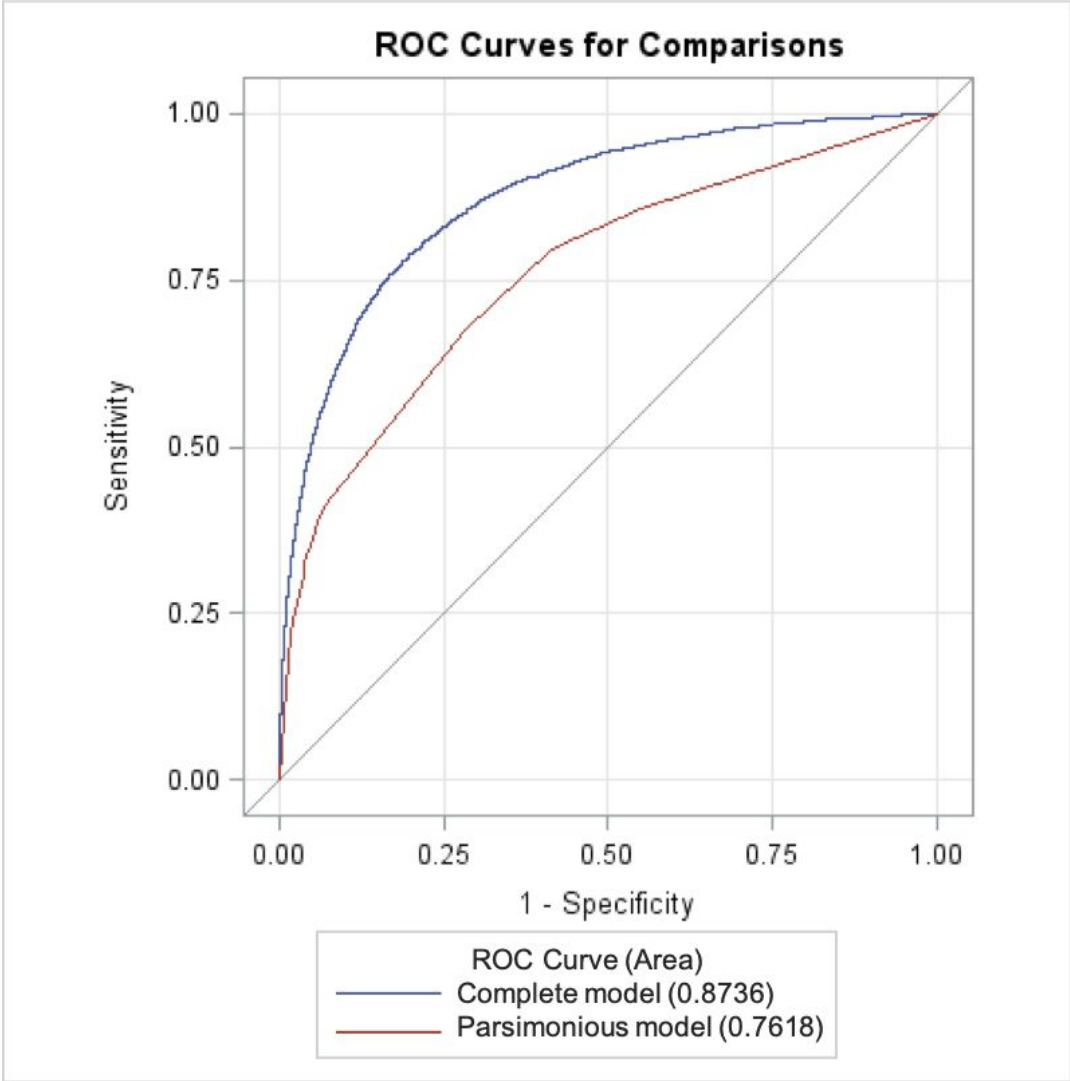
Hydromorphone	1.09	(1.01 – 1.18)	1.26	(1.15 – 1.37)
Oxycodone	1.30	(1.19 – 1.43)	1.24	(1.12 – 1.38)
Butorphanol	11.50	(1.20 – 110.63)	5.35	(0.47 – 60.99)
Fentanyl	38.75	(32.19 – 46.65)	1.17	(0.93 – 1.48)
Meperidine	0.75	(0.53 – 1.07)	1.20	(0.83 – 1.72)
Pentazocine	2.16	(0.29 – 16.27)	1.28	(0.14 – 11.35)
Concomitant products at index date	16.09	(12.44 – 20.80)	1.34	(0.96 – 1.89)
Concomitant products during index dispensing	3.33	(2.79 – 3.98)	2.10	(1.69 – 2.61)
Mode of action				
Short-acting	Reference		Reference	
Long-acting	23.42	(21.48 – 25.53)	6.02	(5.31 – 6.84)
Initial dose (MME/day)				
<30	Reference		Reference	
30-49	0.57	(0.53 – 0.61)	0.91	(0.83 – 0.99)
50-89	0.46	(0.42 – 0.50)	0.85	(0.76 – 0.95)
≥90	1.20	(1.05 – 1.38)	1.24	(1.04 – 1.47)
Initial dispensing duration (days)				
<15	Reference		Reference	
15-29	5.26	(4.79 – 5.79)	2.22	(1.99 – 2.49)
≥30	15.55	(14.38 – 16.82)	4.22	(3.81 – 4.69)
Prescriber's specialty				
General practitioner	Reference		Reference	
Surgeon	0.17	(0.15 – 0.20)	0.31	(0.27 – 0.37)
Gynecologist	0.02	(0.01 – 0.09)	0.09	(0.02 – 0.36)
Emergency physician	0.37	(0.28 – 0.50)	0.67	(0.50 – 0.91)
Urologist	0.08	(0.04 – 0.17)	0.16	(0.07 – 0.36)
Dentist	0.02	(0.00 – 0.11)	0.06	(0.01 – 0.44)
Other	0.08	(0.04 – 0.17)	1.34	(1.17 – 1.52)
Unknown	0.73	(0.47 – 1.14)	0.77	(0.47 – 1.25)

Potential indication for opioid initiation				
Accident, fracture or surgery	Reference		Reference	
Diagnosis associated with chronic pain	5.17	(4.68 – 5.71)	2.41	(2.16 – 2.69)
Other diagnosis associated with pain	1.70	(1.48 – 1.94)	1.44	(1.24 – 1.66)
Hospital visit for unknown diagnosis	1.24	(1.07 – 1.43)	1.21	(1.04 – 1.41)
Unknown indication	4.20	(3.76 – 4.68)	2.55	(2.26 – 2.88)
Psychiatric disorder				
Mood disorder	1.76	(1.54 – 2.01)	1.02	(0.86 – 1.21)
Schizophrenia	1.82	(1.57 – 2.11)	0.93	(0.77 – 1.12)
Anxiety disorder	2.31	(2.04 – 2.62)	1.06	(0.91 – 1.23)
Others	2.46	(2.23 – 2.72)	1.08	(0.92 – 1.26)
Dementia	4.15	(3.65 – 4.71)	1.46	(1.20 – 1.79)
Substance abuse	1.85	(1.53 – 2.25)	1.50	(1.20 – 1.88)
Psychotropic drugs				
Benzodiazepines	2.99	(2.81 – 3.18)	1.57	(1.45 – 1.69)
Antipsychotics	2.68	(2.48 – 2.91)	1.69	(1.53 – 1.88)
Antidepressant	2.41	(2.24 – 2.60)	1.37	(1.25 – 1.50)
AINS				
None	Reference		Reference	
Short-term (<90 days)	1.30	(1.21 – 1.41)	1.23	(1.13 – 1.34)
Long-term (≥90 days)	3.86	(3.55 – 4.21)	1.96	(1.77 – 2.18)
Acetaminophen				
None	Reference		Reference	
Short-term (<90 days)	2.43	(2.21 – 2.67)	1.32	(1.18 – 1.47)
Long-term (≥90 days)	5.41	(5.01 – 5.84)	2.05	(1.86 – 2.25)
Acetaminophen/codeine combination				
None	Reference		Reference	

Short-term (<90 days)	2.01	(1.81 – 2.22)	1.44	(1.28 – 1.62)
Long-term (≥90 days)	15.57	(12.87 – 18.81)	6.30	(4.99 – 7.96)
Gabapentinoid				
None	Reference		Reference	
Short-term (<90 days)	3.88	(3.45 – 4.37)	1.84	(1.61 – 2.12)
Long-term (≥90 days)	5.19	(4.74 – 5.68)	2.02	(1.81 – 2.25)

Note: Odds ratio are adjusted for all other variables listed in this table.

Figure 1. Receiver operating characteristic (ROC) curve for the complete and parsimonious models



Note: The complete model includes all covariates listed in Table 5 and the parsimonious model includes duration of initial prescription and potential indication for an opioid treatment initiation.