Comparing opioid prescribing and adverse events for opioid naive patients treated by emergency and family physicians.

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Abstract

Background: The objective was to describe opioid prescribing patterns by emergency physicians (EP) and family physicians (FP) and to explore the relationship between setting of initiation and adverse events over the subsequent 2 years.

Methods: This was a population-based cohort study using administrative data from Ontario, Canada. Opioid naïve patients aged 15-64 years who received a prescription opioid from an EP or FP between 2008 and 2012 were eligible for inclusion.

Results: 34,713 (43.0%) and 45,952 (57.0%) individuals were initiated on an opioid by an EP and FP, respectively. Both EPs and FPs were most likely to prescribe codeine containing products (58.9% vs 79.6%, respectively), however EPs were twice as likely to prescribe higher potency opioids (both combination and single agent preparations) compared to FPs (40.6% vs 19.9%, Δ 20.7; 95% CI: 20.0 to 21.3). Patients receiving initial prescriptions by EPs received significantly higher daily doses and a higher proportion were initiated on a daily dose exceeding 100 mg MEQ. Individuals who were initiated on opioids by an EP experienced more hospital admissions for opioid toxicity within 2 years (0.5% vs 0.3%, Δ 0.2%; 95% CI: 0.1 to 0.3%), while individuals who were initiated on opioids by a FP more often reached dose escalation beyond 200 mg MEQs within 2 years (0.1% vs 0.7%, Δ 0.6%; 95% CI: 0.5 to 0.7%).

Interpretation: Codeine was the most common opioid prescribed by EPs and FPs. Patients prescribed opioids by EPs received higher initial daily doses, and an increased likelihood of opioid toxicity.

Introduction

North Americans consume nearly two-thirds of the global prescribed opioid supply.[1] In 2014, in the province of Ontario, Canada (population 13 million), nearly 2 million individuals filled 9 million prescriptions for an opioid medication.[2] While opioid prescribing in North America has increased overall, the greatest growth in Ontario has been in high-potency opioids, with hydromorphone dispensing increasing by 70% between 2013 and 2015.[2] Increasing prescription opioid use, and higher doses of these medications, has been associated with significant harm, including the development of opioid use disorder, toxicity, diversion and death.[3-7]

Family physicians (FPs) are the single largest group of opioid prescribers in North America.[2,8,9] Similar to FPs, emergency physicians (EPs) also provide primary care to patients and often prescribe opioids for painful conditions.[10] The relative contribution to overall opioid prescribing by EPs and FPs in Canada remains unknown. Data from the US indicates that opioid use in emergency departments (EDs) increased 90% between 2001 and 2010, and opioids were prescribed at discharge to almost 20% of emergency department (ED) patients.[10-12] While most EPs likely consider opioid medications safe for the relief of acute pain and may therefore regard their role in the current opioid crisis to be limited to preventing diversion, several reports suggest that opioids prescribed in the ED, especially to opioid naive patients, are associated with significant morbidity.[13-15]

In 2014–2015, there were 4,779 hospitalizations due to opioid toxicity in Canada, representing a total of 38,405 days of care provided in Canadian hospitals to patients admitted with a diagnosis of opioid toxicity.[16] Patients admitted for opioid toxicity remained in hospital

for an average of 8.0 days, longer than the length of stay for those admitted for a heart attack, pneumonia or hip replacement surgery.[16]

The primary objective of this study was to describe and compare opioid prescribing patterns by emergency and family physicians and to explore the relationship between setting of initiation and hospital admission for opioid toxicity and dose-escalation exceeding 200 mg morphine equivalents (MEQ).

Methods

Setting

We conducted a population-based cohort study of Ontario residents between the ages of 15 and 64 years who were eligible for public drug coverage and initiated opioids between April 1st 2008 and March 31st 2012. We followed individuals from their first prescription (index date) until the first of death, end of follow-up on March 31, 2014, or a maximum of 2 years to determine outcomes related to opioid dose and toxicity.

Public drug coverage among those aged <65 years is provided to individuals receiving social assistance, disability support or home care services, and individuals residing in long-term care homes or with high drug costs relative to their income. All residents of Ontario are eligible for provincially funded universal health coverage including physician services and hospitalizations. This study was approved by the Research Ethics Board at Mount Sinai Hospital and the institutional review board at Sunnybrook Health Sciences Centre in Toronto, Ontario, Canada.

Data Sources

We used the Ontario Drug Benefit (ODB) claims database to identify prescription drug claims for publicly-funded opioids and other medications dispensed from retail pharmacies over the study period. We used the Registered Persons Database (RPDB) to determine patient demographic characteristics and vital statistics, and the Ontario Health Insurance Plan (OHIP) claims database to capture health services utilization, including visits to a family physician. Further, we used the Canadian Institute for Health Information's National Ambulatory Care Reporting System (NACRS), Discharge Abstract Database (DAD), and Ontario Mental Health Reporting System (OMHRS) to capture details on diagnoses and procedures occurring during ED visits, inpatient hospitalizations, and admissions to designated mental health hospital beds across Ontario, respectively. We used the Ontario Cancer Registry (OCR) to identify persons with a past cancer diagnosis, and the Institute for Clinical Evaluative Sciences (ICES) validated databases of persons with HIV, diabetes, arthritis, and Crohn's disease and colitis to identity patient comorbidities. Finally, the ICES Physician Database (IPDB) was used to determine physician characteristics including prescriber specialty. These datasets were linked using unique encoded identifiers and analyzed at ICES.

Identification of the Cohort

We identified all new users of a prescription opioid to treat pain (including codeine, oxycodone, fentanyl, morphine, hydromorphone, and meperidine) over the study period and defined a patient's index date as the date of their first opioid prescription. New users were defined as individuals with no prescription for any prescription opioid in the 1 year prior to their index date. Furthermore, we excluded individuals with missing patient identifiers, age or sex, those aged <15 or >64 at index date, those with invalid death dates (i.e. death date prior to index

date), and those who were not ODB eligible in the 1 year prior (defined has having no prescriptions for any medication reimbursed by the ODB in the 181 to 365 days prior to index date). Finally, individuals were excluded if they had received palliative care services in the 180 days prior to their index date or had a prior cancer diagnosis to restrict the cohort to individuals initiating opioids for non-cancer pain.

Exposure

The main exposure was the setting (emergency or primary care) in which an individual was initiated on a prescription opioid. This was determined by identifying all ED and FP visits occurring on the index date or in the 2 days prior. FP visits were defined as any office visit to a family physician billed to OHIP. Individuals who had only one visit to either the ED or a FP on their index date or within the 2 days prior were classified accordingly. Individuals who had visits to both the ED and a FP on their index date or within the 2 days prior were classified as having received their prescription from a FP if the prescriber's identification number (ID) on the prescription matched the FP's ID for the office visit; otherwise, prescriptions were assumed to have originated from the ED. Individuals who did not have any record of a visit to the ED or FP on the prescription index date or within the 2 days prior were excluded. Furthermore, individuals whose dose of their index opioid prescription was equal to or greater than 200mg MEQ (a dose associated with an increased risk of death) were excluded because dose escalation beyond this threshold was used as an outcome in this study and it is highly unlikely that an opioid naive individual would be initiated on such a high dose.

Outcome

We followed individuals from their index date until the first occurrence of death, end of follow-up on March 31, 2014, or a maximum of 2 years to determine outcomes related to opioid dose escalation and toxicity. We identified the primary outcome, an opioid-related toxicity event, as an ED visit or inpatient hospitalization (either acute or mental health related) with an admission diagnosis of opioid toxicity (International Classification of Diseases 10th Revision codes T40.0-T40.4, or T40.6) during the follow-up period. The secondary outcome was defined as receipt of an opioid prescription with a daily dose exceeding 200 mg MEQ or higher within their period of continuous opioid use. For this outcome, continuous opioid use was defined as having filled a subsequent prescription for opioids within two times the days' supply of the previous prescription, and opioid discontinuation was added as a censoring criterion. If multiple opioids were filled on one day, we summed the daily dose of both prescriptions. We did not require individuals to be continuous users of opioids for our primary outcome in order to capture those individuals who may transition to obtaining opioids through cash payments or illicit means.

Patient Characteristics

Patient characteristics including demographics (age, sex, income quintile, and urban residence), history of treatment or diagnosis related to substance abuse disorders in the past year (hospital visit for opioid toxicity, other drug toxicity, intentional self-harm, and alcohol use disorder), mental health disorders in the past 2 years, and other medical comorbidities (osteoarthritis, rheumatoid arthritis, inflammatory bowel disease, HIV, and diabetes) were recorded. We measured health services utilization as the number of ED visits, physician office visits, and inpatient hospitalizations in the year prior to index date, and we identified previous use of antidepressants, antipsychotics, benzodiazepines, drugs for neuropathic pain, and other

psychotropic and central nervous system depressants in the past 180 days. The top 10 indications for opioid initiation in each exposure group were identified using the main diagnosis code listed on the ED record (EP initiators) or closest physician billing (for FP initiators) in the 2 days prior to or on the date of opioid initiation. Finally, we characterized index opioid use in several ways, including formulation (long vs. short acting), specific drug, and average daily dose (in mg MEQ).

Statistical Analysis

We used descriptive statistics to summarize baseline characteristics using means and standard deviations (SD), medians with interquartile ranges (IQR), or frequencies. We compared between-group characteristics using standardized differences (SD) where appropriate. Group imbalance was defined as an absolute value of the SD greater than 0.10.[17] Between-group proportional differences were assessed using Pearson's chi-square statistics and reported with 95% confidence intervals (CIs). We used Cox proportional hazards regression models to estimate crude hazard ratios (HR) for dose escalation and opioid toxicity while accounting for follow-up time and censored for death and end-of follow-up. All analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

Of the 176,227 unique patients who initiated an opioid over the accrual period, 80,665 (45.8%) met our inclusion criteria, 34,713 (43.0%) were initiated by an EP and 45,952 (57.0%) were initiated by an FP (Figure 1). Patients initiated by a FP tended to be older (46.1 vs 41.3 years, standardized difference (SD) 0.35), had fewer ED visits (0.9 vs 1.9, SD 0.31), and more

FP visits (11.4 vs 8.8, SD 0.29) in the year prior to their index visit (Table 1). Over half of patients in both groups had a history of psychiatric illness, and 20.9% had been prescribed benzodiazepines within 180 days prior to opioid initiation.

Table 2 outlines the top 10 diagnoses at the time of opioid initiation for both groups. The top three diagnoses associated with ED initiation of opioids were back pain, abdominal pain (unspecified), and dental pain. For those initiated on opioids by FPs, the top three diagnoses were back pain, arthralgias/joint pain, and anxiety/psychiatric related conditions.

There were considerable differences in the type of opioid initiated between patients initiated by FP compared to EP (Table 3). Although initiation on a long-acting (LA) opioid was rare in both groups, patients initiating an opioid by an FP were more likely to start a LA opioid compared to those initiated by an EP (2.3% vs. 0.3%, Δ 2.0; 95% CI: 1.9 to 2.2). Over 90% of patients in both groups were prescribed a combination product, however when prescribing a combination product, EPs were more likely to prescribe oxycodone-containing combination products (37.1% vs 16.5%, Δ 20.6; 95% CI: 19.9 to 21.2), compared to FPs. Among patients initiated on single agent products, EPs were more likely to prescribe hydromorphone and morphine, while FPs were more likely to prescribe codeine, fentanyl and oxycodone. Regardless of opioid type prescribed, patients initiated in the ED were prescribed higher daily doses (38 mg MEQ vs. 19 mg MEQ, SD 0.90) and a higher proportion were initiated on a daily dose exceeding 100 mg MEQ (3.1% vs. 0.9%; Δ 2.1; 95% CI: 1.9 to 2.3).

Table 4 details the crude rate of our primary (hospital admission for opioid toxicity) and secondary (dose escalation to ≥ 200mg MEQ/day) outcomes. Individuals who were initiated on opioids by an EP were significantly more likely to have a hospital visit for opioid toxicity over the two year follow-up period (0.5% vs 0.3%, Δ 0.2; 95% CI: 0.1 to 0.3). In a crude time-to-

event analysis, opioid initiation in the ED was associated with a 77% increased hazard of opioid toxicity (HR = 1.8, 95% CI: 1.4 to 2.2) compared to initiation in FP. In contrast, initiation of opioids from a FP was associated with an increased likelihood of dose escalation beyond 200 mg MEQs (0.1% vs 0.7%, Δ 0.6; 95% CI: 0.4 to 0.7). However, after accounting for censoring (including drug discontinuation), this difference was not statistically significant (HR=1.2, 95% CI: 0.9 to 1.7).

Interpretation:

In this population-based study spanning 6 years, we found that compared to FPs, EPs contributed roughly equally to the total number of opioid prescriptions written for opioid naive patients. Further, our study demonstrates significant differences in prescribing practices between these two provider groups, both in the potency of specific drugs prescribed, and dose at initiation. While EP prescribing did not appear to be associated with dose escalation to greater than 200 mg MEQs/day, we found that individuals who were initiated on opioids by an EP experienced significantly more hospital admissions for opioid toxicity within 2 years.

In this study, almost 30% of all opioid prescriptions provided by EPs exceeded a dose of 50 mg MEQs. While there are no guidelines for opioid prescribing for acute pain, recently published Canadian prescribing guidelines for chronic non-cancer pain recommend that initial prescriptions not exceed the 50 mg MEQs threshold.[18] Previous work by Bohnert et al. demonstrated a nearly 5 fold increase in risk of opioid overdose death for acute pain patients initiated on opioids at doses exceeding 50 mg MEQs, a risk which was equivalent to patients being treated for chronic pain.[3] The subjective nature of pain makes it difficult to determine the appropriateness of prescribing based on diagnosis, but conditions which are obviously painful,

such as extremity fractures, accounted for only 5% of the opioids prescribed in the ED setting. Conversely, the top 5 most common ED diagnoses for which patients were prescribed an opioid (which accounted for 25% of all prescribing), were for conditions (back pain, dental pain, pharyngitis) in which opioids are currently not recommended as first line therapy. Back pain was the most common diagnosis for which opioids were prescribed in both the EP and FP groups, suggesting there is an opportunity to improve physician prescribing practice. Previous research has demonstrated functional outcomes are no better for patients with back pain who are treated with opioids compared to those treated with NSAIDS and other treatment modalities, and current recommendations do not endorse routine prescribing of opioids for this condition.[19-21]

Independent risk factors that have been associated with patients experiencing opioid related harms include; a history of psychiatric illness or substance use disorder, sleep disorders and the use of non-opioid medications with sedating properties, especially benzodiazepines.[22-24] Our study demonstrates that a large number of patients in both the EP and FP groups have known risk factors associated with adverse outcomes related to opioid use. Nearly half of each group had documented anxiety or sleep disorders, and approximately 20% had received a prescription for a benzodiazepine within the previous 180 days. A small, but significant proportion of patients in both groups had been hospitalized within the previous year for other drug toxicity or intentional self-harm. While guidelines recognize these risks and suggest screening for them prior to opioid prescribing, further work is required to determine how to best manage pain, and how to safely prescribe opioids (if at all) in populations with such a high prevalence of risk factors for adverse outcomes.

This study has several limitations. Although all Ontarians have universal access to health care services, prescription drug coverage for those younger than 65 is generally restricted to

socioeconomically disadvantaged individuals, and therefore these findings may not be generalizable to other patients. Additionally, the opioid prescriptions included in this study only represent the volume of opioids that were filled by patients and do not include information on prescriptions that were written, but never filled by a pharmacy. Similarly, the daily opioid dose in mg MEQ was estimated from filled prescriptions reimbursed by the public drug program and did not account for overlapping prescriptions (unless both prescriptions were dispensed on the same day), drugs obtained illicitly, or those paid for with cash. Therefore, the estimates of daily opioid dose may be underestimates of the true daily dose of opioids used by this cohort. Also, we reported crude associations with our outcomes to assess overall differences in risks, without taking into account differences in patient populations since this will give a sense of the relative contribution of each setting to these outcomes. Finally, we were unable to determine if opioid-related ED visits and hospital admissions were a result of prescribed or non-prescribed opioids.

In this cohort of opioid naive patients, codeine was the most common (either combination or single agent) opioid analgesic prescribed by EPs and FPs. Patients initiated on opioids by EPs were prescribed higher initial daily doses and had a higher likelihood of subsequent opioid toxicity events. Our findings suggest that EP prescribing contributes significantly to hospitalizations related to opioid toxicity and supports a recommendation for opioid prescribing guidelines for acute pain. Future study should attempt to elucidate what factors are associated with a higher risk of subsequent hospital admission for opioid toxicity. Creation of physician accessible registries would be useful to monitor opioid prescribing and dispensing, inform clinical practice, and identify patients at high-risk who may benefit from early interventions. However, in the absence of clear guidance for acute opioid prescribing, the utility of such repositories will do little to protect opioid naive patients from potential harms.

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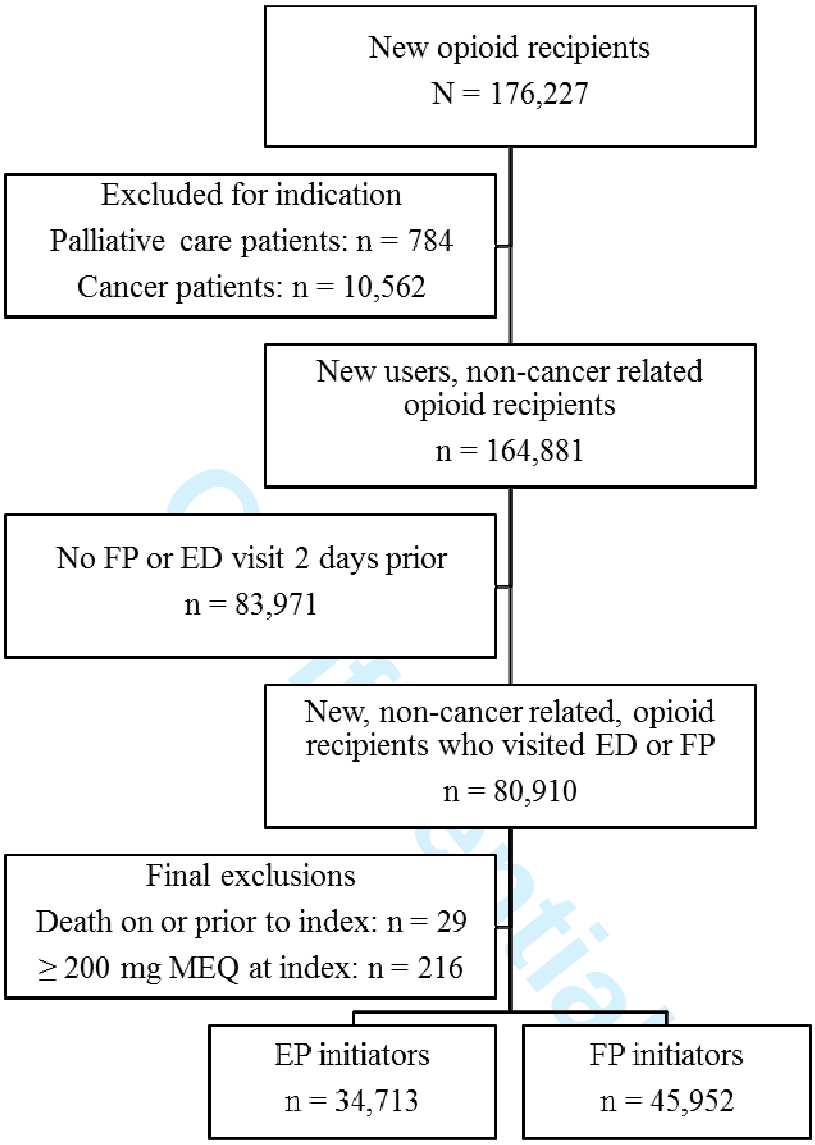
Figure 1. Flow diagram of included patients.



Where: FP = family physician; ED = emergency department; MEQ = morphine equivalents; EP = emergency physician.

Table 1. Baseline characteristics of new opioid users, by location of initial prescription

Variable	EP initiators n = 34,713	FP initiators n = 45,952	Standardized difference†
Demographic variables at cohort entry:			
Age, mean (SD)	41.32 (14.0)	46.05 (12.8)	0.35
Female sex	20,305 (58.5%)	28,178 (61.3%)	0.06
Income quintile			
1	14,844 (42.8%)	19,822 (43.1%)	0.01
2	7,742 (22.3%)	10,291 (22.4%)	0
3	5,262 (15.2%)	7,092 (15.4%)	0.01
4	4,073 (11.7%)	5,219 (11.4%)	0.01
5	2,629 (7.6%)	3,331 (7.2%)	0.01
Missing	163 (0.5%)	197 (0.4%)	0.01
Rural location of residence	5,074 (14.6%)	4,312 (9.4%)	0.16
Comorbidities			
Hospital visit for other drug toxicity (past 1 year)	641 (1.8%)	513 (1.1%)	0.06
Intentional self-harm (past 1 year)	411 (1.2%)	333 (0.7%)	0.05
Hospital visit for alcohol abuse (past 1 year)	1,553 (4.5%)	1,378 (3.0%)	0.08
Osteoarthritis	5,954 (17.2%)	12,387 (27.0%)	0.24
Rheumatoid arthritis	488 (1.4%)	860 (1.9%)	0.04
Past injury	6,129 (17.7%)	4,927 (10.7%)	0.2
HIV	393 (1.1%)	502 (1.1%)	0
Diabetes	6,568 (18.9%)	11,505 (25.0%)	0.15
Crohn's/colitis	505 (1.5%)	544 (1.2%)	0.02
Mental Health disorders			
Affective disorder	4,162 (12.0%)	4,192 (9.1%)	0.09
Anxiety or sleep disorders	15,339 (44.2%)	20,306 (44.2%)	0
Psychoses, agitation, and related disorders	3,893 (11.2%)	3,755 (8.2%)	0.1
All other mental health disorders	11,698 (33.7%)	14,020 (30.5%)	0.07
Any mental health disorder	19,780 (57.0%)	26,056 (56.7%)	0.01
Health services utilization (prior 1 year)			
Number of ED visits, mean (SD)	1.86 (3.8)	0.90 (2.1)	0.31
Number of physician visits, mean (SD)	8.80 (8.3)	11.42 (9.8)	0.29
Inpatient hospitalization	3,780 (10.9%)	4,069 (8.9%)	0.07
Medication use (prior 180 days)			
Antidepressants (SSRIs)	6,647 (19.1%)	8,393 (18.3%)	0.02
Antidepressants (other)	7,149 (20.6%)	10,235 (22.3%)	0.04
Antipsychotics	5,515 (15.9%)	6,260 (13.6%)	0.06
Benzodiazepines	6,745 (19.4%)	10,145 (22.1%)	0.07
Other psychotropic drugs and CNS depressants	1,031 (3.0%)	996 (2.2%)	0.05

Drugs for neuropathic pain	379 (1.1%)	665 (1.4%)	0.03
Hydrocodone (Cough Suppressant)	433 (1.2%)	1,109 (2.4%)	0.09

† Standardized difference = imbalance defined as absolute value greater than 0.10 (small effect size).

Where: EP = emergency physician; FP = family physician; SD = standard deviation; HIV = human immunodeficiency virus; ED = emergency department; SSRI = selective serotonin reuptake inhibitors; central nervous system.

Table 2. Ten most common diagnoses recorded at time of opioid initiation, by location.

ED initiators n = 34,713		FP initiators n = 45,952	
Diagnosis (ICD10-CA)	**n (%)**	**Diagnosis (OHIP Dx)**	**n (%)**
Dorsalgia (M54)	3,113 (9.0%)	Lumbar strain, lumbago, coccydynia, sciatica (724)	4,170 (9.1%)
Abdominal and pelvic pain (R10)	2,127 (6.1%)	Leg cramps, leg pain, muscle pain, joint pain, arthralgia, joint swelling and/or masses (781)	3,899 (8.5%)
Diseases of pulp and periapical tissues (K04)	1,150 (3.3%)	Anxiety neurosis, hysteria, neurasthenia, obsessive compulsive neurosis, reactive depression, claustrophobia, all types of phobias, attempted suicide tendencies (300)	2,061 (4.5%)
Pain in throat and chest (R07)	978 (2.8%)	Diabetes mellitus, including complications (250)	1,962 (4.3%)
Other disorders of teeth and supporting structures (K08)	848 (2.4%)	Osteoarthritis (715)	1,736 (3.8%)
Unspecified renal colic (N23)	827 (2.4%)	Coccyx/neck/low back strain/sprain/other trauma, whiplash (847)	1,669 (3.6%)
Other soft tissue disorders, not elsewhere classified (M79)	776 (2.2%)	Anorexia, nausea and vomiting, heartburn, dysphagia, hiccough, hematemesis, jaundice, ascites, abdominal pain, melena, masses, halitosis, digestive system masses/signs and symptoms not yet diagnosed (787)	1,644 (3.6%)
Fracture of forearm (S52)	689 (2.0%)	Acute nasopharyngitis, common cold, upper respiratory infection, pharyngitis (460)	1,599 (3.5%)
Fracture of lower leg, including ankle (S82)	666 (1.9%)	Essential, benign hypertension (401)	1,494 (3.3%)

Fracture of shoulder and upper arm (S42)	610 (1.8%)	Signs and symptoms not yet diagnosed: Convulsions, ataxia, vertigo, headache, except tension headache and migraine; pyrexia of unknown origin, vaso vagal attack (780)	1,005 (2.2%)

Table 3. Characteristics of newly initiated opioid among new opioid users, by location.

Variable	ED initiators n = 34,713	FP initiators n = 45,952	Standardized difference
>1 prescription dispensed at initiation	217 (0.6%)	339 (0.7%)	0.01
Formulation			
Long-Acting (LA)	87 (0.3%)	1,048 (2.3%)	0.18
Short-Acting (SA)	34,598 (99.7%)	44,779 (97.4%)	0.19
LA and SA	28 (0.1%)	125 (0.3%)	0.05
Opioid type			
Two different opioids at initiation	183 (0.5%)	245 (0.5%)	0
One opioid dispensed at initiation			
Combination products	31,991 (92.6%)	41,941 (91.8%)	0.03
Codeine combination products	20,117 (62.9%)	35,005 (83.5%)	0.48
Oxycodone combination products	11,874 (37.1%)	6,936 (16.5%)	0.48
Single agent products	2,539 (7.4%)	3,766 (8.2%)	0.03
Codeine	328 (12.9%)	1,563 (41.5%)	0.68
Morphine	804 (31.7%)	592 (15.7%)	0.38
Fentanyl	≤ 5*	89 (2.4%)	> 0.1
Oxycodone	33 (1.3%)	394 (10.5%)	0.4
Hydromorphone	1,128 (44.4%)	813 (21.6%)	0.5
Meperidine	241-245*	315 (8.4%)	< 0.1
Daily dose (in morphine equivalents) of first prescription			
Median (IQR)	38 (25-50)	19 (13-32)	0.9
< 20 mg MEQ	5,782 (16.7%)	23,596 (51.3%)	0.79
20-49 mg MEQ	19,123 (55.1%)	17,684 (38.5%)	0.34
50-99 mg MEQ	8,739 (25.2%)	4,238 (9.2%)	0.43
100-199 mg MEQ	1,069 (3.1%)	434 (0.9%)	0.15

† Standardized difference = imbalance defined as absolute value greater than 0.10 (small effect size).

Where: ED = emergency physician; FP = family physician; IQR = interquartile range; MEQ = morphine equivalents.

***** In cases where the number in the cell is less than 6, this number has been suppressed to ensure confidentiality. In cases where there is only one record being suppressed, another record has been suppressed to provide a range in order to avoid residual disclosure.

Table 4. Opioid toxicity and dose escalation outcomes among new opioid users, by location.

Outcome	ED initiators n = 34,713	FP initiators n = 45,952	p-value
Opioid toxicity			
n (%)	172 (0.5%)	129 (0.3%)	--
Rate per 100 PY	0.25	0.14	--
Hazard ratio (95% CI)	1.77 (1.41-2.22)	*Ref*	< 0.0001
Dose escalation			
n (%)	46 (0.1%)	301 (0.7%)	--
Rate per 100 PY	6.19	7.67	--
Hazard ratio (95% CI)	1.25 (0.91-1.72)	*Ref*	> 0.05

Where: ED = emergency physician; FP = family physician; PY = person years; CI = confidence interval.