Prevalence of opioid dispensings and concurrent gastrointestinal medications in Quebec

Rachel E Williams PhD MS, Nevzeta Bosnic BA, Carolyn T Sweeney MPH, Ashlee W Duncan PhD MS, Kristen B Levine MSPH, Michael Brogan BA, Suzanne F Cook PhD

BACKGROUND: Opioids are frequently prescribed for moderate to severe pain. A side effect of opioid usage is the inhibition of gastrointestinal (GI) motility, known as opioid-induced bowel dysfunction (OBD). OBD is typically treated prophylactically with laxatives and/or acid suppressants.

AIM: The present study describes the prevalence of outpatient opioid dispensing, opioid patient demographics, and concomitant dispensing of opioids and GI medications in the Quebec Public Prescription Drug Insurance Plan in 2005.

METHODS: Using a retrospective cohort design, opioid dispensings were identified using claims and reimbursement data. Laxative and acid suppressant dispensings were also identified. Concurrent use was defined as having at least one ‘GI medication-exposed day’ overlapping an ‘opioid-exposed day’.

RESULTS: More than 11% of the drug plan population was dispensed an opioid in 2005, and dispensings increased with age. Approximately two-thirds of patients who received an opioid were given codeine. Approximately one-third of opioid patients were concomitantly dispensed a GI medication, yet only 2% were dispensed a laxative.

CONCLUSIONS: Although the GI side effects of opioids are well known, these side effects appear to increase with age and duration of opioid use. Opioid-related side effects, particularly OBD, should be effectively managed so as not to lead to the cessation of opioid therapy.

Key Words: Dispensings; Epidemiology; Laxative; Opioid; Prevalence; Upper GI medication

Opioids are common treatments for patients with moderate to severe pain (1-3); however, pain management can be compromised by the adverse effects of opioid treatment, including inhibition of gastrointestinal (GI) motility (4-6). Opiates induce a delay in gastric emptying, which may lead to nausea and vomiting, and also slow intestinal and colonic transit, which may lead to constipation (7-11). Taken together, these inhibitory effects on GI motility are termed opioid-induced bowel dysfunction (OBD) and represent an important, and often dose-limiting, side-effect profile of opioid treatment.

Although large, population-based, prospective studies of OBD are lacking, estimates of the prevalence of opioid-induced constipation range from approximately 15% to 50% in nonmalignant pain patients (12,13) and 25% to 90% in cancer patients (14,15). Patients with continuing opioid therapy do not develop a tolerance to constipation, such as they may for
have private group insurance and is administered by the Quebec Public Prescription Drug Insurance Plan. This plan registers more than 4500 over-the-counter and prescription laxatives. Because the majority of the population in Quebec uses the public plan to obtain medications, this cohort can be considered generally representative of the larger Quebec population, excluding those residents with private insurance.

METHODS
Quebec Public Prescription Drug Insurance Plan
There are approximately eight million people residing in Quebec, Canada’s second most populous province. This accounts for over 23% of the Canadian population. The source population for the present analysis includes enrollees covered under the Quebec Public Prescription Drug Insurance Plan. This program is set up to provide services for citizens who do not have private group insurance and is administered by La Régie de l’assurance maladie du Québec. All residents of Quebec, regardless of their financial situation, are eligible for enrollment in this government-based, universal health care plan; however, the plan is intended to enroll the following groups: those without a private health care plan; children of people covered by this public plan; people 65 years of age and older; and welfare recipients. In total, this drug prescription plan covers approximately 3.2 million of the eight million residents of the province.

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Study population
The present study design is a retrospective cohort design, with the analyses conducted at the personal level, using people as the unit of measurement. The study period was defined as January 1, 2005 to December 31, 2005. The inclusion criteria were designed to enroll adults with a full year of coverage in the Quebec Public Prescription Drug Insurance Plan. These criteria included people in the Quebec Public Prescription Drug Insurance Plan who were 18 years of age or older at the start of the study period; eligible for drug benefits for the entire study period; did not die before the end of the study period; and had at least one opioid dispensing between January 1, 2005, and December 31, 2005. Once all eligible patients were identified using the inclusion and exclusion criteria, a random sample of 25% of the patients was received, as per government guidelines.

Opioid dispensings
Opioid dispensings were identified by examining the claims data for opioids that were reimbursed by the Quebec Public Prescription Drug Insurance Plan. Opioids administered orally, by transdermal patch, rectal suppository and nasal spray were included. This included butorphanol tartrate, codeine (codeine phosphate, codeine phosphate with acetaminophen, codeine with codeine sulfate), fentanyl, hydromorphone HCl, meperidine HCl, morphine (morphine HCl, morphine sulfate), oxycodone (oxycodone HCl, oxycodone with acetaminophen), pentazocine and sufentanil citrate.

Due to the nature of the data, all opioid dispensings were to outpatients; data on use of opioids by hospital inpatients were not available in the present study. It is understood that the data reflect no particular legal restriction on the units of opioid medication that may be dispensed. Physicians may prescribe more frequent, shorter-term dispensings rather than less frequent, longer-term dispensings. The data available for each dispensing were as follows: drug name, date of dispensing, number of days supplied, number of units dispensed and strength of units dispensed. To determine the specific days of intended opioid use, the date of dispensing was identified and the number of days supplied for each opioid dispensing. From this information, ‘opioid-exposed days’ were defined as all dates beginning with the date of dispensing through the end of the number of days supplied.

Chronic use definitions
‘Chronic opioid use’ was defined a priori as 60 or more consecutive opioid-exposed days, with no more than seven consecutive days between the end of one dispensing and the start of the next dispensing. This gap in opioid-exposed days was allowed because patients do not always get their prescriptions filled on time and opioid use may be adjusted to meet their pain needs, making an opioid prescription last longer than prescribed. From this definition, ‘chronic users’ were defined as people with at least one period of chronic opioid use in 2005.

A subset of the chronic users, ‘long-term chronic users’ were also defined a priori; these people met the definition of a chronic user and had at least 180 consecutive opioid-exposed days, with no more than seven consecutive days between the end of one dispensing and the start of the next dispensing.

‘Nonchronic users’ were defined a priori as people with an opioid dispensing that did not meet the definition for chronic use during the study period. Hence, nonchronic users had 59 or fewer consecutive opioid-exposed days. Having seven days or less between opioid dispensings was considered consecutive as described above; eight or more days between opioid dispensings was considered a new period of use, and hence, not consecutive.

During the course of the one-year study period, a person may have periods of chronic opioid use and other periods of nonchronic opioid use. For these analyses, people with any chronic opioid use during the study period were considered chronic users for all analyses. A person was considered a...
Concurrent laxative and/or acid suppressants

All dispensings of over-the-counter and prescription laxatives and agents that reduce gastric acid secretion were identified in the study population. Laxatives included bulk laxatives (plantago seed, psyllium hydrophilic mucilloid), emollient laxatives (docusate calcium, docusate sodium, mineral oil), stimulant laxatives (glycerin, lactulose, magnesium hydroxide, sodium bicarbonate, sodium chloride and potassium chloride) and stimulant laxatives (bisacodyl, cascara sagrada, cascara fate, sodium lauryl sulfoacetate, sodium phosphate monobasic) and osmotic laxatives (docusate calcium, docusate sodium, mineral oil), osmotic laxatives (glycerin, lactulose, magnesium hydroxide, sodium citrate) and stimulant laxatives (bisacodyl, cascara sagrada, cascara fate, sodium phosphate monobasic) and stimulant laxatives (bisacodyl, cascara sagrada, cascara fate, sodium phosphate monobasic) and stimulant laxatives (bisacodyl, cascara sagrada, cascara fate, sodium phosphate monobasic). Antacids and absorbents were not included in the present study because they may be used in the population for reasons unrelated to a GI symptom (ie, antacids as a calcium supplement).

Laxative-exposed days and acid suppressant-exposed days were calculated with the same methodology used for opioid-exposed days. These periods included the number of days between the dispensing date of the laxative and/or acid suppressant through the last day supplied for each agent. Use of concurrent laxative medication was defined as having at least one laxative-exposed day that overlapped with an opioid-exposed day. Use of concurrent acid suppressants was defined as having at least one acid suppressant-exposed day that overlapped with an opioid-exposed day.

Analyses

Descriptive analyses were conducted to meet each of the objectives. The prevalence of opioid use was defined as the number of patients in the Quebec Public Prescription Drug Insurance Plan database with at least one opioid dispensing divided by the number of eligible patients enrolled in the prescription drug plan, according to the study inclusion criteria.

All remaining analyses focused on the population of interest – people with at least one opioid dispensing during 2005. Using this study population as the denominator, sex, age, chronicity of use, type of opioid used, and concurrent use of laxatives and/or acid suppressants were described. Data from the Quebec Public Prescription Drug Insurance Plan were analyzed using SAS version 9.1 (SAS Institute Inc, USA).

RESULTS

Prevalence of opioid use in Quebec

In the random sample of 25% of all eligible patients, 11.3% of the population in the Quebec Public Prescription Drug Insurance Plan were dispensed an opioid in 2005. Based on an estimated 2,670,338 people in the eligible population, this proportion (11.3%) may be extrapolated to an estimated 300,660 people in Quebec who were dispensed an opioid in 2005. In the general population, a greater proportion of women (12.6%) were dispensed opioids than men (9.6%). The use of opioids increased with age in both sexes until approximately 80 years of age (Figure 1). Peak prevalence of use (14.8%) occurred in the 70- to 74-year-old group.

Characteristics of people with opioid dispensings

Of the 75,165 people in the study population who received an opioid dispensing, 61.0% were women (n=45,888) and 39.0% were men (n=29,277) (Table 1). Most patients receiving an opioid were given codeine (65.7%), followed by hydromorphone HCl (25.0%), oxycodone (11.4%) and morphine (8.1%). The same pattern and similar percentages were found between men and women.

Chronic opioid use

Three categories of patients were defined a priori based on their opioid dispensings: chronic opioid users, long-term chronic opioid users and nonchronic opioid users. Using these categories, 12.4% of patients who received opioids were chronic users and 87.6% were nonchronic users (Table 1). Furthermore, a similar percentage of men and women were chronic (12.2% and 12.5%, respectively) and nonchronic users (87.8% and 87.5%, respectively). Approximately one-half of the chronic users (6.4% of the 12.4%) were long-term chronic users; the percentage of men and women in this category was similar (6.5% and 6.3%, respectively).

The type of opioid prescribed differed among nonchronic, chronic and long-term chronic users (Table 2). Codeine was dispensed to 69.6% of nonchronic users, followed by hydromorphone HCl (23.3%); all other types of opioids were dispensed to less than 10% of nonchronic users. Among chronic users, codeine was dispensed to 38.4%, followed closely by hydrocodone HCl (37.1%), oxycodone (27.2%), fentanyl (22.3%) and morphine (16.2%). In long-term chronic opioid users, percentages were similar to those in chronic users, although codeine was dispensed less frequently (29.9%) and methadone was dispensed more frequently (11.7%).

Concurrent laxative and/or acid suppressant use

Approximately one-third of people (30.5%) with an opioid dispensing were concomitantly dispensed a laxative or acid suppressant medication. Furthermore, slightly more women...
the data are reported as <0.1%.

(31.9%) than men (28.3%) received a concurrent dispensing of opioids, and a laxative or acid suppressant (Table 3). When patients were examined by age group, a substantial difference in concomitant dispensings of opioids and a laxative or acid suppressant was observed; 23.5% of patients younger than 65 years of age were concurrently dispensed an opioid and a laxative or acid suppressant medication compared with 39.5% of chronic users and 62.7% of long-term chronic users. Additionally, the proportion of subjects who were dispensed acid suppressants at least twice as often as laxatives used were dispensed over the counter.

Interestingly, approximately two-thirds of patients dispensed an opioid received codeine. In comparison, a Canadian survey on chronic pain and prevalence of opioid use found that 16.9% (n=340) of 2012 respondents were taking prescription analgesic medication. Among individuals surveyed with chronic pain who were taking a prescription analgesic medication (n=340), 22.6% (n=77) used an opioid and 67.5% (n=52) of the opioid users reported taking codeine (22). Hence, the data in the Quebec plan and the survey of chronic pain

65 years of age or older had slightly more concomitant opioid and laxative dispensings than those younger than 65 years of age (2.6% versus 1.8%). More concomitant laxatives were dispensed among chronic users (11.3%) and long-term chronic users (15.2%) than nonchronic users (0.8%). The nonchronic users may serve as a surrogate upper bound for patients not prescribed opioids; therefore, the dispensing of laxatives in patients who are also dispensed opioids can be assumed to be at least 10-fold greater than nonopioid users. Among the long-term chronic users, slightly more women (16.8%) than men (12.7%) had concomitant laxative dispensings, and almost all of the laxatives used were dispensed over the counter.

Nearly one-third (29.8%) of patients with an opioid dispensing had a concurrent acid suppressant dispensing (Table 3), and more women than men received a concurrent dispensing of opioids and acid suppressants (31.2% and 27.6%, respectively). Twice as many chronic (56.6%) and long-term (58.5%) opioid users had concomitant laxative dispensings, and almost all of the laxatives used were dispensed over the counter.

DISCUSSION

The results of the present study confirm that a substantial proportion of patients in the Quebec Public Prescription Drug Insurance Plan received an opioid dispensing in 2005. Additionally, the proportion of subjects who were dispensed opioids increased with age, and many of the patients were concurrently dispensed a laxative or acid suppressant medication.

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treatment of associated side effects may be especially important. Therefore, greater focus on pain management and appropriate opioid-related side effects may have a greater impact. Older patients have comorbidities and reduced GI functioning, any potential opioid users. Because the older population is more likely to nonchronic users may represent an upper bound for the non-opioid users than nonchronic opioid users. We believe the populations.

Despite these limitations, there are several strengths to this database analysis study. This drug plan is likely representative of approximately 3.2 million residents of Quebec. All drug dispersions must be prescribed by a physician, even if the medications can be bought over the counter. Drugs are identified by the Canadian Drug Identification Number, which signifies a unique combination of chemical entity, trade name, strength, and form. Unlike insurance claims data in the United States, the database used in the present study contains information on over-the-counter medications obtained from various health plans in Canada may be partially due to differences in filing for reimbursement rather than true differences in the use between the populations.

The gastrointestinal side effects of opioids are well known, and the present study illustrates that these side effects may increase with age and duration of opioid use. As anticipated, the chronic and long-term opioid users had greater concomitant dispensing of GI medications than nonchronic users; laxatives were dispensed at least 10 times more frequently and acid suppressants at least twice as frequently in chronic opioid users than nonchronic opioid users. We believe the nonchronic users may represent an upper bound for the non-opioid users. Because the older population is more likely to have comorbidities and reduced GI functioning, any potential opioid-related side effects may have a greater impact. Therefore, greater focus on pain management and appropriate treatment of associated side effects may be especially important for this population because it is critical that opioid-induced side effects do not lead to cessation of the necessary opioid therapy.

There are several limitations of the present study due to the use of a prescription drug plan database. Although we have actual dispensings of medications, we do not have prescriptions or patient-reported data. Therefore, we cannot account for possible differences between the dispensing data and the instructions given by the physician, or the actual medication use by the patient. When opioids are prescribed on an as-needed basis, the pharmacist has to make the assumption that the number of units per day divided by total number of units equals the number of days supplied; therefore, the number of days supplied may be an underestimate or overestimate of the actual number of days a medication was used. We also do not know if the concomitant GI medications were prescribed due to side effects of the opioid or for other reasons. Considering the large differences between chronic and nonchronic opioid users in both concomitant laxative and acid suppressant use, it is likely that these GI treatments were in response to opioid-related side effects.

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**CONCLUSION**

Opioids represent a frequently dispensed medication. Associated with their use is an increase in concomitant medications to treat OBD; in particular, laxatives and acid suppressant therapies. The use of these medications is essential because, for some patients, cessation of opioid therapy has negative and dramatic consequences due to the requirement of analgesia to relieve their pain.
STATEMENT OF INTERESTS: REW and SFC are employees of GlaxoSmithKline and have stocks and shares in GlaxoSmithKline. CS was a contractor to GlaxoSmithKline and is currently an employee of RTI Health Solutions. AWD is a contractor to GlaxoSmithKline. NB and MB received funding from GlaxoSmithKline for access to data and data analyses. KBL received unrestricted educational grants from GlaxoSmithKline. The present study was funded by GlaxoSmithKline.

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REFERENCES