UTILIZATION OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN QUEBEC: ADHERENCE TO THE CANADIAN CONSENSUS ON PRESCRIPTION GUIDELINES

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ABSTRACT

Background
Adverse events associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) have led to the publication of Canadian prescription guidelines. Prescription practices following the publication of these guidelines and the introduction of COX-2 inhibitors in the Quebec formulary of reimbursed medications remain largely unexplored.

Objectives
To compare the prevalence of contra-indications and selected risk factors for NSAID-toxicity among COX-2 inhibitor users and non-selective NSAID users.

Methods
A case-control analysis was conducted in a random sample of Quebec adult drug plan members who were treated with celecoxib (n=42,422 cases), rofecoxib (n=25,674 cases), full-dose (anti-inflammatory doses) of non-selective NSAIDs (n= 9,673 cases), or low-dose NSAIDs (n=2,745 controls) in the year 2000. Data were obtained from the Quebec prescription and medical services databases (RAMQ).

Results
Patients with a history of gastropathy were more likely to be prescribed COX-2 inhibitors than low-dose NSAIDs; the odds ratios were 1.73 (95%CI: 1.56-1.91) and 1.49 (1.33-1.66), respectively for celecoxib and rofecoxib. Corresponding results for concomitant use of anticoagulants were 1.95 (1.34-2.83) for celecoxib and 1.87 (1.26-2.77) for rofecoxib, and for use of corticosteroids they were 1.29 (1.08-1.54) and 1.23 (1.01-1.49). Conversely, patients with the following characteristics were less likely to receive COX-2 inhibitors than low-dose non-selective NSAIDs: age 75+ (OR=0.64; 0.56-0.72 for celecoxib, OR=0.48; 0.76-0.99 for rofecoxib), hypertension (OR=0.83; 0.75-0.92 for celecoxib, OR=0.87; 0.77-0.97 for rofecoxib), and concomitant use of diuretics (OR=0.72; 0.63-0.82 for celecoxib; OR=0.77; 0.66-0.89 for rofecoxib).

Conclusion
Patients with risk factors for NSAID gastropathy were more likely prescribed COX-2 inhibitors, while the presence of other contra-indications led to the prescription of low-dose non-selective NSAIDs. However, 12.7% of users of full-dose non-selective NSAIDs were age 75+ and 12.0% had a history of gastropathy, which are considered important risk factors for adverse events.

Key Words: *Pharmacoepidemiology, drug utilization, non-steroidal anti-inflammatory drugs, COX-2 inhibitors, prescription guidelines*

Evidence-based prescription guidelines have been published in Canada in order to optimize the prescription of non-steroidal anti-inflammatory drugs (NSAIDs) in musculoskeletal disease.[1,2] In the 1996 consensus guidelines, a series of risk factors that increased the risk of adverse events associated with NSAIDs were identified, with special emphasis on gastrointestinal and renal adverse effects. For these patients, low-dose non-selective NSAIDs and avoidance of long-term use were recommended. In addition, analgesics, such as acetaminophen, should be attempted before non-selective NSAIDs in order to relieve osteoarthritis pain. The adoption of these guidelines in a real-life setting remains largely unexplored to date. Furthermore, these guidelines did not consider COX-2 inhibitors because they had not yet been released on the market at the time of publication. The subsequent inclusion of COX-2 inhibitors in the formulary of reimbursed medications may have introduced channeling of high-risk patients towards these newer agents.

Studies confirming the advantages of COX-2 inhibitors over non-selective NSAIDs with respect to gastropathy have been published both in a pre-marketing[3-11] and post-marketing setting.[12-14] In parallel with the positive evidence on COX-2 inhibitors, editorials or letters have been published which question the safety of these products;[15-23]one of which highlighted the incomplete reporting of adverse events.[24]

An epidemiologic study conducted in the province of Ontario during the year 2000-2001 has been published to assess the risk of gastropathy associated with COX-2 inhibitors and non-selective NSAIDs.[13] It was shown that the short-term risk of hospitalization for upper gastrointestinal haemorrhage was lower for COX-2 inhibitors than for non-selective NSAIDs. However, because the scope of that study was risk assessment, the study population was restricted to the elderly; patients who had received a single dispensing or who were treated for less than 30 days were excluded. In addition, unlike Quebec, the reimbursement of COX-2 inhibitors is restricted in Ontario. Based on the literature, it appears that the assessment of prescription practices of these agents against published guidelines remains largely unexplored.

In an observational setting, such as that of post-marketing, the decision to prescribe one product over another is influenced by the characteristics of the patient, the prescriber and the health care system (e.g. access and cost considerations).[25] Consequently, following the introduction of COX-2 inhibitors, it was not known whether patients with risk factors for NSAID-toxicity were more likely to switch to COX-2 inhibitors or to use low-dose non-selective NSAIDs, as recommended in the 1996 guidelines. Since prescription channeling may introduce confounding in the comparison of risk across products, it is critical to document the profile of patients treated with each product. Recently, one of the COX-2 inhibitors, rofecoxib, has been withdrawn from the market. Still, it remains of interest to analyze the utilization of COX-2 inhibitors in order to appreciate the concordance between prescription patterns and published guidelines. This would determine whether some of the controversies discussed in the literature have played an influential role on the physician's decision to prescribe these agents. Using the published 1996 Canadian consensus guidelines[1] our study aimed to compare the prevalence of selected risk factors for NSAID-toxicity among users of COX-2 inhibitors, low-dose non-selective NSAIDs (defined as being the maximum OTC dose or, for products only available under prescription, dosages below the standard recommended anti-inflammatory dosages), and full-dose (anti-inflammatory doses) of non-selective NSAIDs, at the time COX-2 inhibitors were introduced on the Quebec formulary. Another objective was to compare drug classes for past experience with NSAID use, i.e., multiple use. Although the guidelines were updated at the end of 2000[2] they were not available to the physicians during the entire period covered by this study.Consequently, the 1996 guidelines were retained as the reference.

METHODS

Design

A case-control analysis was conducted whereby users of COX-2 inhibitors or full-dose non-selective NSAIDs listed in Table 1 (the cases) were compared to users of low-dose non-selective

NSAIDs (the controls). The latter group was retained as the reference since it was recommended in the guidelines for high-risk patients. The independent variables consisted of the risk factors for gastric or renal adverse effects, as listed in the Canadian consensus guidelines of 1996. Comparisons were adjusted for potential confounders such as gender, income level, overall health status, prescriber's specialty, and period of the year.

TABLE 1 Non-selective non-steroidal anti-inflammatory drugs considered in the study

Generic Names
• Acetylsalicylic Acid
• Diclofenac (including Voltaren + Cytotec = Arthrotec)
• Diflunisal
• Etodolac
• Fenoprofen
• Flurbiprofen
• Ibuprofen
• Indomethacin
• Ketoprofen
• Mefenamic Acid
• Naproxen
• Piroxicam
• Salsalate
• Tiaprofenic Acid
• Tolmetin

Sources of data

The Régie de l'assurance-maladie du Québec (RAMQ) health databases were used to assemble the study population. More specifically, the dataset was assembled using linkage between three sources of data available in RAMQ: 1) the beneficiary's database; 2) the prescription database and, 3) the medical services database.

Target population

The study targeted all ambulatory adult residents (age 18+) of the province of Quebec who were members of the public drug coverage program. In Quebec, coverage of prescribed medication initially was for all elderly residents (age 65+) regardless of their income and for all welfare recepients. The program was broadened in 1997 to include patients who do not have access to a private insurance program, regardless of age. For everyone, the program now includes a deductible and a co-payment with a monthly maximum that is established according to the beneficiary's income. In practice, the program includes the following segments of the population: the majority of community-dwelling elderly (>94%), welfare recipients, and patients less than 65 years of age who do not have access to private insurance (e.g. self-employed).

Study population

A sample of 100 000 drug plan members who were dispensed at least one celecoxib or rofecoxib prescription (Celebrex® or Vioxx®) between January 1st and December 31st 2000 was randomly selected. A sample of 60,000 non-selective NSAID users was randomly selected during the same time period. Patients who used low-dose aspirin only (ASA <325 mg/day) were excluded. The study population included both new users (incident) and those who have used NSAIDs at least once in the year before (prevalent). The status of the patient with respect to being a COX-2 inhibitor user or a non-selective NSAID user was determined at the end of the study year, consistent with a cumulative incidence sampling strategy.

Patients who had received both a COX-2 inhibitor and a non-selective NSAID were considered as COX-2 inhibitor users. This sampling scheme was based on the principle that the case-control design is a sample of person-time experience from an underlying cohort.[26] The sampling strategy used in the study corresponds to the censoring of patients from the cohort at the time they become a case (i.e. COX-2 inhibitor user) but not when they present the control event (i.e. non-selective NSAID prescription). The index date was defined as the date of the first dispensing of a COX-2 inhibitor or, for the non-selective NSAID group, the date of the first dispensing of a non-selective NSAID during the year.

The following inclusion criteria were applied: 1) to have been a resident of Quebec for at least 2 years prior to the index date and, 2) continuous coverage of medical pharmaceutical services for at least 2 years prior to the index date. These criteria were verified by RAMQ through the beneficiary's database.

Dependent variables

Comparisons involved: celecoxi, rofecoxib and full-dose non-selective NSAIDs versus low-dose non-selective NSAIDs. Prescribed daily dosage at index date was estimated from the number of units dispensed, dosage per unit, and prescribed duration. The cut-off to define low doses of non-selective NSAIDs was the maximum dosage available over-the-counter, or for products available by prescription only, low dose included all dosages lower than the standard recommended anti-inflammatory dosages.

Independent variables

The main independent variables corresponded to the risk factors for NSAID-toxicity identified in the Canadian consensus guidelines, i.e. previous peptic ulcer disease, advanced age (75+), concomitant use of anticoagulants, corticosteroids, or ACE inhibitors as well as comorbid illness including hypertension, diabetes, congestive heart failure, renal failure, hepatic illness. Linkage with the RAMQ medical services database allowed us to obtain data on medical diagnoses for which a medical visit was billed.

Although there is a field for diagnosis coded according to the ICD-9 classification, it is often missing because it is not mandatory for reimbursement. Consequently, for apparent gastropathy, hypertension and diabetes, dispensings were also used as markers for the presence of illness. Although chronic alcoholism was also listed in the consensus as a risk factor, we were unable to obtain data on this factor. Previous attempts with NSAIDs, including switches, were identified from the dispensing of more than one individual product in the year prior to index date. Since COX-2 inhibitors had just been introduced in the formulary during the study period, by design, previous experience with NSAIDs involved non-selective NSAIDs only.

Potential confounders that were considered included: gender, income level (assessed from the level of reimbursement in the provincial drug program and expressed as a dichotomous variable), and overall health status. The Chronic Disease Score (CDS), which is obtained from administrative pharmacy data over a 1-year period quantified the latter.[27] Scores are weighted according to the number of different chronic diseases under treatment and the severity of the diseases. The CDS has been found to predict subsequent mortality and hospitalization rates. Because health status at index date was the variable most likely to influence the physician's prescription, dispensing data from the year before the index date were used for the calculation. Based on the distribution of the scores, four categories were defined: 0, 1-4, 5-9, 10+. Other potential confounders included: prescriber's specialty (specialist versus general practitioner), and period of the year (January-June, July-September, October-December).

Time windows

Two time windows were used to assess the prevalence of risk factors. When diagnosis recorded in the medical database was used to identify the presence of comorbid illness, it was assessed over a period of one year prior to index date because patients are not expected to consult their physician every month especially if the condition is chronic and asymptomatic (e.g. hypertension). On the other hand, when prescriptions were used as evidence of a comorbid illness, active prescriptions were sought in order to ensure that the illness was still ongoing. An active prescription was defined as either a date of dispensing within 30 days prior to index date, or a date of dispensing prior to the 30-day cut-off but with a prescribed duration overlapping the time window.

Statistical analysis

Standard descriptive statistics were performed to compare the characteristics of the patients who received celecoxib, rofecoxib, low-dose non-selective NSAIDs, and full-dose non-selective NSAIDs. Since all study variables were categorical, chi-square tests were conducted to assess heterogeneity of the distribution of the study population into the various categories. The strength of association between a given contra-indication for non-selective NSAID use or patient characteristic and the probability of receiving celecoxib or rofecoxib were assessed through multivariate logistic regression, controlling for all independent variables simultaneously.

The reference category was the prescription of low-dose non-selective NSAIDs since it is recommended for high-risk patients in the 1996 guidelines. All data were analyzed using the SAS

statistical package (SAS 6.12 and 8.0 for Windows, SAS Institute Inc., Cary, NC, USA). The level of statistical significance was set at 0.05 and the statistical uncertainty of the estimates was assessed by 95% confidence intervals.

RESULTS

After applying the eligibility criteria, 42,422 users of celecoxib, 25,674 users of rofecoxib, and 12,418 users of non-selective NSAIDs were included in the study. Compared to COX-2 inhibitors, a greater number of patients in the non-selective NSAIDs group were excluded because they were using ASA only. Non-selective NSAID users were subsequently categorized into users of full-dose (n=9,673) and low-dose (n=2,745). For each class of products, the frequency estimates of the number of different NSAIDs, including low dose ASA, used in the year prior to the index date are reported in Table 2.

TABLE 2 History of non-selective non-steroidal anti-inflammatory drug use (including low dose ASA)

Number of NSAID dispensings in the year before	Non-selective NSAIDs Low dose (% users) (n=2,745)	Non-selective NSAIDs Anti-inflammatory dose (% users) (n=9,673)	Celecoxib (% users) (n=42,422)	Rofecoxib (% users) (n=25,674)
Patients with prior use of gastroprotective agents*				
	(n=581)	(n=1,157)	(n=12,706)	(n=6,240)
0	94 (16.2)	380 (32.8)	5,373 (42.3)	3,214 (51.1)
1	400 (68.9)	560 (48.4)	5,222 (41.1)	2,352 (37.7)
2+	87 (15.0)	217 (18.8)	2,111 (16.6)	674 (10.8)
Patients with no prior use of gastroprotective agents				
	(n=2 164)	(n=8 516)	(n=29,716)	(n=19,434)
0	492 (22.7)	5,274 (61.9)	16,978 (57.1)	12,522 (64.4)
1	1,473 (68.0)	2,662 (31.3)	9,990 (33.6)	5,804 (29.9)
2+	199 (9.2)	580 (6.8)	2,748 (9.3)	1,108 (5.7)

$p<0.001$

* Assessed through dispensings during the year prior to index date

Chi-square statistics were used to compare the distribution of past NSAID use across the various NSAID classes. Patients were stratified according to prior use of gastroprotective agents since it was hypothesized that history of gastropathy would likely modify the observed distribution. For patients with no evidence of history of gastropathy, as shown by the absence of dispensings of gastroprotective agents, previous experience with NSAIDs was more frequent among users of low-dose non-selective NSAIDs than among users of the other classes of products. Surprisingly, similar trends were found for patients with a history of gastropathy. For all NSAID classes, multiple NSAID use during the year prior to index date was more frequent among patients with no evidence of history of gastropathy. Past use of gastroprotective agents was further categorized into patients who were still using these drugs at the index date and those who only used them in the past (31 to 365 days prior to index date). The proportion of patients who were still using gastroprotective agents at index date was: 5.7% for patients who received

full-dose non-selective NSAIDs, 11.8% for low-dose non-selective NSAIDs, 16.1% of celecoxib, and 12.6% of rofecoxib. The proportion of past use only of gastroprotective agents was: 5.8% for full-dose non-selective NSAIDs, 9.0% of low-dose non-selective NSAIDs, 13.0% of users of celecoxib, and 10.9% of users of rofecoxib ($p<.001$ for heterogeneity of distribution). These results show that prescribers do not seem comfortable using an NSAID that is not a COX-2 inhibitor if the patient is or had been on a gastroprotective agent. Results from the bivariate analyses on the prevalence of risk factors for NSAID-toxicity are presented in Tables 3 and 4.

TABLE 3 Prevalence of characteristics and concomitant medications that are risk factors for nonsteroidal anti-inflammatory drugs (NSAID)-toxicity

	Non-selective NSAIDs (% users)		Celecoxib (% users)	Rofecoxib (% users)	P Value
	Low Dose	Anti-inflammatory dose			
	(n=9,673)	(n=2,745)	(n=42,422)	(n=25,674)	
Age 18-54	420 (15.3)	5,480 (56.7)	8,543 (20.2)	7,317 (28.5)	
Age 55-74	1,045 (38.1)	2,968 (30.7)	19,663 (46.4)	11,209 (43.7)	
Age 75+	1,280 (46.6)	1,225 (12.7)	14,216 (33.5)	7,148 (27.8)	< 0.001
Male	1,236 (45.0)	4,300 (44.5)	13,843 (32.6)	8,858 (34.5)	< 0.001
Lower income	271 (9.9)	1,564 (16.2)	4,614 (10.9)	2,935 (11.4)	< 0.001
CDS					
0	649 (23.6)	5,223 (54.0)	11,690 (27.6)	8,689 (33.8)	
1-4	1,006 (36.7)	2,463 (25.5)	14,248 (33.6)	8,381 (32.6)	
5-10	826 (30.1)	1,606 (16.6)	13,121 (28.6)	6,510 (25.4)	
10+	264 (9.6)	381 (3.9)	4,363 (10.3)	2,094 (8.2)	< 0.001
Specialist	438 (16.0)	1,267 (13.1)	6,224 (14.7)	3,023 (11.8)	< 0.001
Prior use of gastroprotective agents	581 (21.2)	1,157 (12.0)	12,706 (30.0)	6,240 (24.3)	< 0.001
Concomitant use					
Diuretics	717 (26.1)	991 (10.3)	9,153 (21.6)	4,760 (18.4)	< 0.001
ACE inhibitors	267 (9.7)	394 (4.1)	3,051 (7.2)	1,838 (7.2)	< 0.001
Anticoagulant	30 (1.1)	83 (0.9)	1,061 (2.5)	594 (2.3)	< 0.001
Corticosteroid	170 (6.2)	491 (5.1)	3,801 (9.0)	1,897 (7.4)	< 0.001

TABLE 4 Prevalence of co-morbid illnesses that are risk factors for non-selective non-steroidal anti-inflammatory drugs (NSAID)-toxicity

	Non Selective NSAIDS (% users)		Celecoxib (% users)	Rofecoxib (% users)	P Value
	Low Dose	Anti-Inflammatory Dose			
	(n=2,745)	(n=9,673)	(n= 42,422)	(n=25,674)	
Hypertension					
- Prescription*	974 (35.5)	1,354 (14.0)	11,624 (27.4)	6,341 (24.7)	< 0.001
- Diagnosis**	834 (30.4)	1,199 (12.4)	10,521 (24.8)	4,288 (16.7)	< 0.001
Diabetes					
- Prescription	373 (13.6)	484 (5.0)	4,073 (9.6)	2,080 (8.1)	< 0.001
- Diagnosis	329 (12.0)	454 (4.8)	3,818 (9.0)	1,540 (6.0)	< 0.001
Nephrosclerosis	5 (0.18)	6 (0.06)	38 (0.09)	8 (0.03)	0.005
Hypertensive heart	2 (0.07)	1 (0.01)	8 (0.02)	5 (0.02)	0.28
Glomerulonephritis	3 (0.11)	6 (0.06)	25 (0.06)	10 (0.04)	0.41
Chronic renal failure	28 (0.95)	22 (0.23)	174 (0.41)	59 (0.23)	< 0.001
Chronic hepatitis	1 (0.04)	4 (0.04)	8 (0.02)	5 (0.02)	0.59
Congestive heart failure	5 (0.18)	11 (0.11)	55 (0.13)	18 (0.07)	0.10

* Based on concomitant dispensing as evidence of illness

** Diagnosis as it appears in the medical services database (ICD-9 category) during the previous year

P-values are derived from the chi-square statistics that were used to assess the difference in the proportion of patients with the risk factor across NSAID classes. The prevalence of all contra-indications for non-selective NSAIDs use was lower among users of full-dose non-selective NSAIDs than users of low-dose NSAIDs: age 75+ (12.7% versus 46.6%), history of gastroprotective agent use (12.0% versus 21.2%), concomitant use of corticosteroids (5.1% versus 6.2%), anticoagulants (0.9% versus 1.1%), diuretics (10.3% versus 26.1%), and ACE inhibitors (4.1% versus 9.7%). All differences were statistically significant (p<.001).

However, the channeling of patients towards COX-2 inhibitors or low-dose NSAIDs differed according to the contra-indications for non-selective NSAIDs use. Emerging from the tables is the observation of prescription channeling towards COX-2 inhibitors for patients with a history of gastroprotective agent use. The prevalence of age 75+, hypertension, diabetes, concomitant use of diuretics or ACE inhibitors was higher among low-dose non-selective NSAID users than users of COX-2 inhibitors and users of full-dose non-selective NSAIDs.

Differences across NSAID classes were statistically significant for all risk factors (p<.0001). Conversely, the prevalence of risk factors for NSAID-gastropathy, such as history of apparent gastropathy, (which included gastroprotective agents as a surrogate), concomitant use of anticoagulants or corticosteroids, was significantly greater among COX-2 inhibitors users than low-dose non-selective NSAID users. For the majority of risk factors examined, the prevalence estimates were significantly greater for celecoxib than for rofecoxib. It should nevertheless be noted that full-dose non-selective NSAIDs are still prescribed to patients who have one of the risk factors. For example, as shown in Table 3, 10.3% of patients who used full-dose non-selective NSAIDs were using diuretics concomitantly, and 5.1% were using corticosteroids.

Prescription channeling also occurred for other patient characteristics that are not contra-indications but could act as potential confounders. The prevalence of males was lower among COX-2 inhibitor users than among non-selective NSAID users (32.6% for celecoxib, 34.5% for rofecoxib, 45.0% for low-dose non-selective

NSAIDs, and 44.5% for full dosages of non-selective NSAIDs). The prevalence of low income patients was lower among COX-2 inhibitor users than full-dose of non-selective NSAIDs users (10.9% for celecoxib, 11.4% for rofecoxib, 16.2% for full-dose of non-selective NSAIDs), but not of low-dose non-selective NSAIDs (9.9%). The prevalence of high chronic disease scores (CDS10+) was lowest among users of non-selective NSAIDs at full-dose, and highest among celecoxib users (10.3% for celecoxib, 8.2% for rofecoxib, 3.9% for full-dose of non-selective NSAIDs, 9.6% for low-dose of non-selective NSAIDs).Results from the multivariate logistic regression analysis are reported in Table 5.

TABLE 5 Results from multivariate logistic regression analysis on the association between patient characteristics and the prescription of celecoxib, rofecoxib, anti-inflammatory doses of non-selective NSAIDs, relative to low-dose NSAIDs; Adjusted odds ratio (95% CI).

	Celecoxib (n=42,422)	**Rofecoxib** (n=25,674)	**Non-selective NSAIDs Anti inflammatory doses** (n=9,673)
Age 18-54	Reference	Reference	Reference
Age 55-74	1.11 (0.98- 1.26)	0.86 (0.76- 0.99)	0.36 (0.32-0.42)
Age 75+	0.64 (0.56-0.72)	0.48 (0.43- 0.56)	0.14 (0.12- 0.17)
Gender (male)	0.60 (0.55- 0.65)	0.63 (0.58- 0.69)	0.94 (0.85- 1.04)
Income (lower)	0.87 (0.76- 0.99)	0.79 (0.68- 0.92)	0.93 (0.79- 1.08)
CDS 0	Reference	Reference	Reference
CDS 1-4	0.88 (0.78-0.99)	0.91 (0.80-1.03)	0.71 (0.62-0.82)
CDS 5-9	1.18 (1.01-1.38)	1.11 (0.93-1.31)	0.84 (0.69-1.01)
CDS 10 +	1.29 (1.03-1.54)	1.21 (0.94-1.54)	0.84 (0.63-1.13)
General Practitioner	Reference	Reference	Reference
Specialist	0.89 (0.80-0.99)	0.78 (0.70-0.89)	0.90 (0.79-1.03)
History of gastropathy	1.73 (1.56-1.91)	1.49 (1.33-1.66)	0.94 (0.83-1.07)
Hypertension	0.83 (0.75-0.92)	0.87 (0.77-0.97)	0.76 (0.66-0.87)
Diabetes	0.78 (0.69-0.88)	0.73 (0.64-0.84)	0.72 (0.61-0.84)
Diuretics	0.72 (0.63-0.82)	0.77 (0.66-0.89)	0.81 (0.68-0.96)
ACE inhibitors	0.96 (0.83-1.12)	1.05 (0.89-1.24)	1.02 (0.84-1.25)
Anticoagulants	1.95 (1.34-2.83)	1.87 (1.26-2.77)	1.62 (1.03-2.55)
Corticosteroids	1.29 (1.08-1.54)	1.23 (1.01-1.49)	1.23 (0.98-1.54)
Prior NSAID use			
[0]	Reference	Reference	Reference
[1]	0.21 (0.20-0.23)	0.31 (0.27-0.37)	0.39 (0.34-0.43)
[2+]	0.42 (0.36-0.49)	0.20 (0.18-0.23)	0.77 (0.64-0.92)
Acetaminophen	2.04 (1.84-2.25)	1.75 (1.57-1.96)	1.19 (1.05-1.34)

* Using low-dose non-selective NSAIDs as the reference category

Adjusted for year quarter and all other variables included in the table.

It was found that age was by far the most important confounder, and many prevalence differences observed in the bivariate analyses were not significant in the multivariate model. Low-dose non-selective NSAIDs were more likely to be prescribed than COX-2 inhibitors for

patients in the older age groups, men, lower income, patients with hypertension, diabetes, or concomitant use of diuretics. The concomitant use of ACE inhibitors had no apparent effect on prescription practices. Conversely, history of apparent gastropathy, concomitant use of corticosteroids or anticoagulants, which are risk factors for upper gastrointestinal bleeding, were significantly associated with the prescription of COX-2 inhibitors, whether it was celecoxib or rofecoxib. When age was taken into account, the chronic disease score decreased the probability of being prescribed full-dose of non-selective NSAIDs, but did not influence the prescription of COX-2 inhibitors over low-dose non-selective NSAIDs. Adjusting for history of apparent gastropathy, patients with previous experience with NSAIDs were more likely to receive low-dose non-selective NSAIDs than any other classes. Conversely, patients with prior use of acetaminophen were more likely to receive COX-2 inhibitors than low-dose non-selective NSAIDs.

DISCUSSION

This study has underlined the importance of distinguishing between low-dose and full-dose of non-selective NSAIDs when assessing prescription channeling. It was clear that patients at risk for NSAID-toxicity were either prescribed low-dose non-selective NSAIDs, as recommended in the guidelines, or COX-2 inhibitors. However, the patterns of channeling differed across classes. Risk factors for NSAID-gastropathy, such as history of apparent gastropathy or concomitant use of anticoagulants or corticosteroids, were associated with the prescription of COX-2 inhibitors. On the other hand, risk factors for renal adverse effects such as concomitant use of diuretics were associated with the prescription of low-dose non-selective NSAIDs. Concomitant use of ACE inhibitors did not have a significant effect on prescription practices. Such findings must nevertheless be interpreted with caution because the indications for the prescription of low-dose non-selective NSAIDs were not known.

It is important to underscore that these findings are probably generalizable only to the year 2000 for two reasons. First, the study year corresponds to the period of introduction in the formulary of the COX-2 inhibitors. Now that a longer experience with the use of these drugs in real-life setting has been gained, one would expect that the prescribing practices, and the resulting patterns of dispensings, have also evolved. Second, a new Consensus was published in the fall of 2000. Although the content and guidelines are somewhat similar to the first Consensus in terms of contra-indications, more physicians probably became aware of the guidelines because they have been “exposed” to two published sets of guidelines as opposed to one at the time the study was conducted.

Comparisons of celecoxib and rofecoxib users indicate that the channeling patterns did not significantly differ in the multivariate model when age was taken into account. The multivariate regression analysis demonstrated that patients who had comorbid illnesses that were risk factors for NSAID-toxicity, such as hypertension, were more likely to be prescribed low-dose non-selective NSAIDs than COX-2 inhibitors. This highlights the potential relationship between the study timing and the early availability of COX-2 inhibitors on the market place coupled with evolving arthritis treatment guidelines. The lack of clinical experience with a new molecule may lead initially to more careful prescribing. A new study using a more contemporary data set might be able to validate this relationship. Nevertheless, these preliminary findings indicate that a number of subjects treated with full-doses non-selective NSAIDs would have qualified for treatment with either COX-2 inhibitors or low-dose NSAIDs, based upon their risk profile.

Overall, 55% of the patients had not used non-selective NSAIDs previously. Such findings may partly be attributed to the time window that was used. Past use was assessed during the year before the index date. However, there may have been patients who had tried non-selective NSAIDs beyond the one year and remained untreated or poorly treated until the introduction of COX-2 inhibitors. The one-year time window for the assessment of prior NSAID use might not have been sufficient to delineate this trend. Another reason may have been the absence of data on OTC low-dose NSAIDs. Exclusive users of such products could not have been sampled from the database since they had to receive at least one prescribed NSAID to be in the database. It is true that some patients may have tried an OTC which

did not work, and subsequently received a prescribed NSAID at a higher dosage, or a coxib. This would lead to an under-estimation of history of NSAID use, which would result in an over-estimation of first-time use. It is not possible to predict from the database whether it would have been similar or different across product classes.

Finally, the reliability of the markers used for the assessment of comorbid illness greatly depends on their sensitivity and specificity for the underlying indication. Although their positive predictive value has not been evaluated in this study, it is expected that the dispensing of insulin or oral hypoglycemic agents is a very reliable indicator of diabetes. Hypertension, however, is more problematic given that drugs other than antihypertensives can be prescribed to treat this condition, such as diuretics. For this reason, diagnosis was also used as evidence of hypertension. The use of gastroprotective agents as a surrogate for gastropathy would also include patients with isolated gastro-esophageal reflux disease, which may not be a risk factor for NSAID gastropathy.

This study has shown that during the first year of use of the COX-2 inhibitors on the Quebec formulary, low-dose non-selective NSAIDs were still prescribed more frequently to older patients, and in the presence of selected contra-indications. This study has shown that patients with risk factors for NSAID-gastropathy were channeled towards COX-2 inhibitors, while those with risk factors for other adverse events, such as renal effects, were prescribed low-dose non-selective NSAIDs, in accordance with the prescription guidelines. COX-2 inhibitors were predominantly prescribed to patients at risk of gastropathy based on the use of gastroprotective agents. Over time, more data have been published on the safety of COX-2 inhibitors in a real-life setting, and consequently prescription channeling may have evolved. The monitoring of prescription practices relative to evidence-based guidelines is a priority in the post-marketing setting to ensure optimal therapy.

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REFERENCES

1. Tannenbaum H, Davis P, Russell AS et al. An evidence-based approach to prescribing NSAIDs in musculoskeletal disease: a Canadian consensus. CMAJ 1996; 155: 77-88.
2. Tannenbaum H, Peloso PMJ, Russell A, Marlow B. An evidence-based approach to prescribing NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis: The Second Canadian Consensus Conference. Can J Clin.Pharmacol. 2000; 7(suppl.A): 4-16A.
3. Simon SL, Weaver LA, Graham YD et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: A randomized controlled trial. JAMA 1999; 282: 1921-1928.
4. Emery P, Zeilder H, Kvien KT et al. Celecoxib versus diclofenac in long-term management of rehumatoid arthritis: randomised double-blind comparison. The Lancet 1999; 354: 2106-2111.
5. Silverstein FE et al. Gastrointestinal toxicity with celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. JAMA 2000; 284: 1247-1255.
6. Geba GP, Weaver AL, Polis AB et al. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee. JAMA 2002; 287: 64-71.
7. Day R, Morrison B, Luza A et al. Randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. Arch. Intern. Med. 2000; 160: 1781-1787.
8. Bombardier C, Laine L, Reicin A, et al. For the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N. Engl. J. Med. 2000; 343: 1520-1528.
9. Langham JM, Jensen MD, Watson JD, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999; 282: 1929-1933.
10. Watson JD, Harper ES, Zhao PL, et al. Gastrointestinal tolerability of the selective Cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2

inhibitors in osteoarthritis. Arch. Intern. Med. 2000; 160: 2998-3003.
11. Scott JL, Lamb MH. Profil d'un nouveau médicament: Rofecoxib. Adis International, Drugs 1999; 58: 409-506.
12. Singh DK, Goldstein JL, Pettitt D, Burke TA, Schwartz S. Relative gastrointestinal toxicity of specific and nonspecific cyclooxygenase inhibitors within a high-risk managed care population. Ann Rheum Dis 2001;60 (Suppl 1):82.
13. Mamdani M, Rochon PA, Juurlink DN, Kopp A, Anderson GM, Naglie G, *et al*. Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs. BMJ 2002;325:624-629.
14. Laine L, Connors LG, Reicin A, Hawkey CJ, Burgos-Vargas R, Schnitzer TJ, Yu Q, Bombardier C. Serious lower gastrointestinal clinical events with nonselective NSAID or coxib use. Gastroenterology. 2003 Feb;124(2):288-92.
15. Jüni P, Rutjes AWS, Dieppe PA. Are selective COX-2 inhibitors superior to traditional non-steroidal anti-inflammatory drugs? BMJ 2002; 324: 1287-1288.
16. Skelly MM, Hawkey CJ. Potential alternatives to COX-2 inhibitors. Editorials BMJ 2002; 324: 1289-1290.
17. Pathak A, Boveda S, Defaye P, et al. Celecoxib-associated torsade de pointes. Letter. Ann.Pharm. 2002; 36: 1290-1291.
18. Letters for Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286: 2808-2813.
19. Lichtenstein RD, Wolfe MM. COX-2 selective NSAIDs: New and Improved? JAMA 2000; 284: 1297-1299.
20. The University of British Columbia Department of Pharmacology & Therapeutics. Therapeutics initiative evidence based drug therapy. COX-2 inhibitors update: Do journal publications tell the full story? Therapeutic letter 2001-2002; 43 (Nov/Dec/Jan).
21. Peterson LW, Cryer B. COX-1 Sparing NSAIDs-Is the enthusiasm justified? JAMA 1999; 282:1961-1963.
22. Jones R. Efficacy and safety of COX-2 inhibitors. New data are encouraging but the risk: benefit ratio remains unclear. BMJ 2002; 325: 607-608.
23. Graham DJ, Campen D, Cheetham C et al. Risk of acute cardiac events among patients treated with cyclooxygenase-2 selective and non-selective nonsteroidal antiinflammatory drugs. Pharmacoepidemiol. & Drug Safety 2004; 13: S 287(abstr.).
24. McCormack JP, Rangno R. Digging for data from the COX-2 trials (Letter). CMAJ 2002; 166: 1649-1650.
25. Donabedian A. Aspects of medical care administration. Harvard University Press, Cambridge 1973.
26. Rothman KJ, Greenland S. Modern Epidemiology. 2nd Edition. 1998. Lippincott-Raven Publishers.
27. Von Korff M, Wagner E, Saunders K. A chronic disease score from automated pharmacy data. J. Clin. Epidemiol. 1992;45: 197-203.