Utilization and Cost Comparison of Current and Optimal Prescribing of Nonsteroidal Antiinflammatory Drugs in Quebec, Canada

ELHAM RAHME, YOUSSEF TOUBOUTI, and JACQUES LELORIER

ABSTRACT. ***Objective***. Clinical practice guidelines recommend prophylactic use of gastroprotective agents (GPA) with nonselective nonsteroidal antiinflammatory drugs (nsNSAID) for patients at risk of gastrointestinal (GI) complications. We estimated the costs of cyclooxygenase-2 selective inhibitors, nsNSAID, and concurrent GPA prescribed in 2002 in Quebec, Canada, and compared these to estimated costs if prescribing followed guideline recommendations.

Methods. We used the Quebec government medical and pharmaceutical claims database (RAMQ). All prescriptions for NSAID and concurrent GPA dispensed between January 1 and December 31, 2002, were evaluated for continuously covered beneficiaries 18 years of age or older. Prescriptions were stratified by patient GI risk factors determined at the dispensing date of each prescription into low-, moderate-, elevated-, and high-risk categories. Five scenarios of "appropriate" NSAID therapy were identified using clinical practice guidelines. The potential effect on the prescription drug budget of implementing each of these scenarios was estimated.

Results. In total, 503,671 patients filled 1,863,171 prescriptions for NSAID, representing 41.1 million days of treatment with total expenditures of about $94 million CDN for NSAID and concurrent GPA. Average actual daily costs for coxibs (rofecoxib and celecoxib), celecoxib, nsNSAID, and concurrent GPA were $1.94, $2.06, $1.19, and $2.30, respectively. Prescribing nsNSAID with GPA to all patients at moderate and elevated risks while prescribing NSAID without GPA to patients at low risk, and celecoxib with a GPA to patients at very high risk would have cost $36.4 million more, mainly due to the additional cost of GPA.

Conclusion. Compared to actual prescribing patterns, a prescribing strategy consistent with clinical practice guidelines can increase drug acquisition costs to the healthcare payer. (J Rheumatol 2006; 33:588–96)

Key Indexing Terms:
COST ANALYSIS CYCLOOXYGENASE-2 INHIBITORS ANTI-ULCER AGENTS
NONSTEROIDAL ANTIINFLAMMATORY AGENTS PRESCRIPTIONS

Although clinical practice guidelines recommend nonsteroidal antiinflammatory drugs (NSAID) for treatment of pain in chronic conditions such as arthritis[1-4], it has long been known that use of nonselective NSAID (nsNSAID) increases the risk of upper gastrointestinal (GI) adverse events[5-7]. These can severely impair patient quality of life[8] at an increased cost of 2 to 8 times the cost of nsNSAID therapy itself[9].

Risk factors for nsNSAID-related upper GI events include a history of peptic ulcer disease, concurrent use of aspirin, anticoagulants or corticosteroids, and advanced age[10]. In addition, while controversy exists regarding the impact of concurrent illness on the risk of NSAID-related GI events, the presence of a significant comorbid condition will increase the risk of death in patients who actually develop a GI complication[10]. To reduce the burden of upper GI events due to NSAID, clinical practice guidelines recommend that patients with GI risk factors treated with nsNSAID should receive prophylaxis with a gastroprotective agent (GPA), including misoprostol, proton pump inhibitors, and histamine-2 receptor antagonists (H2RA)[1-4,11,12]. Alternatively, these guidelines recommend use of cyclooxygenase-2-selective inhibitors (coxibs). Currently, celecoxib is the only coxib covered by the government drug plan in Quebec, Canada. Celecoxib has similar efficacy to nsNSAID but fewer GI side effects[13,14]. Recently, a clinical trial found an increased risk of thromboembolic events with celecoxib compared to placebo[15]; however, other published evidence does not indicate that this risk differs for celecoxib compared to nsNSAID or placebo[16-21].

Despite recommendations to prescribe either a GPA with an nsNSAID or a coxib for patients at risk of GI side effects,

From the Department of Medicine, McGill University, and the Research Institute, McGill University Health Centre; and the Groupe de recherche en pharmacoépidémiologie et pharmacoéconomie, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada.

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E. Rahme, PhD; Y. Toubouti, MSc, Department of Medicine, McGill University and the Research Institute, McGill University Health Centre; J. LeLorier MD, PhD, Groupe de recherche en pharmacoépidémiologie et pharmacoéconomie, CHUM.

Address reprint requests to E. Rahme, Division of Clinical Epidemiology, Montreal General Hospital, 1650 Cedar Avenue, L10-408, Montreal, Quebec H3G 1A4. E-mail: elham.rahme@mcgill.ca

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studies have reported underutilization of these gastroprotective strategies in clinical practice[22-26]. Such failure to consider GI risk factors when prescribing nsNSAID likely accounts for a major share of the medical and economic burden of NSAID-related gastropathy.

Prescribing coxibs without regard to GI risk factors also imposes unnecessary costs on healthcare budgets. Although celecoxib is not medically contraindicated for patients who have no GI risk factors, nsNSAID without GPA are an appropriate treatment option for these patients[11,12]. Economic models indicate that celecoxib is not as cost-effective in patients without GI risk factors as nsNSAID that have lower acquisition costs[27-29]. Nevertheless, coxibs are often prescribed to low-risk patients[24,30,31].

We compared the GI risk profiles of users of NSAID [rofecoxib, celecoxib, and non-aspirin nsNSAID (hereafter nsNSAID)] using data obtained from the prescription drug and physician claims databases of the Quebec government health agency, the Régie de l'Assurance Maladie du Québec (RAMQ). Direct costs of NSAID were compared with estimates for 5 scenarios of "appropriate" NSAID prescribing to estimate the potential effect on the drug plan budget of bringing NSAID prescribing into conformity with clinical practice guidelines.

MATERIALS AND METHODS

Study design. We used the RAMQ pharmaceutical and medical services administrative database for the period from January 1, 2001, through December 31, 2002. RAMQ covers physician visits and medical services provided by clinics and hospitals for all Quebec residents. As of July 1, 2002, 7.3 million individuals were covered by RAMQ for their medical services[32]. RAMQ also covers the cost of prescription drugs for residents 65 years of age or older, social assistance recipients, and those without access to private drug plan coverage. RAMQ has provided unrestricted coverage of celecoxibs since October 1999 and provided unrestricted coverage of rofecoxib from April 2000 until September 30, 2004, when Merck & Co., Inc. announced the voluntary worldwide withdrawal of rofecoxib from the market in response to new clinical trial results that indicated an increased relative risk for confirmed cardiovascular (CV) events[33]. RAMQ also provides unrestricted coverage of GPA. In October 2004, a generic version of omeprazole was added to the provincial drug formulary. The acquisition cost per 20 mg capsule is $1.25 CDN for generic omeprazole and $2.20 for the brand-name drug[34]. In 2002, about 3.2 million individuals had RAMQ drug coverage[35-37]. Data in the RAMQ database have been validated and found to be accurate and reliable[38].

Data. Demographic, prescription drug, and medical services data were retrieved for all patients in the RAMQ database aged 65 years or older, and a 25% random sample of those aged 18 to 64 years. All prescriptions for NSAID dispensed between January 1 and December 31, 2002, were evaluated for those individuals who were covered for at least one year prior to the prescription. The one year requirement was necessary to provide sufficient prior data to assess GI risk level at the time of the prescription.

Encrypted patient identification codes permitted matching of prescription data to patient medical records. For each prescription, the preceding year of data was used to assess patient GI risk factors. RAMQ procedure codes, prescription records, and International Classification of Diseases, 9th Revision (ICD-9) codes[39] were used to identify risk factors. The derivation of patient characteristics and risk factors is shown in Table 1.

Gastrointestinal risk categories. Prescriptions were stratified by patient GI risk factors into one of 4 mutually exclusive categories: low risk, moderate risk, elevated risk, and high risk (Table 2). Criteria for GI risk and appropriate NSAID therapy for each category were determined prospectively using clinical practice guideline recommendations. When evidence was uncertain or guidelines differed concerning a GI risk factor, that factor was assigned to the lowest applicable risk category. For example, Hunt, *et al* listed age 60 years and older as a risk factor[11], whereas Dubois, *et al* specified 65 years and older[12]. In this study, therefore, age 60 to 64 years was not considered a GI risk factor and did not lead to a higher-risk categorization. Because guidelines are not unanimous about appropriate NSAID prescribing, different scenarios of appropriate prescribing were modeled.

Prescriptions for patients with no identified GI risk factors were assigned to the low-risk group. For these patients, guidelines judge nsNSAID to be appropriate therapy, and although celecoxib is not medically inappropriate for this group, it is uncertain whether its GI benefit justifies the higher acquisition cost[2,11,12]. As a result, in this study nsNSAID therapy was the only therapy considered to be appropriate for low-risk patients.

Guidelines differ on criteria for intermediate GI risk, so 2 intermediate risk categories were created, moderate risk and elevated risk. As shown in Table 2, the moderate-risk category was characterized by any one of the following risk factors: age 65 to 69 years, a prior uncomplicated GI event, chronic obstructive pulmonary disease, diabetes, or concomitant use of low-dose acetylsalicylic acid (ASA). A prior uncomplicated GI event was inferred from a record in the year preceding each NSAID dispensing date of an upper digestive tract examination or dispensing of a GPA. Three alternative NSAID-prescribing scenarios were considered to be appropriate for the moderate-risk category: celecoxib or a nsNSAID with or without a GPA[2,11,12,40].

Patients in the elevated-risk category had either 2 or more risk factors from the moderate-risk category or a single risk factor judged to be more serious than those in the moderate-risk category: multiple concomitant NSAID use, more advanced age (≥ 70 yrs), concomitant use of systemic corticosteroids, or an episode of perforation, ulcer or bleeding that did not require hospitalization. Three gastroprotective strategies were considered appropriate therapeutic options for the elevated-risk category: celecoxib alone, celecoxib with a GPA, or nsNSAID with a GPA[2,11,12,40].

The high-risk category comprised patients receiving anticoagulants or those who had been admitted to hospital for perforation, ulcer, or bleeding in the prior year[11]. Concurrent therapy with celecoxib and a GPA was considered the only appropriate therapy for patients in the high-risk category[12,40,41].

Analyses. Each filled prescription for an NSAID was assigned to a risk category according to patient GI risk level at the prescription filling date. Each prescription was assigned to only one risk category, the highest applicable. For example, a prescription for a patient with GI risk factors that would satisfy criteria for the moderate-, elevated-, and high-risk categories would be assigned to the high-risk category. Concurrent GPA use, defined as dispensing of a GPA at the same dispensing date as the NSAID, was also assessed. Drug acquisition costs were calculated for each prescription from records in the pharmaceutical services database. Only costs for NSAID and concurrent GPA were considered. A concurrent GPA was a GPA dispensed at the same date as the NSAID. All costs are reported in Canadian dollars. Costs included the cost of medication reimbursed by the RAMQ, patient co-payments, and pharmacist dispensing fees. Because the study cohort included a 25% random sample of enrolees 18 to 64 years of age, the cost of drugs prescribed to patients in this age group were multiplied by 4. Costs were aggregated by patient GI risk level into the 4 GI risk categories. For each group of medications (i.e., all coxibs, celecoxib alone, nsNSAID, or GPA), mean daily costs were calculated as the total cost for all prescriptions in that group filled in 2002 divided by the total number of days of corresponding medication supplied in 2002.

Estimated total costs of concurrent GPA were obtained in 2 ways: first, using the average actual daily concurrent GPA cost for 2002 estimated from the data (total GPA cost divided by the total number of days of GPA dispensed, multiplied by the number of days dispensed for the corresponding NSAID); and second, assuming that all GPA prescriptions would be for generic omeprazole, at a daily cost of $1.25 plus the average pharmacist dispensing fee for GPA in 2002 ($1.25 plus total pharmacist fees for all GPA dis-

Table 1. Sources of variables associated with NSAID prescriptions.

Variable	Source
Age	Year of dispensing minus year of birth
Socioeconomic status	Social assistance (yes/no) for patients aged 18–64 yrs and guaranteed income supplement (yes/no) for those ≥ 65 yrs
Prescriber specialty	Rheumatologist, general practitioner, or other, for the evaluated NSAID prescription
Rheumatoid arthritis or osteoarthritis	Diagnostic code in the year preceding the dispensing date
COPD	Diagnostic code in the year preceding the dispensing date
Diabetes	Drug code (metformin, hypoglycemic agent, insulin) in the year preceding the dispensing date
Ischemic heart disease	Diagnostic code in the year preceding the dispensing date
Cardiac insufficiency	Diagnostic code in the year preceding the dispensing date
Concomitant use of low-dose ASA	ASA ≤ 325 mg/day overlapping the dispensing date
Concomitant use of a systemic corticosteroid	Drug code in the 3 mo preceding the dispensing date
Concomitant use of an anticoagulant	Drug code (warfarin) in the 3 mo preceding the dispensing date
Multiple NSAID	Two different drug codes for nsNSAID in the year preceding the dispensing date
Concurrent GPA (PPI, H2RA, misoprostol)	Drug code at the dispensing date
Prior use of anti-ulcer drugs (PPI, H2RA, misoprostol, or sucralfate)	Drug code in the year preceding the dispensing date
Upper digestive tract examination	Claim for an endoscopic or barium examination in the year preceding the dispensing date
Outpatient clinic diagnosis of gastric or duodenal PUB	Outpatient clinic diagnostic code in the year preceding the dispensing date
Hospitalization for gastric or duodenal PUB	Hospital center diagnostic code in the year preceding the dispensing date

ASA: acetylsalicylic acid; COPD: chronic obstructive pulmonary disease; GPA: gastroprotective agent; H2RA: H2-receptor antagonist; NSAID: nonsteroidal antiinflammatory drug; nsNSAID: nonselective NSAID; PPI: proton pump inhibitor; PUB: perforation, ulcer, or bleeding.

pensed divided by the number of GPA prescriptions dispensed, multiplied by the number of days dispensed for the corresponding NSAID).

Actual acquisition costs were compared with estimated costs under 5 scenarios of appropriate NSAID prescribing according to the GI risk criteria listed in Table 2. In all 5 scenarios, nsNSAID alone was the only appropriate therapy for patients in the low-risk group, and celecoxib plus GPA was the only appropriate therapy in the high-risk group. The scenarios differed only by the following prescriptions in the moderate- and elevated-risk groups, respectively:

Scenario 1: Celecoxib; Celecoxib
Scenario 2: Celecoxib; Celecoxib and GPA
Scenario 3: nsNSAID and GPA; nsNSAID and GPA
Scenario 4: nsNSAID; nsNSAID and GPA
Scenario 5: nsNSAID; Celecoxib

Costs were projected for each scenario by multiplying the observed total days of medication supplied within each GI risk group in 2002 by the average daily acquisition cost for appropriate treatments.

RESULTS

Baseline characteristics of NSAID users. A total of 4,462,731 prescriptions for NSAID filled by 503,671 patients (of whom 225,851 were 65 yrs of age or older) were evaluated. Table 3 shows that patients who received coxibs were older, more likely to be female, and more likely to receive social assistance than those who received nsNSAID. Coxib recipients had more concomitant prescriptions for medications known to increase the risk of NSAID-related gastropathy — corticosteroids, anticoagulants, and ASA — than recipients of nsNSAID. Prior acetaminophen use was also more prevalent among coxib than nsNSAID recipients. A higher percentage of coxib recipients than nsNSAID recipients suffered from arthritis or a serious comorbid condition (diabetes, a cardiovascular disorder, or chronic obstructive pulmonary disease), or had experienced a GI event in the prior year.

A higher percentage of coxib users than nsNSAID users (53% vs 39%, respectively) were in the elevated- or high-risk categories (Figure 1); coxib recipients were more likely to fill a concurrent GPA prescription than nsNSAID recipients (11.0% vs 7.5%). Even within a given GI-risk category, the prevalence of concurrent GPA use was similar or higher among coxib users than nsNSAID users (Figure 2). Among all NSAID users in the high-risk category, only 19% filled GPA prescriptions with their first prescription in 2002 for an

Table 2. Criteria of GI risk levels and appropriate NSAID use according to GI risk factor.

Risk Level	Criteria	Appropriate NSAID Prescription
Low	No identified risk factor	nsNSAID[2,11,12,40] Coxib[2,11,12,40]
Moderate	Presence of only one of the following risk factors: • Age 65–69 yrs[10,11,47] • Upper digestive tract examination in the year preceding dispensing date[3,10,11] • Dispensing of a PPI, H2RA, misoprostol, or sucralfate in the year preceding dispensing date[10,47] • Serious comorbid conditions: COPD, diabetes[3,10] • Concomitant use of ASA (low dose)[3,10,11,40,48]	nsNSAID & GPA[2,12,40] nsNSAID[11]
Elevated	Presence of at least one of the following risk factors: • Two or more factors in the moderate risk category[11] • Use of ≥ 2 NSAID in the year preceding dispensing date[11] • Age ≥ 70 yrs[3,10,11,47] • Concomitant use of a systemic corticosteroid[3,10,11,47] • Outpatient clinic diagnosis of gastric or duodenal PUB in the year preceding dispensing date[3,10,11,47]	Coxib[2,11,12,40] nsNSAID & GPA[2,11,12] Coxib & GPA[11]
High	Presence of at least one of the following risk factors: • Concomitant anticoagulant use[3,10,11] • Hospitalization for gastric or duodenal PUB in the year preceding dispensing date[3,10,11,47]	Coxib & GPA[12,40,41]

ASA: acetylsalicylic acid; COPD: chronic obstructive pulmonary disease; GPA: gastroprotective agent; H2RA: H2-receptor antagonist; NSAID: nonsteroidal antiinflammatory drug; nsNSAID: nonselective NSAID; PPI: proton pump inhibitor; PUB: perforation, ulcer, or bleeding.

NSAID (their index date) and 40% had a GPA prescription dispensed prior to the index date with days of GPA supplied including the index date.

Cost of actual and optimal NSAID prescribing. RAMQ beneficiaries generated total expenditures of about $94 million for NSAID and concurrent GPA in calendar year 2002 (Table 4). Prescriptions in the elevated-risk group were responsible for 66% of costs, with the low-, moderate-, and high-risk groups accounting for 14%, 18%, and 3% of costs, respectively. In all GI-risk groups, coxibs comprised the greatest proportion of costs. The cost of concurrent GPA exceeded expenditures on nsNSAID in the moderate-, elevated-, and high-risk groups, but the reverse was true for the low-risk category. The proportion of costs allocated to concurrent GPA increased with increasing GI risk, from 3% in the low-risk group to 30% in the high-risk group. Overall, coxibs, nsNSAID, and concurrent GPA accounted for 67%, 11%, and 22%, respectively, of the total cost of these medications. Coxibs were responsible for 86% and nsNSAID for 14% of the about $73 million expenditures for all NSAID. Mean daily costs for coxibs, celecoxib, nsNSAID, and GPA were $1.94, $2.06, $1.19, and $2.30, respectively. Average daily cost of generic omeprazole was estimated at $1.41.

Predicted budgetary effect of 5 different scenarios of appropriate NSAID prescribing is shown in Table 5. As previously described, in all 5 scenarios, patients in the low-risk group received only nsNSAID, while those in the high-risk group received celecoxib with concurrent GPA. In scenario 1, celecoxib was prescribed for all patients at moderate and elevated GI risk. This scenario saved more than $12.2 million compared to actual prescribing in 2002, primarily due to reduced expenditures on GPA. The savings would increase to $13.2 million if generic omeprazole were used for all GPA prescriptions. Scenario 2 differed in that patients in the elevated-risk group received concurrent GPA in addition to celecoxib. Costs in this scenario were about $49.9 million higher than actual prescribing as a result of large increases in GPA expenditure. The cost increase would be $24.3 million with use of generic omeprazole. Scenario 3 differed from the first 2 scenarios in that patients in the moderate- and elevated-risk groups received nsNSAID with GPA and no celecoxib. In this scenario, costs were about $36.4 million higher than actual prescribing, because substantial savings on coxibs were more than offset by higher expenditures for GPA and nsNSAID. This cost increase was $4.6 million with the use of generic omeprazole. When this scenario was altered so that GPA were not prescribed to patients in the moderate-risk group (scenario 4), costs were about $20.8 million higher than actual prescribing, but there would be a cost savings of $4.9 million relative to actual prescribing if generic omeprazole were used for all GPA prescriptions. Finally, if nsNSAID without GPA was chosen as an appropriate option for patients at moderate GI risk and celecoxib was given to patients at elevated GI risk as per scenario 5, coxib and GPA expenditures would be reduced for a net savings of $18.0 million, or $19.0 million with use of generic omeprazole.

Table 3. Baseline characteristics of patients who were prescribed coxibs and nsNSAID.

	Coxibs	nsNSAID
No. of patients	334,418	169,253
Age ≥ 65 yrs, %	53.5	27.7
Women, %	65.2	57.3
Receiving guaranteed income supplement or social assistance, %	41.4	34.5
Concomitant corticosteroid use, %	2.3	2.0
Concomitant anticoagulant use, %	1.9	0.8
Concomitant ASA (low-dose), %	18.0	9.5
Prescriptions in the preceding year, %		
Acetaminophen	26.4	19.1
nsNSAID	8.5	32.4
Coxib	50.2	13.7
Antihypertensive agents	37.5	22.5
Antidiabetic agents	10.1	6.7
Prescriber, %		
Rheumatologist	2.7	1.8
General practitioner	86.9	87.2
Other	10.4	11.0
Diagnosis in the preceding year, %		
Rheumatoid arthritis	2.5	1.8
Osteoarthritis	18.5	8.4
Ischemic heart disease	11.4	6.2
Cardiac insufficiency	5.7	3.0
COPD	5.1	2.8
GI event in the preceding year, %	33.7	21.4
Hospitalization for PUB	0.6	0.4
Upper GI tract examination	5.3	3.4
Outpatient clinic diagnosis of PUB	1.1	0.7
Anti-ulcer treatment	30.0	18.3
PPI prescription	25.3	14.5
Visit to a gastroenterologist	6.9	4.6
GPA dispensed at the index date*, %	11.0	7.5

ASA: acetylsalicylic acid; COPD: chronic obstructive pulmonary disease; GPA: gastroprotective agent; NSAID: nonsteroidal antiinflammatory drug; nsNSAID: nonselective NSAID; PPI: proton pump inhibitor; PUB: perforation, ulcer, or bleeding. * The index date is the dispensing date of the patient's first prescription in 2002 for a coxib or nsNSAID.

DISCUSSION

Under actual prescribing patterns in Quebec in 2002, a larger proportion of patients receiving coxibs (71.7%; Figure 1) was at higher risk for GI events than patients receiving nsNSAID (50.9%; Figure 1). This agrees with findings of a regression analysis that used the same RAMQ database to evaluate prescriptions for Quebec seniors in 2000[26], and results of studies conducted elsewhere[24,42]. These results suggest that prescribing decisions of Quebec physicians are influenced by clinical practice guidelines that recommend coxibs for patients at risk for NSAID-related gastropathy. However, only 19% of patients in the high-risk group filled a GPA prescription at the index date, and 40% had a concomitant GPA prescription overlapping the index date for both coxibs and nsNSAID (Figure 2). This indicates inadequate recognition of the need for gastroprotection among high-risk patients, and also suggests that physicians may not distinguish between coxibs and nsNSAID for their patients who use GPA. Conversely, potentially unnecessary use of GPA among coxib users in the moderate-risk category was relatively high: nearly 14% of these patients filled a GPA prescription at the index date and 25% had a concomitant GPA prescription overlapping the index date.

The majority of costs for non-ASA NSAID in this study were for coxibs (86%). This is a higher percentage than the 64% of Canada-wide non-ASA NSAID sales that these 2 drugs were responsible for in the year ending February 29, 2004[43]. The rate of prescribing coxibs was higher in Quebec, where their drug-plan coverage is unrestricted, than in other Canadian provinces, many of which have restricted coverage. In 2000, a US study of Medicare enrolees with osteoarthritis found that the prevalence of coxib use increased with increasing generosity of drug coverage[42]. When 76% to 100% of annual drug spending was paid by insurance, prevalence of coxib use was 2.2 times higher than among Medicare enrolees with no drug coverage. These findings suggest that the patterns of NSAID prescribing observed among RAMQ benefi-

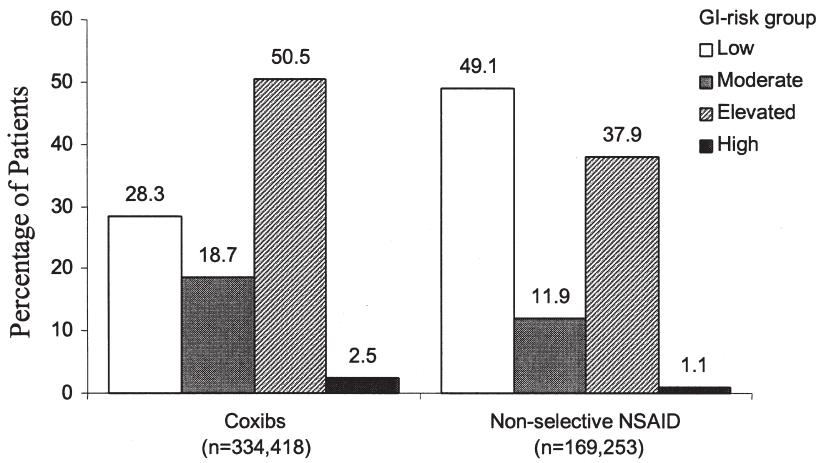

Figure 1. Distribution of coxib and nsNSAID recipients by level of risk for NSAID-related gastropathy. GI: gastrointestinal; NSAID: nonsteroidal antiinflammatory drug. For definitions of GI risk levels see Table 2.

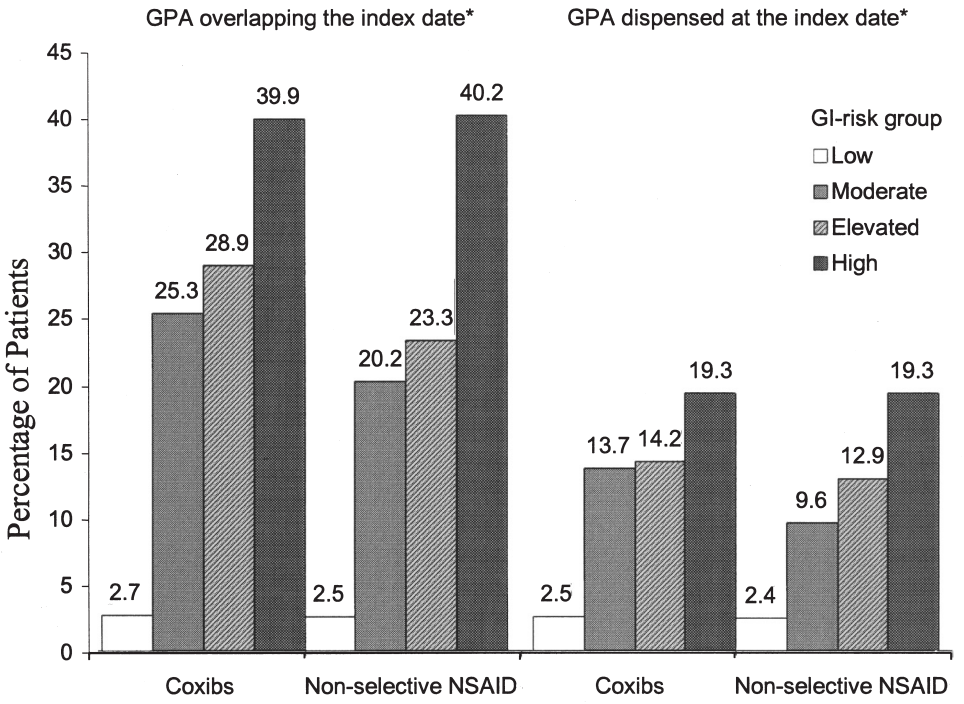

Figure 2. Prevalence of concurrent GPA use among coxib and nsNSAID recipients by level of risk for NSAID-related gastropathy. GI: gastrointestinal; GPA: gastroprotective agent; NSAID: nonsteroidal antiinflammatory drug. For definitions of GI risk levels see Table 2. *The index date is the dispensing date of the patient's first prescription in 2002 for a coxib or nsNSAID.

Table 4. Costs of NSAID prescriptions in the RAMQ database by prescription type and GI-risk group.

	GI-Risk Group				
	Low	Moderate	Elevated	High	Total
No. of dispensations	365,244	289,330	1,158,719	49,878	1,863,171
Coxibs	250,808	254,403	824,860	42,709	1,372,780
nsNSAID	114,436	34,927	333,859	7,169	490,391
No. of days of treatment dispensed	6,697,952	6,651,729	26,702,735	1,051,764	41,104,180
Coxibs	5,473,744	6,181,636	19,755,619	919,719	32,330,718
nsNSAID	1,224,208	470,093	6,947,116	132,045	8,773,462
Actual acquisition cost ($CDN)					
Coxibs	10,957,887	12,161,246	37,707,771	1,746,889	62,573,793
nsNSAID	1,614,460	591,090	8,076,162	156,940	10,438,652
Concurrent GPA	343,430	3,885,576	15,594,127	825,485	20,648,618
Total	12,915,777	16,637,912	61,378,060	2,729,314	93,661,063

GI: gastrointestinal; GPA: gastroprotective agent; NSAID: nonsteroidal antiinflammatory drug; nsNSAID: nonselective NSAID.

ciaries may not apply in other jurisdictions that have different drug reimbursement programs.

Despite already high celecoxib utilization in Quebec, comparison of actual and appropriate medication expenditures for 2002 indicates that prescribing celecoxib to more patients with GI risk factors may actually decrease costs for the provincial drug plan by reducing the number of patients receiving more costly combination therapy with nsNSAID and GPA. The daily cost of combination therapy was $0.54 higher than that of celecoxib even if the newly available generic omeprazole was chosen for all GPA prescriptions. Replacing celecoxib with nsNSAID among low-risk patients who do not require concurrent GPA can also reduce costs.

The budgetary impact of appropriate NSAID prescribing depended on which of several possible appropriate treatment strategies were modeled. In all scenarios, patients at low GI

Table 5. Actual costs versus estimated costs for appropriate NSAID prescribing.

Scenario*		nsNSAID	Coxibs	GPA (actual)	Generic Omeprazole	Total with Actual GPA use	Total with Generic Omeprazole
Actual	Costs	10,438,652	62,573,793	20,648,618	NA	93,661,063	NA
1	Costs	7,983,959	70,980,048	2,449,558	1,477,728	81,413,565	80,441,735
	Budgetary impact	–2,454,693	8,406,255	–18,199,060	–19,170,890	–12,247,498	–13,219,328
2	Costs	7,983,959	70,980,048	64,640,228	38,995,071	143,604,235	117,959,078
	Budgetary impact	–2,454,693	8,406,255	43,991,610	18,346,453	49,943,172	24,298,015
3	Costs	47,742,480	2,169,789	80,132,105	48,340,750	130,044,374	98,253,019
	Budgetary impact	37,303,828	-60,404,004	59,483,487	27,692,132	36,383,311	4,591,959
4	Costs	47,742,480	2,169,789	64,640,228	38,995,071	114,552,497	88,907,340
	Budgetary impact	37,303,828	–60,537,841	43,991,610	18,346,453	20,757,597	–4,887,560
5	Costs	15,912,820	57,257,531	2,449,558	1,477,728	75,619,909	74,648,079
	Budgetary impact	5,474,168	–5,316,262	–18,199,060	–19170,890	–18,041,154	–19,012,984

GPA: gastroprotective agent; NSAID: nonsteroidal antiinflammatory drug; nsNSAID: nonselective NSAID. * Appropriate prescriptions for low, moderate, elevated, and high GI-risk levels are, respectively: Scenario 1: nsNSAID; Celecoxib; Celecoxib; Celecoxib & GPA. Scenario 2: nsNSAID; Celecoxib; Celecoxib & GPA; Celecoxib & GPA. Scenario 3: nsNSAID; nsNSAID & GPA; nsNSAID & GPA; Celecoxib & GPA. Scenario 4: nsNSAID; nsNSAID; nsNSAID & GPA; Celecoxib & GPA. Scenario 5: nsNSAID; nsNSAID; Celecoxib; Celecoxib & GPA.

risk received only nsNSAID and those at high risk received celecoxib plus GPA. The most expensive scenario of appropriate prescribing was when celecoxib was used by patients in the moderate-risk group and celecoxib with GPA by those in the elevated-risk group. This strategy would have cost $49.9 million more than actual prescribing in 2002. The least expensive scenario of appropriate prescribing was when nsNSAID alone were prescribed to patients at moderate GI risk and celecoxib to those at elevated risk. This strategy would have saved an estimated $18.0 million compared to actual prescribing in 2002. However, some guidelines do not recommend nsNSAID without gastroprotection for patients with risk factors corresponding to the moderate-risk category in this study[2,11,12]. Of the 2 gastroprotective strategies, celecoxib was less costly than nsNSAID plus GPA. It should be noted, however, that the expenditures for the different prescribing scenarios depend critically on the costs of these medications, which can differ regionally and over time.

These simulations agree with pharmacoeconomic analyses of coxib therapy in the US and Canada that report lower daily acquisition costs for coxibs than nsNSAID plus GPA[27,44,45]. This study assessed only costs of non-ASA NSAID and GPA, whereas previous cost-effectiveness studies have included treatment costs for GI complications of NSAID therapy[27-29,44,45]. However, the conclusion of previous studies that the cost-effectiveness of coxibs compared to nsNSAID is sensitive to the rate of GPA co-prescription and patient GI-risk level is acknowledged in these simulations by considering coxibs and GPA to be inappropriate prescribing options for low-risk patients.

In our study, concurrent therapy with a coxib and a GPA was considered appropriate only for patients in the elevated- and high-risk category. It should be noted, however, that authors of some recent reviews have concluded that coxib-GPA co-prescriptions are advisable for patients with certain combinations of risk factors that we classified in the moderate-risk category, including patients who use ASA and have one other GI risk factor[12,40,41]. This prescribing strategy would greatly increase overall treatment costs.

Strengths of this study include the use of a comprehensive, validated administrative database for drug costs and medical service utilization. Data for the appropriate prescribing scenarios were derived from actual population risk factors and real average daily drug costs rather than clinical trial data that may not reflect real-world clinical practice. Nevertheless, this study has limitations. A comparison of RAMQ claims data and medical chart review found that the RAMQ database does not capture all cases of diagnosed illness[46]. For example, 28% of patients with chart-documented peptic ulcer and 64% of those with diabetes can be detected using diagnostic codes in the RAMQ claims data. This weakness was partially addressed by inferring some medical conditions — including prior GI disease and diabetes — from drug claims data. However, sensitivity limitations remained for other medical conditions that were scored on the basis of diagnostic codes, such as chronic obstructive pulmonary disease, for which 46% of chart-documented cases are identifiable from the RAMQ database[46]. Our study may therefore underestimate the level of GI risk among NSAID recipients in Quebec.

Another limitation is that over-the-counter medication purchases are not recorded in the RAMQ database, so nonprescription use of nsNSAID and GPA was not accounted for (coxibs are only available by prescription in Quebec). According to Santé Québec, a government health agency, in 2000 17.0% and 1.1% of elderly residents who consumed nsNSAID or GPA, respectively, acquired them over the counter[26]. Our study considered only patients with a prescription for an NSAID or a coxib, who are less likely to also use over-the-counter NSAID, and patients have a financial incentive to

obtain nsNSAID and GPA by prescription since prescriptions are covered by RAMQ.

Because risk categories were assessed separately for each prescription on the basis of data in the year prior to the dispensing date, the risk category for sequential prescriptions for a given patient could change during the study period. The risk level for a given patient could increase as a result of new medical events during 2002, or decrease if an event occurred within one year preceding prescriptions early in 2002 but more than one year prior to later prescriptions. As a consequence of the latter possibility, more prescriptions may have been allocated to a lower risk category than would have been the case had all risk factors been counted for all prescriptions for a given patient. However, the one-year window for counting risk factors ensured that all prescriptions were evaluated on the same basis.

An additional limitation is that only GPA dispensed at the dispensing date of an NSAID were included in cost calculations for actual prescribing patterns. This criterion was applied to increase the likelihood that only GPA used for NSAID-related GI prophylaxis were considered. However, this underestimates the total cost of GPA used for this purpose, because patients do not necessarily fill multiple prescriptions on the same date, and refill schedules may differ between NSAID and GPA.

As previously noted, the only expenditures assessed in this study were for coxibs, nsNSAID, and GPA. Changing prescribing patterns for these agents may result in different health outcomes, such as a change in the incidence of GI complications, and therefore have economic impact on the medical system beyond that considered here. Examination of these effects was beyond the scope of this analysis, but should be considered when making policy decisions to change prescribing patterns.

In conclusion, compared to actual prescribing patterns, tailoring prescriptions of coxibs, nsNSAID, and GPA to patient GI risk levels can potentially yield a substantial increase in drug acquisition costs to a healthcare payer depending on the choice of appropriate treatment: celecoxib, nsNSAID plus GPA, or celecoxib plus GPA.

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