

The rate of prescribing gastrointestinal prophylaxis with either a proton pump inhibitor or an H₂-receptor antagonist in Nova Scotia seniors starting nonsteroidal anti-inflammatory drug therapy

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BACKGROUND: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used agents that can cause serious gastrointestinal (GI) side effects. For patients at increased risk of NSAID-related GI complications, prophylaxis with either a nonselective NSAID plus gastroprotective agent (GPA) or, alternatively, therapy with a cyclooxygenase-2 selective inhibitor with or without a GPA such as a proton pump inhibitor (PPI), is recommended.

AIM: To describe the rate, timing and duration of GI prophylaxis in Nova Scotia seniors receiving nonselective NSAIDs.

METHODS: The Nova Scotia Seniors' Pharmacare Program beneficiaries for the years 1998 to 2002 were studied. A cohort of incident NSAID and GPA users was selected from all nonselective NSAID users (no prescribed NSAID dispensed 12 months before the index month and no GPA dispensed two months before the index prescription). Monthly coprescribing rates were calculated by dividing the number of patients in the cohort using GPAs by the number of NSAID users. GI prophylactic coprescribing was defined as the coprescribing rate present at the first month (index month) of prescribing an NSAID.

RESULTS: The cohort consisted of 12,906 patients. Seventy-five per cent of the nonselective NSAID prescriptions dispensed were for up to two months duration, with only 2.3% longer than one year. GI prophylaxis was given to only 3.8% of patients starting NSAIDs who were not on a GPA in the two months before starting NSAIDs. Of this 3.8%, 92.7% of the patients received H₂-receptor antagonists (H₂RAs), and 7% received PPIs. The rate of H₂RA coprescribing increased with the number of consecutive months on an NSAID from 3.5% in the first month to 24.1% at 48 months. For PPIs, the coprescribing rate increased from 0.3% to 1.9% of all NSAID users in the cohort. The rate of gastroprophylaxis coprescribing for patients receiving NSAIDs did not rise with increasing age.

CONCLUSION: In Nova Scotian seniors using nonselective NSAIDs, the rate of GI prophylaxis was low. Most patients received H₂RAs as GPAs despite evidence that they offer insufficient protection.

Key Words: Cohort study; Cyclooxygenase-2 selective inhibitor; Drug utilization; Gastrointestinal prophylaxis; Histamine-2 receptor antagonist; Misoprostol; Nonsteroidal anti-inflammatory drugs; NSAIDs; Proton pump inhibitor; Prescribing; Seniors

Le taux de prescription d'une prophylaxie gastro-intestinale au moyen d'un inhibiteur de la pompe à protons ou d'un antagoniste des récepteurs H₂ chez les personnes âgées de la Nouvelle-Écosse qui amorcent un traitement aux anti-inflammatoires non stéroïdiens

HISTORIQUE : Les anti-inflammatoires non stéroïdiens (AINS) sont des produits largement utilisés qui peuvent provoquer de graves effets secondaires gastro-intestinaux (GI). Chez les patients plus vulnérables aux complications GI liées aux AINS, une prophylaxie au moyen d'un AINS non sélectif associé à un agent gastroprotecteur (AGP) ou une thérapie au moyen d'un inhibiteur sélectif de la cyclo-oxygénase de type 2 associé ou non à un AGP comme un inhibiteur de la pompe à protons (IPP) est recommandée.

OBJECTIF : Décrire le taux, le moment et la durée de la prophylaxie GI chez des personnes âgées de la Nouvelle-Écosse qui reçoivent des AINS non sélectifs.

MÉTHODOLOGIE : Les bénéficiaires du programme d'assurance-médicaments pour les personnes âgées de la Nouvelle-Écosse entre 1998 et 2002 ont fait l'objet de l'étude. Les chercheurs ont sélectionné une cohorte d'utilisateurs concomitants d'AINS et d'AGP auprès de tous les utilisateurs d'AINS non sélectifs (aucun AINS prescrit dispensé 12 mois avant le mois de référence et aucun AGP dispensé deux mois avant la prescription de référence). Les taux mensuels de coprescription ont été calculés en divisant le nombre de patients de la cohorte utilisant des AGP par le nombre d'utilisateurs d'AINS. La coprescription de prophylactiques GI était définie comme le taux de coprescriptions présent le premier mois (mois de référence) de prescription d'AINS.

RÉSULTATS : La cohorte se composait de 12 906 patients. Soixante-quinze pour cent des prescriptions d'AINS non sélectifs dispensés l'étaient pour une durée maximale de deux mois, et seulement 2,3 % dépassaient un an. La prophylaxie GI n'était administrée qu'à 3,8 % des patients qui amorçaient les AINS et qui n'avaient pas pris d'AGP dans les deux mois précédents. De ces 3,8 %, 92,7 % des patients ont reçu des antagonistes des récepteurs H₂ (ARH₂), et 7 %, des IPP. Le taux de coprescription d'ARH₂ augmentait proportionnellement au nombre de mois consécutifs à prendre un AINS, passant de 3,5 % au cours du premier mois à 24,1 % au bout de 48 mois. Pour ce qui est des IPP, le taux de coprescription est passé de 0,3 % à 1,9 % de tous les utilisateurs d'AINS de la cohorte. Le taux de coprescription de gastroprophylaxie pour les patients qui recevaient des AINS n'augmentait pas avec l'âge.

CONCLUSION : Chez les personnes âgées de la Nouvelle-Écosse qui prenaient des AINS non sélectifs, le taux de prophylaxie GI était faible. La plupart des patients recevaient des ARH₂ comme AGP, malgré les données probantes indiquant qu'ils offrent une protection insuffisante.

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The risk of gastrointestinal (GI) complications attributable to nonsteroidal anti-inflammatory drugs (NSAIDs) varies according to the presence of one or more risk factors including advanced age, history of gastroduodenal ulcers, use of concomitant medications such as warfarin, acetylsalicylic acid and corticosteroids, concurrent diseases, use of higher doses of NSAIDs and duration of therapy (1-5). The RR of NSAID complications increases to 1.5 for individuals 60 to 69 years of age, and to 2.8 for patients 70 years of age and older compared with individuals younger than 65 years of age (6-8).

The recommended preventive treatment strategies for patients at increased risk of GI complications from NSAIDs are prophylaxis with gastroprotective agents (GPAs) or, alternatively, therapy with a cyclooxygenase-2 selective inhibitor (COXIB) with or without a proton pump inhibitor (PPI). Both approaches have demonstrated a similar risk reduction profile (9-11). The following GPAs have proven efficacy in decreasing the risk of gastroduodenal ulcers: once daily dosing with a PPI, misoprostol given in doses of 200 µg two to four times a day, and high-dose therapy with an H₂-receptor antagonist (H₂RA) (eg, famotidine 40 mg twice a day) (12,13). Importantly, the standard dose of H₂RA has not been shown to provide adequate protection (14). However, NSAID prophylaxis is often not prescribed when it is indicated (15-17). Underprescribing of GPAs, especially in older patients or those with other risk factors, can lead to serious GI complications, mainly upper GI bleeding from ulcers, which can result in hospital admissions, the need for surgery and death. On the other hand, overprescribing GPAs and COXIBs for individuals without risk factors exposes patients to the side effects of these drugs (18,19) and unnecessarily increases health care costs.

The objectives of the present study were to describe the rate, timing and duration of GI prophylaxis in Nova Scotia seniors (individuals older than 65 years of age) receiving non-selective NSAIDs.

METHODS

Study population

A retrospective drug claims database analysis of the Nova Scotia Seniors' Pharmacare Program (NSSPP) (www.gov.ns.ca/health/Pharmacare/seniors_pharmacare/seniors_pharmacare_q_n_a.asp) for the fiscal years 1998 to 2002 (April 1, 1998, to March 31, 2003) was conducted. More than 75% of Nova Scotia's seniors were eligible to participate in the NSSPP. During the period from 1998 to 2002, the number of eligible seniors in the NSSPP decreased from 92% (113,437 of 123,178) to 78% (101,010 of 128,908). This decrease was mainly due to a change in eligibility and cost-sharing requirements (20).

Beneficiaries pay a premium that is waived if the beneficiary receives the guaranteed income supplement from the federal government. Beneficiaries pay a copayment with a maximum annual copayment. All prescriptions are captured in the NSSPP database regardless of whether they are paid for by the Pharmacare program.

Drugs studied

The WHO Anatomical Therapeutic Chemical codes and drug identification numbers were used to identify the drugs selected for the present study. All nonselective NSAIDs marketed in Canada are listed in the formulary of the NSSPP. All NSAIDs

for which generic drugs were available were subject to the maximum allowable cost (MAC) policy. Under this policy, if the drug was available from multiple manufacturers, the maximum cost paid by Pharmacare was based on the lowest price among the interchangeable group of products. Beneficiaries must pay the difference between the total price for a drug and the MAC price for prescriptions covered under the MAC pricing policy. In addition, reimbursement of the MAC price started only when beneficiaries reached the yearly required deductible. Before reaching the deductible, beneficiaries must pay a portion of the entire cost of the prescription (16).

The COXIB drugs were included in the NSSPP formulary with a MAC stipulation on November 1, 1999, for celecoxib and on June 15, 2000 for rofecoxib. These two drugs were covered until rofecoxib was withdrawn from the market in September 2004. The use of acetylsalicylic acid was incompletely captured in this database because most seniors buy over-the-counter acetylsalicylic acid, which is less expensive than obtaining it by prescription.

Since 1992, PPIs have had specific criteria for reimbursement – in contrast to H₂RAs and misoprostol, which have no restrictions (21). Specific criteria for NSAID prophylaxis with PPIs included the following:

1. For the treatment of NSAID-induced complicated peptic ulcers (bleeding ulcer, perforation, etc) when the NSAID is discontinued. Coverage duration: up to eight to 12 weeks.
2. For the treatment and prophylaxis of NSAID-induced complications in patients who experienced previous NSAID-related ulcers or ulcer complications for which NSAID therapy cannot be discontinued. Coverage duration: while on NSAID or a maximum of one year with reassessment.
3. For the prophylaxis of NSAID-induced complications in patients who are at high risk.

For nonselective NSAIDs, the NSSPP covered ibuprofen for both the 300 mg and 400 mg doses. The NSSPP had a MAC policy for other NSAIDs including diclofenac, diflunisal, etodolac, fenoprofen, flectafenine, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, mefenamic acid, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, sulindac, tenoxicam, tiaprofenic acid and tolmetin. Acetylsalicylic acid 325 mg, 500 mg and 650 mg were also covered. Prescribing details of the different NSAIDs were not investigated in the present study.

High risk was defined as receiving NSAID therapy plus two other risk factors including advanced age (older than 65 years), and concomitant anticoagulant or oral corticosteroid therapy. Coverage duration was for the duration of NSAID therapy up to 12 months, after which a reassessment was required. The age of the patient being older than 65 years, by itself, was not a sufficient criterion to qualify for coverage.

Data analysis and patient cohort selection

The present study was approved by the Dalhousie Health Sciences Ethics Review Board (Halifax, Nova Scotia). Data were extracted from the Population Health Research Unit, which houses and administers the databases. Data were imported into a Microsoft Access (Microsoft Corporation, USA) database. Structured query language and visual basic

were used to analyze the data and patient cohort selection. SAS (www.ansi.org/) (SAS Inc, USA) statistical software was used for data extraction and regression analysis. Several analyses were performed.

Use rates of NSAIDs and GPAs

The use rates of NSAIDs and GPAs for all eligible Pharmacare beneficiaries were calculated. The yearly use rate of a particular drug was defined as the average of the monthly use rates – calculated by dividing the total number of individuals eligible for Pharmacare in the same month by the number of people using a particular medication.

Cohort selection

Cohort of incident NSAID users (incident NSAID, prevalent GPA cohort): A cohort of incident NSAID users was selected by eliminating all patients who never used an NSAID during the five-year study period. From the remaining sample, patients were required to be non-NSAID users in the 12 months before their index prescription (ie, the first NSAID prescription during the study period) and eligible for the Pharmacare program for at least 13 months (12 months before the index month plus at least the index month).

This cohort included patients who may have been taking a GPA at the time the NSAID was started. In this cohort, it was not possible to determine whether a decision was made to institute NSAID prophylaxis (ie, protecting the patients against upper GI complications) at the time the NSAID was started.

Cohort of incident NSAID and GPA users (incident NSAID, incident GPA cohort): This cohort was created from the incident NSAID cohort by eliminating patients who used GPAs in the two months before their index NSAID prescription. It was assumed that a decision for NSAID prophylaxis was made at the time the GPA was dispensed or within the first month of the NSAID dispense event. By eliminating individuals who used GPAs in the preceding two months, confounding by patients who started the GPA for reasons other than NSAID prophylaxis (eg, because of gastroesophageal reflux disease symptoms), was avoided. In this cohort, the effect of NSAID therapy duration on the rate of coprescribing was also analyzed, as was the effect of increasing age.

Duration of NSAID prescriptions

This analysis was performed in the incident NSAID incident GPA cohort. To classify NSAID prescriptions according to duration, it was necessary to eliminate prescriptions for which duration was uncertain. These prescriptions occurred either when patients were on an NSAID treatment course until the final month of the study period or when patients were on an NSAID treatment course when they lost their eligibility for the Pharmacare program. In both cases, these prescriptions may have continued but the data documenting their length were not available. After eliminating these 1560 prescriptions (original number of prescriptions = 18,265, with 16,725 after elimination), the proportion of NSAID prescriptions of a particular duration was calculated as the total number of prescriptions of a particular duration divided by the total number of treatment courses of all individuals in the cohort. An interval of at least one month without NSAIDs was used to separate the two treatment courses. The average duration of NSAID therapy was also calculated. Logistic regression was used to

calculate whether the OR of being coprescribed a GPA during an NSAID treatment course increased with each month of duration of NSAID therapy and whether the patient's age at the start of the prescription influenced initiation of a GPA.

Coprescribing rates

In both cohorts, coprescribing rates were calculated according to the type of GPA (H₂RA, PPI and misoprostol) and to age group. Coprescribing rates were calculated for each of the 48 months of NSAID prescriptions as the number of patients using one of the three GPAs in a particular month divided by the total number of NSAID users in the same month.

The prophylactic coprescribing rate is the rate at which GPAs were started at or within the first month (index month) as NSAIDs in the NSAID-GPA cohort. It is the coprescribing rate in the first month in the NSAID-GPA cohort.

A logistic regression analysis was performed to evaluate whether coprescribing changed with age. First, age was considered to be a continuous variable and calculated as the OR for being coprescribed in the index month over all age groups. All age groups were subsequently compared with the reference group (individuals 65 to 69 years of age).

In the present study, other risk factors for NSAID complications, such as the use of other antiplatelet agents, warfarin and corticosteroids, were not evaluated.

Analysis of prescription claims

Pharmacare eligibility data and prescription claims were combined into person-month records of use. For each individual, their period of Pharmacare eligibility (or the study start and end dates if their eligibility was covered by the entire study period) was divided into 30-day increments (study month) and numbered from the start date of the study period (April 1, 1998). The start and end dates of each prescription – based on prescription filled date and the days supply field – were indexed to study months in the same manner. These two sets of person-month records were combined, with use flagged in the study months covered by a prescription. It was only necessary that a supply of drugs was available at any point during the month – it was not necessary for drug supply to be available for the entire month.

Individual patient prescriptions were aggregated into treatment courses based on prescription dates and the dispensed days supply of those prescriptions. Each prescription was assumed to start on the date it was filled, and ended on the fill date plus the days supply. For scenarios in which there was a gap between the end of the nth prescription and the start of the nth+1 prescription of less than 30 days, patients were assumed to be taking the NSAID and/or GPA over the entire period but at less than the prescribed daily dose. For instances in which there was a gap of greater than 30 days, it was assumed that the patient had stopped taking NSAIDs/GPAs and the treatment course had ended. A patient's treatment course was defined as the period from the initial prescription to the end of the last prescription with less than a 30-day gap. Within the treatment course, the available days supply was adjusted for 'hoarding' (ie, refilling a prescription before the expected end date) and 'stretching' (ie, refilling a prescription after the expected end date). For the final prescription in a treatment course, the expected end date was adjusted according to the average ratio of the dispensed days supply to the interval between the nth and

TABLE 1
Yearly use rates* of gastroprotective agents, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 selective inhibitors (COXIBs) in Nova Scotia Seniors' Pharmacare Program beneficiaries (1998 to 2002)

Fiscal year	Eligible, n	Proton pump inhibitors, %	H ₂ -receptor antagonists, %	Misoprostol, %	Nonselective NSAIDs, %	COXIBs, %
1998	113,437	1.8	13.6	0.23	8.1	0
1999	110,188	2.5	14.4	0.25	7.3	1.2
2000	102,374	3.3	15.0	0.21	5.7	5.5
2001	101,439	4.0	15.1	0.19	5.1	6.4
2002	101,010	4.6	15.2	0.36	5.0	5.4

*Average of monthly use rates, which were calculated by dividing the number of people using a particular drug in a month by the total number of eligible Pharmacare beneficiaries in the same month

TABLE 2
Duration of therapy with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) in Nova Scotia Seniors' Pharmacare Program beneficiaries (cohort of incident NSAID incident gastroprotective-agent users)

Prescription duration, months	NSAID prescriptions, n (%)*
1	5438 (33.0)
2	7241 (43.0)
3	1184 (7.1)
≥4	2862 (16.9)
>1 year	378 (2.3)
Total	16725 (100.0)

*Based on total number of treatment courses – cohort of 12,906 incident non-selective NSAID incident gastroprotective-agent users followed for four years

nth+1 prescription observed within the treatment course. The start and end dates of each treatment course were used to define NSAID and/or GPA use within any study month.

Two methods were used to calculate the use rates for selected drugs. First, a yearly use rate was calculated by dividing the number of patients who had at least one drug prescription during the fiscal year by the total number of people eligible for Pharmacare in that year. Second, the yearly use rates were calculated as an average of monthly use rates, which were determined by dividing the number of people using a particular medication in a month by the total number of people eligible for Pharmacare in the same month. In the analysis, no adjustments were made for dose or duration of the NSAIDs prescribed. Any adjustments that may have occurred due to the changes in the eligibility criteria for seniors to receive Pharmacare coverage were not factored in the analysis. Information regarding the use of over-the-counter NSAIDs and H₂RAs was not tracked.

RESULTS

Use rates

The yearly use rates (based on average monthly use rates) of H₂RAs, PPIs, misoprostol, NSAIDs and COXIBs for NSSPP beneficiaries are shown in Table 1. PPI use rates increased from 1.8% in 1998 to 4.6% in 2002. There was a slight increase in the use of H₂RAs from 13.63% in 1998 to 15.21% in 2002. The use rate for misoprostol was very low (0.2% to 0.4%); factors affecting its use were not explored further. The rate of non-selective NSAID use decreased from 8.1% in 1998 to 5.0% in 2002. During this time, COXIB use increased from 0% in 1998

to a high of 6.4% in 2001. The total percentage of patients receiving either a nonselective NSAID or COXIB increased from 8.1% in 1998 to 11.5% in 2001.

Duration of NSAID prescriptions

Only 2.3% of NSAID prescriptions had a continuous duration of more than one year, while 76% of prescriptions were for two months duration or less (Table 2).

Coprescribing rates of NSAIDs and GPAs

A total of 40,511 patients received at least one prescription for a nonselective NSAID during the five-year study period. Using the specified inclusion criteria, a cohort of 16,240 incident NSAID users (incident NSAID, prevalent GPA cohort) was selected, with 3334 (21%) of these patients already receiving a GPA at the time the NSAID prescription was started. After eliminating patients who used a GPA in the two months before the index NSAID prescription, the incident NSAID incident GPA cohort was formed with the remaining 12,906 incident NSAID incident GPA users.

Coprescribing rate according to GPA

The monthly coprescribing rates of NSAIDs and GPAs are shown in Figures 1 and 2. In the incident NSAID prevalent GPA cohort, the coprescribing rate for all GPAs in the first month was 21.2% of all NSAID users; 83.4% of all patients in this cohort were coprescribed an H₂RA (Figure 1). In this cohort, coprescribing of H₂RA increased from 17.7% of all NSAID users in the first month to 35.2% in month 48. PPI use increased from 3.7% of all NSAID users in the first month to 7.2% in month 39, and decreased to 4.2% in month 48.

In the incident NSAID incident GPA cohort, coprescribing rates were much lower. In the first month, the coprescribing rate for all GPAs (prophylactic coprescribing) was 3.8% of all nonselective NSAID users; 92.6% of all patients in this cohort were coprescribed an H₂RA, 7% were coprescribed a PPI and 0.4% were coprescribed misoprostol. Logistic regression analysis showed that the OR of being coprescribed a GPA during an NSAID treatment course increased by 6% with each month of duration of NSAID use and by 10% with each five-year increase in age at the start of the treatment course. The rate of coprescribing with H₂RAs increased with the duration of time patients were on NSAIDs, increasing from 3.5% of all NSAID users in the first month to 24.1% in month 48, while the rate of PPI coprescribing remained low, increasing from 0.3% to 1.9% of all NSAID users. The coprescribing of a PPI was very low and showed only a very small increase over the 48 months. Given that the average duration of NSAID prescriptions was short,

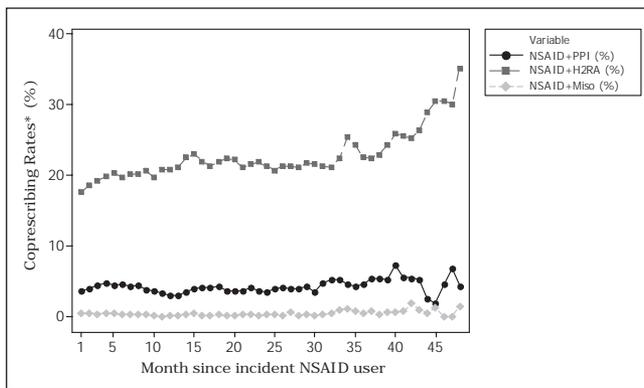


Figure 1 Coprescribing rate according to gastroprotective agent. Incident nonsteroidal anti-inflammatory drug (NSAID) cohort in Nova Scotia Seniors' Pharmacare Program beneficiaries 1998 to 2002. *Calculated as a per cent of all NSAID users. H2RA H₂-receptor antagonist; Miso Misoprostol; PPI Proton pump inhibitor

these data also indicate that GPAs were continued in many seniors even after the NSAID was discontinued. Therefore, it would be important to determine whether there was another reason for the continuation of PPI prescriptions.

Coprescribing rate according to age

Table 3 shows the effect of age on GPA coprescribing in the incident NSAID prevalent GPA cohort, and incident NSAID incident GPA cohort. The rate of coprescribing in the index month increased with age but was less pronounced in the incident NSAID incident GPA cohort in which the prophylactic coprescribing rate was calculated. The OR of receiving NSAID prophylaxis was statistically significant compared with the reference group starting from age 80 years and older in the prevalent but not the incident GPA cohort.

DISCUSSION

A striking finding in our study was that, despite an overall high frequency of use of acid suppression in Nova Scotia seniors, the rate of gastroprophylaxis (ie, starting a GPA at the time the NSAID was initiated) with either an antisecretory agent (PPI, H₂RA) or misoprostol was low during the study period (1998 to 2002). During the study period, no generic PPIs were available in the Canadian market, and many provinces – including Nova Scotia – required special authorization for use of PPIs in their seniors' Pharmacare programs. The fact that special authorization was required may be one explanation for the present study's findings; however, this could not be formally evaluated. Even taking this into account, the rate of coprescribing PPIs with NSAIDs seemed inappropriately low. Although reimbursement criteria for PPI use may be one explanation for the findings, there are other possibilities. One explanation may be a belief among Nova Scotia physicians that NSAID prophylaxis with GPAs is not required. This seems less likely because coprescribing rates in Quebec and other provinces were higher than in Nova Scotia. It is possible that physicians are insufficiently aware of the toxicity concerns of NSAIDs without GPAs and, hence, more education should be targeted to address this knowledge gap. Such education should also explain that prophylaxis with a standard-dose H₂RA is insufficient. Computerized

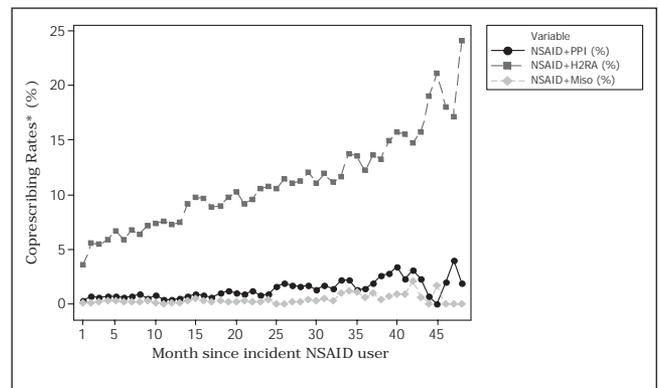


Figure 2 Coprescribing rate according to gastroprotective agent. Incident nonsteroidal anti-inflammatory drug (NSAID) incident gastroprotective agent cohort in Nova Scotia Seniors' Pharmacare Program beneficiaries 1998 to 2002. *Calculated as a per cent of all NSAID users. H2RA H₂-receptor antagonist; Miso Misoprostol; PPI Proton pump inhibitor

TABLE 3
The effect of age on coprescribing in the incident nonsteroidal anti-inflammatory drug (NSAID) gastroprotective agent (GPA) prevalent cohort (NSAID cohort) and the incident NSAID incident GPA cohort (NSAID-GPA cohort)

	Coprescribing according to age, OR (95% CI)	
	NSAID cohort	NSAID-GPA cohort
Age (as a continuous variable)	1.11 (1.08–1.14), P<0.001	1.068 (1.003–1.136), P<0.038
Age group, years		
65–69	Reference	Reference
70–74	0.94 (0.84–1.04)	0.78 (0.61–1.00)
75–79	1.12 (1.00–1.25)	0.85 (0.65–1.11)
80–84	1.26 (1.12–1.43)	1.10 (0.83–1.46)
≥85	1.47 (1.29–1.66)	1.29 (0.96–1.72)

clinical decision support systems at the time of prescribing or dispensing the NSAID to patients at significant risk of GI complications may also be helpful. The NSSPP covers medication costs for approximately 80% of seniors living in Nova Scotia. The use rate of antisecretory medication in this population is very high. The monthly rates of H₂RA use varied from 13.6% to 15.2%, and PPI use increased from 1.8% to 4.6%. Overall, misoprostol use was very low (less than 1%). The reasons for this are unclear but are likely related to the more frequent need of dosing throughout the day (two to four times) and to the adverse effect profile, which, in clinical trials, led to a withdrawal rate of 8.5% (12). Despite the fact that overall GPA use was high, the striking finding in our study was that the rate of initiating a GPA at the time an NSAID was prescribed (NSAID prophylaxis) was low, although it did increase by 10% with each five-year increase in age at the start of the treatment course. The rate of coprescribing a GPA increased by 6% for each month that prescription of the NSAID was continued. The latter suggests that, at least to some extent, physicians more likely coprescribe a GPA with increased duration of NSAID use. We did not factor in any changes that may have occurred in the eligibility criteria for seniors to receive

Pharmacare coverage in our analysis. We also did not track information regarding changes in the use of over-the-counter NSAIDs.

It is well recognized that age is an important risk factor for NSAID complications. We did not analyze other risk factors for NSAID complications such as use of warfarin or corticosteroids, which may have influenced physicians' behaviours in deciding to prescribe GPAs as NSAID prophylaxis. In the United Kingdom (National Institute for Health and Clinical Excellence guidelines [22]) and the Netherlands (23), an age of 65 years or older is a sufficient criterion to receive NSAID prophylaxis; that is, providing the patient with either a PPI or misoprostol at the time the nonselective NSAID is started to decrease the risk of serious upper GI complications. Others (24) make similar recommendations including the American College of Rheumatology guidelines for the treatment of osteoarthritis (25). In Nova Scotia, age older than 65 years, in itself, is not a sufficient criterion to qualify for reimbursement of PPIs. In contrast, Nova Scotia has no specific eligibility criteria for the use of standard-dose H₂RAs and misoprostol. This is possibly one explanation for the high use rate of H₂RAs relative to PPIs. In our study, the use of NSAID prophylaxis (starting an antisecretory agent or misoprostol at the time that conventional NSAIDs are prescribed) was low – 3.8% of all NSAID users. This rate was much lower than what has been reported in other studies (15,26-29) in which rates of coprescribing with gastroprophylactic drugs varied between 10.2% and 15% of NSAID users. The fact that in Quebec, where there is no restriction on PPI drug insurance coverage, the rate of coprescribing of a gastroprophylactic drug and an NSAID in a cohort of nonselective NSAID users older than 65 years of age was 10.2% suggests that the NSSPP-specific reimbursement criteria regarding PPIs may influence physician prescribing behaviour for patients receiving NSAIDs (28). An alternative explanation may be that with the easy availability of GPAs for NSAID prophylaxis in Quebec, physicians working there have developed a different attitude to this issue and, consequently, have a much lower threshold for prescribing NSAID prophylaxis. Of concern is also the fact that 92% of Nova Scotia patients received H₂RAs while on NSAIDs. Of these H₂RA prescriptions, more than 90% were for the standard dose (30). The literature contains convincing evidence that the standard dose of H₂RA offers insufficient gastric protection against NSAID damage. In a randomized trial (14), the standard dose of ranitidine protected against the development of duodenal ulcers but not gastric ulcers. There was only one study (13) that used high-dose famotidine 40 mg twice a day, which demonstrated protection against both gastric and duodenal ulcers. However, at that dose, costs are higher than the once daily use of a PPI. Therefore, our results not only indicate that the rate of NSAID gastroprophylaxis in Nova Scotia was lower than that reported in other studies, but also that when gastroprophylaxis is initiated, the large majority are for the standard dose of H₂RA, which provides insufficient protection.

Regarding age, not only is age older than 65 years clearly identified as a risk factor for NSAID complications, but advancing age increases the risk further (1-4,6). In a multivariate analysis (7) of risk factors in the Misoprostol Ulcer Complication Outcomes Safety Assessment (MUCOSA) trial, age older than 65 years was an independent risk factor for serious GI bleeding events and the risk increased further with increasing age. Using

age as a continuous variable in our study, we demonstrated a very small (but statistically significant) increase in the rate of prescribing with increasing age. However, considering five-year age strata in the incident NSAID incident GPA cohort, the increase in coprescribing was not significant even at age older than 85 years. This is in contrast to observations in the province of Quebec (28), where coprescribing rates clearly increased with advancing age. Our results demonstrated that the likelihood of patients receiving an antisecretory agent while they were taking NSAIDs increased as they aged. Whether this was because the patient became symptomatic with, for example, dyspepsia symptoms, which would trigger a prescription with an acid-suppressive agent, or whether the prescribing physician became more concerned with the increased duration of the NSAID is unclear. It would be interesting to know whether the low rate of NSAID prophylaxis in our population translates into an increased risk of serious complications such as bleeding ulcers, a need for surgery, hospitalization or death. This is a subject for further study. There are data from other studies that also indicate that NSAID prophylaxis is underprescribed in other populations (17,31).

Our data also showed that the duration of a substantial proportion of NSAID prescriptions were for a relatively short period of time, with 83% of patients using NSAIDs for three months or less. Only 2.3% of treatment courses lasted for more than 12 months. Whether this short duration of NSAID use is an explanation for the low NSAID prophylaxis rate is also unknown. When started in elderly patients, the duration of NSAID use is often unknown. Short duration should not influence the decision on whether to prescribe NSAID prophylaxis because the risk of complications starts early (2). A meta-analysis (2) showed that the risk of serious GI complications (hospitalization, bleeding, perforation and death) in NSAID users is greatest in the first month after the start of NSAIDs (OR=8 versus OR=1.9 after more than three months of NSAID use).

It is also well known that there is synergy between NSAIDs and acetylsalicylic acid use, and the increased risk of GI bleeding complications (5). Unfortunately, our database did not reliably capture acetylsalicylic acid use in this cohort because it is generally cheaper for patients to buy acetylsalicylic acid over the counter than to pay the pharmacist's dispensing fee and any applicable copayment fees. Because acetylsalicylic acid use in senior citizens is likely substantial, this would further increase the risk of GI complications and would be a further reason to use NSAID prophylaxis.

During the period from 1998 to 2002, the rates of non-selective NSAID use decreased while at the same time, the rates of COXIB use increased sharply after their introduction to the Canadian market in 1999. Importantly, there was an overall increase in the number of patients receiving either an NSAID or a COXIB. These trends for the Nova Scotia market are similar to those found in similar populations (age older than 66 years) in other jurisdictions such as Ontario (32). These data indicate that physicians are influenced by the type of medication that is available for a particular indication (eg, osteoarthritis). Whether this is due to effective marketing by pharmaceutical companies, restrictions on drug formularies, differences in side effects (eg, COXIB having a lower risk of GI bleeding complications) or other factors, is unknown.

Our study had several limitations. Patients excluded from the NSSPP due to private coverage may have limited representativeness, although over the five-year study period, coverage ranged from 78% to 92% of all seniors. As discussed, we could not evaluate the impact of the previous authorization policy on the rate of coprescribing. Our data cover the period from 1998 to 2002, and because generic PPIs are available and the authorization policy in Nova Scotia for PPIs has changed, the current rate of coprescribing may be higher. In addition, the awareness of the risk of adverse events related to NSAID use is likely much higher after all the publicity surrounding the use of COXIBs over the past few years. This may also have increased the awareness of the need for coprescribing. We did not assess the effect of switching from nonselective NSAIDs to selective COXIBs when calculating the use rates of all NSAIDs. Because COXIBs are associated with a lower rate of GI complications, this may have influenced NSAID prophylaxis coprescribing rates. We did not have access to other clinical diagnostic information and did not assess other risk factors such as use of warfarin or corticosteroids, which increase the risk of NSAID complications. Information regarding the presence of conditions such as gastroesophageal reflux disease, which can influence the use of GPAs, was also not collected. In Nova Scotia, some nonselective NSAIDs are available over the counter without a prescription, but this could not be assessed, nor could the concomitant use of acetylsalicylic acid, which may further increase the risk of serious GI side effects. The use of traditional nonselective NSAIDs was, therefore, probably underestimated in the present study population. We did not adjust for prescription channelling, in which patients with a different risk profile are more likely to end up on certain medications, which, in our study, would be PPI therapy. We did not investigate other risk factors such as use of other medications, anticoagulants or corticosteroids. We did not examine the cost-effectiveness of NSAID prophylaxis with a GPA. We also did not analyze whether any changes in the eligibility criteria for seniors to receive Pharmacare coverage occurred, nor did we study whether changes in eligibility influenced drug use; however, we believe it is unlikely that this would have significantly affected our results. Finally, our database reported dispensed medication and did not assess patient adherence to treatment.

CONCLUSION

The rate of prescribing NSAID prophylaxis with a GPA in Nova Scotia seniors during the period from 1998 to 2002 was low, and most prophylaxis that was prescribed was for standard-dose H₂RAs, which offer insufficient protection. The low coprescribing rate of PPIs with NSAIDs may, in part, have been due to the Pharmacare reimbursement criteria for PPIs for seniors, which do not include seniors who have no additional risk factors apart from age. Further work is needed to determine the reasons for the low rate of gastroprophylaxis for patients receiving NSAIDs, how this is influenced by policies that provide specific reimbursement criteria for PPIs, whether the infrequent use of NSAID prophylaxis translates into an increased risk of serious GI complications (eg, bleeding ulcers, perforation and death) and the cost effectiveness of approaches to NSAID prophylaxis with GPAs.

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