Cost of prescribed NSAID-related gastrointestinal adverse events in elderly patients

Elham Rahme,¹ Lawrence Joseph,¹ Sheldon X. Kong,² Douglas J. Watson² & Jacques LeLorier³

¹Department of Epidemiology and Biostatistics, McGill University, Montreal, Canada, ²Outcomes Research, Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A. and ³Research Centre, Centre hospitalier de l'Université de Montréal – Hôtel-Dieu, Montreal, Canada

Aims It is well established that nonsteroidal anti-inflammatory drugs (NSAIDs) have gastrointestinal (GI) side-effects. However, the cost of health care resources spent on preventing and managing these side-effects is not clear. The objective of this study was to estimate the direct cost of NSAID-related GI events in an elderly population.

Methods From the Régie de l'assurance-maladie du Québec (RAMQ) database, we obtained medical, pharmaceutical and demographic records of a 10% random sample ($n = 49\,033$) of seniors who, between January 1, 1993 and December 31, 1997, had a dispensed prescription of a NSAID. Patients who did not have any GI events during the year prior to their first dispensed prescription were included in the cohort. All patients were followed-up for 2 years. The daily direct Canadian dollar costs of GI events that were incurred by these patients while they were on NSAID therapy were compared with those of GI events that were incurred by these same patients while they were not on NSAID therapy. The difference in these daily costs was attributed to NSAIDs.

Results A total of 12 082 new NSAID users were included in the study. Two hundred and seventeen (1.8%) were hospitalized for GI-related problems; of these, 130 (60%) had their GI hospitalization as their first GI event; 3257 (27.0%) used gastroprotective agents (GPAs), and 857 (26.3%) took GPAs without any apparent prior GI symptoms; 801 (6.6%) had GI diagnostic tests; and 661 (5.5%) died. The average direct costs of GI side-effects per patient-day on NSAIDs were 3.5 times higher than those of a patient-day not on NSAIDs. The direct cost of GI side-effects per patient-day on NSAIDs was \$1.34, of which more than 70% (\$0.94) was attributed to GI events resulting from NSAID treatment.

Conclusions Approximately one Canadian dollar was added to patient costs for every day he/she was on NSAID therapy. Safer therapies and appropriate patient risk management may potentially reduce NSAID-related health care resource use.

Keywords: adverse events, cost, gastrointestinal, NSAIDs

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most common classes of medications used worldwide [1]. They are usually prescribed for analgesic and anti-inflammatory indications, although aspirin

(acetylsalicylic acid), the original NSAID, has been increasingly employed at low doses for antithrombotic purposes. Unfortunately, all NSAIDs, including aspirin at low doses, have been associated with both minor gastrointestinal (GI) side-effects such as dyspepsia and abdominal discomfort, and major side-effects such as ulcers, perforation, and bleeding [2–12]. To reduce the risk of NSAID-related GI adverse events, non-NSAID alternatives such as paracetamol as first-line analgesic therapy, and the coprescription of gastroprotective agents (GPAs) with NSAIDs have been recommended for high risk patients [13–17]. The elderly are considered most

Correspondence: Jacques LeLorier, MD, PhD, Research Center, Hôtel-Dieu du Centre Hospitalier de l'Université de Montréal 3850 Saint-Urbain, Montreal, Quebec H2W 1T8, Canada. Tel.: (514) 890 800 Ext. 14080; Fax: (514) 412 7174; E-mail: massica@jonction.net

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at risk to develop GI adverse events from NSAIDs [1]. Concomitant use of certain GPAs with NSAIDs has been proven to reduce serious GI complications [18–21], but adds to the cost of NSAID therapy [22–25].

Severe GI events associated with NSAIDs have received a significant amount of attention from clinicians and healthcare policy decision-makers because they are costly, require hospitalization, and may be fatal. However, minor GI side-effects (nuisance symptoms) and prophylactic gastroprotection against NSAID-related side-effects have not been given as much scrutiny. From the perspective of the healthcare system, these minor side-effects may consume more healthcare resources than do more severe events because of their high prevalence. This study estimated the rate of GPA use, GI-related medical interventions, and hospitalizations due to GI events as well as the direct cost of these GI-related events attributable to prescription NSAIDs in a sample of the Quebec population 65 years old and over who had newly started NSAID therapy.

Methods

Study population

In Quebec, all persons aged 65 years or older are eligible for coverage under the Provincial Healthcare Fund administered by the Régie de l'Assurance Maladie du Québec (RAMQ). The fund covers the costs of prescription drugs, physician visits and other medical services offered in private clinics or hospitals. For reimbursement, all healthcare providers (including pharmacists, physicians, and hospitals) must submit claims to the Provincial Government. All claims are captured by the RAMQ database which contains information on patient age and gender, medication use, medical procedures, diagnoses, the specialty of the physician who directed the claim to the RAMQ, the place where this procedure was performed (private clinics or hospitals), and the reimbursement for that claim. Prescription data contain information on all filled prescriptions including drug name, dispensation date, dosage, drug form, duration, and quantity of the drug dispensed, as well as reimbursement for the prescription. Drugs dispensed to patients during stays in hospitals or public nursing homes, and over-the-counter drugs are not included in the database. The RAMQ prescription claims database has been validated and found to be both accurate and reliable [26]. In August 1996, the RAMQ introduced a new cost-sharing drug insurance plan. With this change, a choice was given to persons aged 65 years or older to subscribe to the RAMQ drug plan or to any other collective drug insurance plan. A small number of these persons (3.0%) subscribed to other drug insurance plans in 1997. However, they

continued to be covered by the RAMQ for all other medical services.

Cohort participants

From the RAMQ database, we obtained medical, pharmaceutical and demographic records of a 10% random sample ($n=49\,033$) of all patients aged 65 years or older who, between January 1, 1993 and December 31, 1997, had at least 1 dispensed NSAID prescription. From this sample, we selected a cohort of patients aged 66 years or older who, between January 1, 1994 and December 31, 1995, had a dispensed NSAID prescription. The date of the first dispensed NSAID prescription for a patient was termed his/her index date. All patients included in the cohort had a potential of 1 year of observation prior to their index date; during that year, patients who did not have any dispensation of NSAIDs (including aspirin) or any GI event defined by: dispensation of a GPA, visit to a gastroenterologist, upper GI diagnostic test (i.e. an endoscopy or a barium sulphate), or GI hospitalization were included in the cohort. A hospitalization was classified as a GI hospitalization if the patient underwent an endoscopy or GI surgery during the first 2 days of that hospitalization (Figure 1). Since drugs that are dispensed to patients during stays in hospitals are not included in the RAMQ database, we did not know if patients who were hospitalized during the year prior to their index dates were given NSAIDs in hospital. We believe that in most cases patients who were administered NSAIDs during their hospitalization would have been dispensed NSAIDs at their release. Therefore, we also excluded from our study all patients whose index dates coincided with the dates of release from a hospital when their hospital stay exceeded 1 day. If a patient did not fulfil the inclusion criteria at his/her first dispensed NSAID prescription, then he/she was entered in the

Patients who did not use any NSAIDs, GPAs, GI diagnostic tests, visits to gastroenterologists, or GI hospitalizations during the past 12 months were followed up for 24 months after they started on NSAIDs

Figure 1

cohort at a later date provided all inclusion criteria were fulfilled; this later date was then termed the index date for that patient. All patients were followed-up for 2 years or until death if death occurred within 2 years of the index-date.

Measurements

This study focused on the use of NSAIDs for analgesic and anti-inflammatory indications; therefore, unless otherwise stated, aspirin was not considered among the NSAIDs. However, since aspirin can cause GI adverse events, even at low doses, we reported the average number of days the patients used prescription aspirin both during days on NSAIDs and days not on NSAIDs. Days on NSAIDs were defined as days between the date of dispensation and the end of its duration. All other days in the follow-up were considered as days not on NSAIDs. A patient in the cohort may eventually have had aspirin, paracetamol (acetaminophen), stopped the NSAID therapy, changed the NSAID class or taken different NSAIDs concomitantly.

The demographic characteristics of the patients and their baseline comorbidity were examined. Baseline comorbidity for a patient was estimated by the number of drugs the patient was taking at the index date, and by his/her chronic disease score. Classes of drugs were assigned scores (0–5) according to the severity of the disease for which they were prescribed. The chronic disease score was then the sum of the scores of the drugs the patient took during the year preceding the index date [27].

Costs of GI adverse events

We calculated the direct costs in Canadian dollars of GPAs, pharmacist fees, visits to general practitioners that resulted in a dispensed prescription of a GPA with no other coprescribed drug, visits to gastroenterologists, GI diagnostic tests, and GI hospitalizations. The cost of a GI hospitalization included the cost of in-hospital medical procedures reimbursed by the RAMQ; it also included the cost of in-hospital days either in a regular ward or intensive care. The cost per day in a regular ward was estimated at \$500, and the cost per day in intensive care was estimated at \$1000 [Canadian Institute for Health Information (1997) and Statistics Canada (1996)]. Cost estimates for a day of GI hospitalization in Canada vary from \$407 to \$1287, depending on the complications. The mean cost of a day in a regular ward of a nonteaching hospital in Canada was estimated at \$517.5 by Statistics Canada in 1996. No additional cost was added for patients who underwent a GI surgery. A hospitalization was considered to have

happened during days on NSAIDs if the day of admission to the hospital fell during the timespan of a dispensed NSAID prescription.

Study design

We considered that a GI event that was not related to NSAID use would occur equally likely on any day of the follow-up period. Therefore, we used a self-controlled design where we calculated separately both the daily average direct cost of GI events that were incurred by a patient during his/her days on NSAIDs and the daily average direct cost of GI events that were incurred by this same patient during his/her days not on NSAIDs. The latter was considered as a baseline daily cost of GI events that were not related to NSAID use. The difference in these daily costs was considered to be the average direct cost of NSAID-related GI events for a day on NSAID therapy. From the direct cost of NSAID-related GI events for a day on NSAID therapy, we calculated the GI iatrogenic cost factor for NSAIDs. The GI iatrogenic cost factor was defined as the ratio of the GI-related shadow price of NSAIDs to the cost of NSAIDs. The GI-related shadow price of NSAIDs was defined as the direct cost of the NSAID product plus all the medical care expenses of diagnosing, treating and preventing their adverse effects [21]. The average daily cost of NSAID product was estimated from the data. Arthrotec is a special NSAID consisting of a fixed combination of the NSAID diclofenac, and the GPA misoprostol. A patient who had a dispensed prescription of Arthrotec was considered to have taken a GPA only if he/she was dispensed a separate GPA prescription. No partial cost of GPA was attributed to the misoprostol contained in the Arthrotec composition. The cost of each GPA was the actual cost that appeared in the lists of medications published by the RAMQ in the corresponding years; to this cost, we added the pharmacist fee, estimated at \$6.77 for each dispensed prescription, the average figure provided by the RAMQ. We used the cost of the GPAs instead of reimbursement by the RAMQ for that GPA, since a policy change for the reimbursement of prescription drugs was adopted by the RAMQ in August 1996. Drug costs did not change substantively during the years considered in this study, but the amount reimbursed by the RAMQ for drugs changed significantly after the new health plan. Since the patients were enrolled at a date of dispensed prescription of NSAIDs, some of the days on NSAIDs were by design before August 1996, and therefore may falsely cost more than the comparison days if RAMQ reimbursement was used. Reimbursement by the RAMQ for GPAs and actual costs were compared to evaluate the effect on the final results.

Sensitivity analysis

We also calculated the average direct cost of NSAID-related GI events for a day on NSAID therapy, taking into account the Canadian inflation rate during the years 1994–97 and cost estimates per day of hospitalization both in a regular ward and in intensive care. This was done to investigate how the average direct cost of NSAID-related GI events for a day on NSAID therapy would be affected by such variations.

Study perspective

This study was conducted from the perspective of the Provincial Government of Quebec (a single payer system). The pricelist or reimbursement rate by the Provincial

Government was used whenever possible. Cost-sharing by patients was not included in the analysis.

Results

Baseline characteristics of patients and the use of NSAIDs during follow-up

A total of 12 082 patients fulfilled the inclusion criteria and were included in the cohort. Twenty percent of these patients were not enrolled at their first dispensed prescription of NSAIDs but at a later date where they met all the inclusion criteria. The baseline characteristics of the patients are summarized in Table 1. Their mean age was 74.5 years and 61% of them were females. The median number of comedications (other than NSAIDs, GPAs, or paracetamol) was 1 with lower and upper quartiles of 0 and 3, respectively, and the median chronic disease score was 1 with lower and upper quartiles of 0 and 4, respectively. The median number of days on NSAIDs for these patients was 34 days (Table 2). The total number of individual NSAID prescriptions dispensed over the 2 year follow-up was 51 621. Naproxen accounted for 26.3% of NSAID dispensations, diclofenac for 15.5% and Arthrotec for 14.1% (data not shown). The mean number of days on NSAIDs for a patient was 81.1 days, and the mean number of days not on NSAIDs was 629.6 days over the 2 year follow-up. One thousand, six hundred and sixty-seven (13.8%) patients were dispensed aspirin during the follow-up, and of these 1331 (11% of the total cohort) used aspirin with a median dosage of 1 pill per day, suggesting that at least half of their dispensations were for antithrombotic indications. The mean number of days on prescription aspirin concomitantly with NSAIDs was 3.2 (2.4% of days on NSAIDs), and the mean number of days

Table 1 Baseline characteristics and GI events during the follow-up.

Number of new NSAID users (total study population)	12,082
Mean age $\pm$ s.d.	74.5 $\pm$ 6.34
Female gender (%)	61.3
Median number of comedications* (25%, 75% quartiles)	1 (0, 3)
NSAID Rx by rheumatologist at index date (%)	1.3
Median chronic disease score† (25%, 75% quartiles)	1 (0, 4)
<i>Number of patients (%)</i>	
All cause death	661 (5.5)
GPA during follow-up	3257 (27.0)
GPA at index date	857 (7.1)
Hospitalizations	217 (1.8)
Diagnostic tests	801 (6.6)

*The number of comedications was the average median of drugs other than NSAIDs, paracetamol (acetaminophen), or GPAs a patient was taking at the index date. †The chronic disease score was the sum of the scores (0–5) assigned to drugs the patient took during the year preceding the index date.

Table 2 Number of days on NSAIDs and Canadian dollars of GI adverse events.

	On NSAIDs	Not on NSAIDs	Total
<i>Number of days (s.d.)</i>			
Median days (25%, 75% quartiles)	34 (15, 90)	692 (624, 716)	731 (731, 731)
Mean days (s.d.)	81.1 (118.8)	629.6 (149.5)	710.7 (98.4)
Mean days on aspirin (s.d.)	3.2 (25.2)	26.2 (94.8)	29.5 (103.5)
<i>Average daily \$cost of GI events</i>			
GPAs + pharmacist fee	0.17	0.05	0.07
Hospital medical procedures	0.14	0.04	0.05
Days in hospitals			
Regular ward at \$500 per day	0.81	0.23	0.31
Intensive care at \$1000 per day	0.18	0.05	0.08
Gastroenterology and diagnostic tests	0.02	0.02	0.02
Visits to GPs \$42.5	0.02	0.01	0.01
Total cost per patient-day (95% CI)	1.34 (0.84, 2.0)	0.40 (0.31, 0.53)	0.54 (0.42, 0.67)

95% CI = 95% confidence interval.

s.d. standard deviation.

on aspirin while not on NSAIDs was 26.2 (4.1% of days not on NSAIDs). Five thousand, six hundred and six (46.4%) patients used paracetamol some time during the follow-up, and of these 4314 (35.7% of the total cohort) continued to use NSAIDs (data not shown).

GI events

There were 13 743 separate prescriptions of GPAs dispensed during the follow-up: ranitidine accounted for 32.6%, omeprazole for 20.7% and misoprostol for 17.3% (data not shown). The GI events that occurred during the follow-up period are presented in Table 1. Three thousand, two hundred and fifty-seven (27.0%) patients had a GPA dispensation during the follow-up, and of these 857 (7.1% of the total cohort) had a GPA dispensation at the index date. Eight hundred and one (6.6% of the

total cohort) had GI diagnostic tests and 217 (1.8%) were hospitalized; 8 (0.7%) patients underwent a GI surgery.

Figure 2 displays the GI events in chronological order with the average direct cost of GI-related adverse effects at each end-event. In this figure, GI events were censored after hospitalization. Of the 3544 patients who experienced a GI event some time during the follow-up, 3009 (85%) had a GPA without any prior GI diagnostic tests or a GI hospitalization. Two hundred and seventeen (1.8%) patients were hospitalized for a GI cause, and 130 (60%) of them had their GI hospitalization as their first GI event.

Cost of GI events

The direct costs of GI events in a patient-day on NSAIDs and those in a patient-day not on NSAIDs are enumerated in Table 2. For the eight patients who underwent GI

Figure 2 GI events with the average direct cost of GI-related adverse effects at each end-event.

surgery, the cost of surgery was included in the cost of in-hospital medical procedures. No additional cost was added for the use of the operating room. The total direct cost, in Canadian dollars, of GI-related adverse events that occurred during the 2 year follow-up was \$2 916 121.30. The average direct cost of GI-related adverse events for a patient-day on NSAIDs was \$1.34 (95% confidence interval \$0.84, \$2.01), and the average direct cost for a patient-day not on NSAIDs was \$0.40 (95% confidence interval \$0.31, \$0.53). Thus, the average direct cost of NSAID-related GI events for a day on NSAID therapy was $\$1.34 - \$0.40 = \$0.94$ (95% confidence interval: \$0.42, \$1.59). Therefore, 70.1% ($\$0.94/\1.34) of the direct cost of GI events that occurred during a day on NSAIDs was attributed to NSAIDs and the other 29.9% was attributed to baseline GI events. The daily costs of NSAID therapy varied according to the specific product used. Average daily costs for all NSAIDs in the RAMQ list were employed to estimate the average GI iatrogenic cost factor. The average daily cost of NSAIDs (branded and generics) for patients included in this study was \$1.28. Thus, the average GI iatrogenic cost factor for NSAIDs therapy was estimated at $(0.94 + 1.28)/1.28 = 1.73$ (95% confidence interval: 1.28, 2.18) which meant that for each Canadian dollar spent on NSAIDs during the years of the study, an additional \$0.73 was spent on managing and treating their side-effects.

The average amount reimbursed by the RAMQ for a GPA during the 2 year follow-up was \$38.09; the average cost of dispensed GPA prescription including the pharmacist fee at \$6.77 was \$38.50. However, the average cost of GPAs including the pharmacist fee during the first 7 months of 1996 (before the change of policy) was \$41.30 and the amount reimbursed by the RAMQ was \$40.89. In the last 5 months of 1996 (after the change of policy), the average cost of a GPA was \$41.45 while the amount reimbursed by the RAMQ was \$32.50.

Sensitivity analysis

This study spanned several years (1994–97). During these years, the annual inflation rate in Canada has been estimated to be between 1% and 3% (Statistics Canada, Canadian Economic Observer). We analysed the direct costs of GI events that occurred during follow-up, accounting for a constant yearly discount rate of 2%. For example, to account for the discount rate, GPA costs, and reimbursement for medical claims during the years 1994, 1995 and 1996 were multiplied by 1.06, 1.04 and 1.02, respectively, and then added to the costs spent in 1997. We also varied the average cost per day in hospital to investigate how this change would affect the cost attributable to NSAIDs. The results are shown in Table 3. As expected, the daily costs of both a day on NSAIDs and

Table 3 Average direct costs of GI adverse events per patient-day on NSAIDs in comparison with those per patient-day not on NSAIDs, accounting for a yearly inflation rate of 2%, and for different values of the mean cost of an in-hospital day during a GI hospitalization.

<i>Cost per day in regular ward</i>	<i>Cost per day in intensive care</i>	<i>Cost per day on NSAIDs</i>	<i>Cost per day not on NSAIDs</i>
500	1000	1.35	0.40
517.5	1287	1.43	0.43
600	800	1.48	0.44
600	1000	1.52	0.45
650	1000	1.48	0.44

a day not on NSAIDs did not change substantively when we accounted for the discount rate (Table 3, first row). These costs fluctuated when we varied the average costs of an in-hospital day, but the excess daily cost did not change substantively.

Discussion

This study estimated the risks of GI events in an elderly population that newly started NSAID therapy and that did not apparently have any GI-related symptoms necessitating a GPA or a diagnostic test during the 12 month period prior to their first NSAID dispensation. Many of these patients (27%) took GPAs during follow-up. The risk of a GI hospitalization was found to be particularly high since many events (60%) seemed to have been unexpected, occurring as a first GI event. The direct costs of GI adverse events attributable to NSAIDs were also estimated. The cost of GPAs, GI-related tests, visits to clinicians and GI hospitalizations for those who started on NSAIDs was \$1.34 per patient-day on NSAIDs. Of this \$1.34, \$0.94 (70.1%) was attributed to NSAIDs. The GI iatrogenic cost factor for NSAIDs was found to be 1.73. This meant that for each Canadian dollar of direct cost spent on NSAIDs, an additional \$0.73 was spent on the prophylaxis and treatment of NSAID-related GI events. Approximately one Canadian dollar (\$0.94) was added to the cost of a patient for every day he/she was on NSAID therapy. The total number of days on NSAIDs estimated from the RAMQ data for the total population of elderly Quebec patients during the years 1993–97 was 97 159 340 days and the number of patients who had a dispensed prescription of NSAIDs during these years was estimated at 490 330. The patients enrolled in this study were newly prescribed NSAIDs and did not have any GI event during the 12 months prior to their enrolment date. If we assume that all patients who had a dispensed prescription of NSAIDs during these years but were not in the study cohort would develop at least as many GI events as those

seen in this study, then an estimate of at least \$91 329 780 (\$0.94 × 97 159 340) Canadian dollars could have been spent for NSAID-related GI events in Quebec during these years.

Although this study was conducted from the perspective of the provincial healthcare system of Quebec, we used the actual costs of GPAs instead of the reimbursement by the RAMQ for reasons explained in the study design. However, the actual cost of a GPA and the amount reimbursed by the RAMQ were found to be very close on average (\$38.1 *vs* \$38.5). Moreover, any difference between the two costs would appear in the same proportion both in the days on NSAIDs and in the days not on NSAIDs and would not affect the comparison.

The data and methodology used in this study are different from those employed in other investigations dealing with the same issue. For example, Johnson *et al* [20] found a GI iatrogenic factor of 1.35 but the patients included in their study were dispensed ibuprofen 50% of the time while in our study, ibuprofen accounted for 7.8% of dispensations. While we assumed in our study that the GI side-effects did not differ among the different NSAIDs, the costs of these NSAIDs varied, thereby affecting the denominator of the iatrogenic factor. De Pouvoirville [21] reported GI iatrogenic cost factors ranging from 1.36 for naproxen to 2.12 for etodolac in the French population.

It is possible that the baseline costs of GI events may have been overestimated because some patients were using aspirin that could have increased the occurrence of GI adverse events during the days not on NSAIDs since the proportion of days of aspirin use concomitant with NSAIDs (2.4%) was lower than the proportion of days the patients were taking aspirin alone (4.1%).

This study has several limitations. We assumed that the patients were newly prescribed NSAID therapy, but, this assumption was not verifiable due to limitations of the database. Some of the patients included in this study may have subscribed to private drug insurance plans after August 1996. If so, data on their drug consumption may have been lost after that date, but, their medical services continued to be covered by the RAMQ. However, the proportion of these patients did not exceed 3%. The RAMQ database does not capture 'over-the-counter' use of NSAIDs/aspirin or GPAs although, they were very limited in the elderly population of Quebec during the years of the study. According to Santé Québec, a government of Quebec's Public Health agency, of the elderly who consumed NSAIDs, aspirin or GPAs 0.5%, 0.3% and 0.4%, respectively, acquired these agents over-the-counter. From the perspective of a health care provider, NSAID-related GPA use constitutes an additional burden, therefore we considered any GPA use among the GI adverse events even though some GPAs may have been prescribed for preventing GI events, and in some

people such events never occur. To estimate the cost of a GI hospitalization we used an average cost per day of hospitalization based on figures published by the Canadian Institute for Health Information (1997) and Statistics Canada (1996). Under the assumption that hospital capacity is increased to accommodate patients with NSAID-related GI perforations or bleeds, the per diem incorporating these costs is appropriate. With the assumption that they are marginal to the overall functioning of the hospital and do not require additional resources the per diem is probably an overestimate of the marginal cost [28]. Prescriptions of NSAIDs do not necessarily correspond to their use. Hence, it is difficult to directly link actual NSAID use and subsequent adverse events using the kind of database as was used in this study. Such misclassification would have resulted in an under estimation of the NSAID GI adverse events since some of the days considered under NSAID treatment were actually days where NSAIDs were not taken and conversely. Since the cause of death was not available from the database, deaths from an aggravated GI event could not be accounted for in this study.

A considerable amount of money is spent every year to protect against or manage GI adverse events induced by NSAIDs. Safer therapies and appropriate patient risk management may be potential means of reducing NSAID-related healthcare resource use.

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