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ORIGINAL ARTICLE

The Iatrogenic Costs of NSAID Therapy: A Population Study

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Objective. **To estimate the iatrogenic costs of nonsteroidal antiinflammatory drug (NSAID) treatment from the perspective of the Italian National Health Service.**

Methods. **We conducted a retrospective cohort study using the primary and secondary care claims data registered in the regional health service database in the Friuli-Venezia Giulia (Italy). The study cohort comprised all persons (265,114) who received at least one prescription for any NSAID between August 1996 and July 1998. The outcomes of interest were the costs of medical interventions for upper gastrointestinal disorders following NSAID treatment (i.e., prescriptions for gastroprotective drugs, hospitalizations, and outpatient diagnostic procedures).**

Results. **The study population received a total of 660,311 NSAID prescriptions for a cost of 6,587,533 Euros (€) (€0.53 per treatment day). The cost of medical interventions for gastrointestinal events added 58% to the cost of NSAID therapy (€0.31 per NSAID treatment day, up to 64% directly attributable to NSAID use). The iatrogenic costs were generated by 12.4% of the patients, 77% of whom had a positive history of gastrointestinal disorders and 82% of whom were older than 50 years. Co-prescriptions for gastroprotective drugs accounted for 78.6% of the overall iatrogenic costs. The iatrogenic costs did not differ between cyclooxygenase (COX) nonselective and COX-2 preferential drugs within strata of age and prior history of gastrointestinal disorders, but were significantly higher for the parenteral NSAIDs than the oral or rectal formulations.**

Conclusions. **In Italy, the iatrogenic costs of NSAID therapy add 58% to the cost of NSAID treatment; most of the cost is generated by co-prescriptions of gastroprotective drugs to elderly NSAID users or patients with a history of gastrointestinal disorders.**

KEY WORDS. Nonsteroidal antiinflammatory drugs; Costs; Gastrointestinal disorders; Adverse effects.

INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) are used widely to relieve the symptoms of a variety of inflammatory diseases, including osteoarthritis (OA), rheumatoid arthritis (RA), and gout, as well as other conditions characterized by acute pain. However, the therapeutic benefits of NSAIDs are accompanied by gastrointestinal (GI) toxicity due to the inhibition of the constitutive cyclooxygenase 1 (COX-1) enzyme, with clinical manifestations that include gastritis, erosions, ulcers, hemorrhage, perforation, and even death (1,2). Several studies have shown that people taking NSAIDs prior to the availability of COX-2 inhibitors have a 3- to 4-fold increased risk of severe upper GI bleeding (UGIB) compared to nonusers, which varies

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according to the type of NSAID, dosage, age, sex, and other patient characteristics (3–15).

Upper GI diseases associated with the use of NSAIDs generate iatrogenic costs, the extent of which is still undefined in the various types of health care delivery systems. Data derived from US claims databases suggest that medical costs related to GI events (GIE) increase treatment costs of RA or OA by 36–41% (16–18). European estimates are based on models, and do not consider that some NSAIDs preferentially (meloxicam, nabumetone) or selectively (celecoxib, rofecoxib) inhibit cyclooxygenase 2 (COX-2) rather than COX-1 enzyme, and may therefore cause less GI toxicity (19–23).

We conducted a retrospective cohort study in an Italian region to estimate the costs to the National Health Service (NHS) of GI toxicity following treatment with NSAIDs, stratified by selected characteristics of interest.

METHODS

Data source. The Friuli-Venezia Giulia (FVG) region in northeast Italy has a health information system that contains accurate data on outpatient prescriptions (drug name, strength, formulation, price, date of dispensing, and number of packages dispensed since 1992), hospitalizations (including date of admission and discharge and all discharge diagnoses since 1985), outpatient procedures (including gastric endoscopies and breath tests since January 1998), and deaths relating to the 1.2 million residents registered with the NHS (registration is universal for Italian citizens).

The prescription data include NHS-reimbursed drugs sold by all private and public pharmacies; the hospitalization data refer to all public and private hospitals in FVG, whereas outpatient procedures are registered if reimbursed by the NHS (private, nonreimbursed procedures are excluded). For some drugs, reimbursement is bound by strict rules requiring a confirmed indication for treatment and a treatment regimen of limited duration (e.g., most NSAIDs are reimbursed only for patients with RA, OA, or gout; gastroprotective drugs are reimbursed only for patients with gastritis, ulcers, Zollinger-Ellison syndrome, or reflux esophagitis). The characteristics of the population in FVG and their access to health care are representative of the larger population of NSAID users in Italy and, to some extent, in other countries with an NHS providing universal coverage.

Study cohort. The source population consisted of all FGV residents aged less than 90 years who were registered with the NHS during the study period (August 1, 1996 to July 31, 1998), which was designed to begin with the introduction in Italy of (still applied) restrictions on the prescription of NSAIDs. Within the source population, we defined a cohort including all of the subjects who received at least 1 reimbursed prescription for any of the NSAIDs (indomethacin, sulindac, diclofenac, fentiazac, acemetacine, proglumethacine, intravenous ketolorac, diclofenac sodium with misoprostol, cinnoxicam, piroxicam, tenoxicam, droxicam, meloxicam, furprofen, ibuprofen, naproxen, ketoprofen, flurbiprofen, tiaprofenic acid, mefenamic acid, amtolmetine, nabumetone, niflumic acid, nimesulide, morniflumate). NSAIDs were eligible for reimbursement if prescribed for the treatment of OA, gout, selected arthropathies, and neoplastic pain. We excluded all people hospitalized for chronic liver disease, Mallory-Weiss syndrome, alcoholic gastritis, Crohn's disease, ulcerative colitis, blood diseases (coagulation disorder, hemorrhage), or neoplasm of the GI tract before or during the study period. Each cohort member was followed starting at the date of the first prescription for any NSAID and ending at the conclusion of the study period, transfer of the member out of the region, or at the death of the member.

NSAID exposure. NSAID exposure was expressed in terms of person-days and characterized by the use of a specific active principle and route of administration (i.e., oral, injectable, or rectal), as well as other variables of interest (e.g., age, sex, history of GI disease, cancer). To define mutually exclusive treatment periods of the current use of different compounds administered alone ("single") or in combination with other NSAIDs ("combinations"), we applied an algorithm based on the following rules: 1) the theoretical duration of each prescription was calculated by dividing the quantity of dispensed drug by the standard Italian Defined Daily Dose (DDD); 2) consecutive prescriptions of the same drug (i.e., occurring within the theoretical duration plus 20% of the preceding prescription) were combined in 1 treatment period; 3) the periods of single use of a given NSAID were censored in the case of the start of a prescription for a different formulation of the same NSAID or the prescription of another NSAID; and 4) the contribution to the "combinations" category started on the first day of concomitant use and lasted for the theoretical duration of overlapping prescriptions.

The adoption of these procedures allowed us to obtain mutually-exclusive person-time categories of the current use of different compounds alone or in combination. Each period of current use started on day 1 of the treatment period and ended at the end of that treatment period; on the date of start of a treatment period with another NSAID; upon hospitalization with a primary discharge diagnosis of any of the study outcomes; or at the end of followup. A person could contribute information to different exposure categories if he or she was prescribed more than one NSAID during the study period.

Outcomes. The outcomes of interest for this study were medical interventions for upper GI disorders following NSAID treatment and the related costs to the NHS (i.e., NHS reimbursements). The medical interventions included the prescription of gastroprotective drugs (H2-receptor antagonists, proton pump inhibitors, sucralfate, misoprostol, magnesium, aluminum and calcium complexes), hospitalizations with a primary discharge diagnosis of one of the selected conditions (ICD-9 codes 520.1, 530.1, 531–533, 55–537, 578) (24), and selected outpatient diagnostic procedures (C13 breath test, endoscopy). To minimize potential misclassifications, we did not consider hospitalization with a secondary, tertiary, or quaternary

Table 1. Number of patients and dispensed prescriptions of NSAIDs, by age*

	Patients		Prescriptions		Prescriptions/patient				
					1	2	3	4	5+
Age (years)	Number	%	Number	%	%	%	%	%	%
<30	20,983	7.9	28,259	4.3	6.2	1.1	0.3	0.1	0.1
30–39	26,109	9.8	41,182	6.2	6.8	1.8	0.6	0.3	0.3
40–49	36,383	13.7	68,355	10.4	8.2	2.8	1.2	0.6	0.9
50–59	52,248	19.7	118,823	18.0	10.3	4.3	2.1	1.1	2.0
60–69	54,180	20.4	149,973	22.7	9.0	4.3	2.4	1.5	3.2
70–79	49,659	18.7	164,132	24.9	7.5	3.9	2.2	1.4	3.8
80–89	25,552	9.6	89,587	13.6	3.9	1.9	1.1	0.7	2.1
Total	265,114	100.0	660,311	100.0	51.8	20.1	9.9	5.7	12.5

* NSAIDs = nonsteroidal antiinflammatory drugs.

discharge diagnosis of interest. Because of changes in Italian privacy legislation, we could not validate the diagnoses using the original medical records, but we knew from previous work that the quality of the computerized records in Sistema Informativo Sanitario Regionale (SISR) for most of the primary discharge diagnoses listed in Table 1 is high, with positive predictive values of up to 97% (14,25). We also excluded patients affected by comorbidities involving a high risk of hospitalization for GI bleeding regardless of NSAID use or clinically distinct from the purpose of this study.

The reimbursed costs were obtained from the records of the SISR database, and the Italian currency was converted to Euros (€). The current exchange rate is 1 Euro = 1 US dollar. Gastroprotective drugs were reimbursed only if prescribed for specific GI indications, or for prevention of GI bleeding in patients with long-term NSAID use (misoprostol). Costs were not discounted because of the limited duration of followup and they reflect the costs at the time they were incurred from the perspective of the NHS (inflation not accounted for, the inflation rate was less than 3% during the study period). This implies that costs did not represent opportunity costs, but were fixed charges as reimbursed by the NHS.

Because data on outpatient procedures were available for only the last 7 months of the study period, we estimated the number of procedures and their costs during the entire study period by dividing the observed numbers by 7 and then multiplying it by 24.

Cost attribution. For the purposes of cost attribution, we defined directly and indirectly related events on the basis of their temporal relationship to NSAID exposure. The costs were directly attributed to NSAIDs (directly related events) when an event occurred within a time period (risk window) that included either the duration of a treatment period plus a variable carryover period (15 days plus 20%, or 100% of the length of the treatment period for consecutive or isolated prescriptions respectively), or simply the duration of the treatment period without any carryover (when the treatment period was censored). The costs generated by events occurring outside the risk window (indirectly related events) were attributed to a treatment if an event of interest had already occurred within the risk window; the attribution of indirectly related costs to a drug category ended with the start of a new NSAID treatment regimen or the end of followup. For example, the cost of hospitalization for a study outcome falling outside the risk window of a given NSAID exposure was attributed to that NSAID if another hospitalization had occurred within the risk window, or if a gastroprotective drug had been dispensed, or if an endoscopic procedure had been performed within the risk window.

To obtain baseline-reimbursed GIE costs (as independent as possible of NSAID exposure), we estimated the costs generated by GI-related hospitalizations and prescriptions of gastroprotective drugs 4–6 months before entering the study in all of the subjects who had not used NSAIDs for at least 9 months prior to enrollment.

Statistical analysis. All days of exposure experienced by every study subject for each NSAID category were accumulated. We calculated the costs of NSAID therapy and GIE-related costs as total costs and cost/day of actual therapy, using costs as the numerator and the total person-time of actual treatment duration (without carryover) as the denominator, and taking into account potential risk factors for GIE such as age, sex, history of GI disease (defined as either a hospital discharge for one of the GI conditions considered as outcomes in this study or a reimbursed prescription of one of the gastroprotective drugs within 7 months prior to the beginning of the study period), cancer, previous NSAID use, number of prescriptions, and drug category. Ninety-five percent confidence intervals (CI) were calculated around the sum of the costs on the basis of the normal distribution weighted by the number of person-days. Whenever appropriate, comparisons were made using the chi-square test for categorical data, and the Student's *t*-test for continuous data.

RESULTS

We identified 269,942 subjects who received at least one reimbursed prescription for an NSAID during the 2-year study period, 4,828 of whom were excluded (88.9% because of neoplasm of the GI tract). The final study cohort consisted of 265,114 subjects who received a total of

Table 2. Gastrointestinal events directly and indirectly related to NSAID treatment and total costs*

Type of event	Number	%	Cost	%	%†
Hospitalization					
Directly related	146	81.1	443,747	82.4	
Indirectly related	34	18.9	94,563	17.6	
Total	180	100.0	538,310	100.0	14.0
Antiulcer prescriptions					
Directly related	74,628	60.0	1,642,247	54.6	
Indirectly related	49,573	40.0	1,365,920	45.4	
Total	124,201	100.0	3,008,167	100.0	78.6
Procedures					
Directly related	1,687	39.2	114,122	40.4	
Indirectly related	2,612	60.8	168,204	59.6	
Total	4,299	100.0	282,327	100.0	7.4
All events					
Directly related			2,200,116	57.5	
Indirectly related			1,628,687	42.5	
Total			3,828,803	100.0	100.0

* Costs in Euros. NSAID = nonsteroidal antiinflammatory drug.
† Percentage costs, using the total cost of "All events" as the denominator.

660,311 NSAID prescriptions (Table 1). Fifty-two percent of the study population received only one prescription; the estimated median duration of treatment was 27 days. The female:male ratio was 1.6:1; women were older ($P < 0.001$), and were treated longer than men ($P < 0.001$), and thus accounted for two-thirds of all the prescriptions (data not shown).

The cohort experienced a total of 12,459,713 person-days (409,859 person-months) of NSAID exposure, amounting to a cost of €6,587,533 (€0.53/day of NSAID treatment). The total costs of medical interventions for upper GIE following NSAID use amounted to €3,828,803 and represented a 58% addition to the daily NSAID treatment costs. The GIE costs per actual treatment day were €0.31 (95% CI, 0.30–0.32) and increased to €0.34 (95% CI, 0.33–0.36) when we included the costs of hospitalizations for a study outcome that was not recorded as the primary discharge diagnosis. The GIE costs were generated by 12.4% of the study cohort, who contributed 21.5% of the person-time of NSAID exposure. Seventy-seven percent of the cost generators had a positive history of GI diseases, and 82% were older than 50 years of age; the total costs/person during the study period ranged from €1.91 to €19,698.70. The GIE costs/day of treatment decreased from €0.38/day for persons who had only one prescription to €0.25/day for persons with 5 or more prescriptions.

The baseline GIE costs/day were €0.028 (95% CI 0.026–0.031); they increased to €0.029 (95% CI 0.027–0.031) when secondary, tertiary, and quarternary diagnoses were included. Considering the baseline costs, up to 64.2% of the GIE costs/day may be directly attributable to NSAID use. Table 2 shows the distribution of directly- and indirectly-related GIE by type of outcome, and their cost to the NHS. A majority of the costs (57.5%) were generated by directly-related events. Each type of event contributed differently to the directly- and indirectly-related costs: 81.1% of all hospitalizations with a primary discharge diagnosis of interest occurred within the risk window for NSAID exposure, whereas 40% of antiulcer prescriptions and 60.8% of GI-related procedures contributed to the analysis as indirectly related events. Overall, prescriptions accounted for 78.6% of the iatrogenic costs, hospitalizations for 14%, and procedures for 7.4%.

Table 3 shows the type, number, and cost of hospitalizations and reimbursed prescriptions of the gastroprotective drugs included in the analysis. Almost 90% of the hospitalizations were due to GI bleeding or ulcers; the median hospital cost of the hospitalized subjects was €2,492 (data not shown). Among the gastroprotective drugs, H_2-receptor antagonists and proton pump inhibitors accounted for 62.2% of the prescriptions and 81.8% of the costs; the median cost of treatment of the patients receiving gastroprotective drugs was €31.3. As expected, prostaglandins were prescribed mainly during treatment, whereas all other gastroprotective drugs were prescribed in a more evenly distributed pattern during and after NSAID treatment (data not shown).

Although the overall iatrogenic costs amounted to €0.31/treatment day, there were differences according to the type of NSAID, route of administration, and selected patient characteristics, including comorbidities (Table 4). At univariate analysis, the iatrogenic costs/day of NSAID treatment increased with age (from €0.06 below 30 years of age up to €0.39 above 80 years), were 1.4 times higher in men than in women (€0.39 versus €0.27), 11.8 times higher among subjects with a positive history of GI disorders than in those without (€1.01 versus 0.09), and 45.1 times higher in cancer patients than in cancer-free subjects (€13.66 versus €0.30). The iatrogenic costs for subsequent prescriptions were 8% lower than for the first prescription. Gastroprotective drug prescriptions accounted for the largest part of the total costs in all patients (78.6%), but even more so in individuals with a positive GI history (84.2%); hospitalizations accounted for most of the costs (82.7%) among patients with cancer.

Table 5 shows the overall and per NSAID treatment-day GIE costs by individual NSAID and different pharmaceutical formulations. The average GIE cost/treatment day was

Table 3. Number and costs of NSAID-related hospitalizations and prescriptions of gastroprotective drugs*

Primary discharge diagnosis	ICD-9 code	Number	%	Cost	%
GI bleeding	578	113	62.8	323,383	60.1
Duodenal ulcer	532	23	12.8	88,513	16.4
Gastric ulcer	531	20	11.1	60,574	11.3
Gastritis/duodenitis/esophagitis	530.1, 535	18	10.0	51,096	9.5
Stomach function disorders	536, 537	5	2.8	12,495	2.3
All other peptic ulcers	533, 534	1	0.6	2,250	0.4
Total		180	100.0	538,310	100.0
Gastroprotective drugs	**ATC code**	**Number of prescriptions**	**%**	**Cost**	**%**
H_2 receptor antagonists	A02BA	40,899	32.9	1,179,551	39.2
Proton pump inhibitors	A02BC	36,350	29.3	1,282,549	42.6
Complexes of Mg^{+} AI^{3+} and Ca^{2+}	A02AD	23,379	18.8	182,802	6.1
Sucralfate	A02BX02	15,120	12.2	177,382	5.9
Prostaglandins	A02BB	8,453	6.8	185,883	6.2
Total		124,201	100.0	3,008,167	100.0

* Costs in Euros. Totals may differ from the sum due to rounding. NSAID = nonsteroidal antiinflammatory drugs; GI = gastrointestinal.

comparable for oral and suppository formulations (€0.24 versus €0.25), but was more than 3 times higher for injectable preparations (€0.91); within this group, it was 2.5 times higher for ketorolac (€1.73) than for piroxicam (€0.63). The cost differences between the oral NSAIDs were less pronounced, although there was a different distribution of iatrogenic costs by source (hospitalization, prescriptions, procedures) when COX nonselective NSAIDs were compared with either COX-2 preferential NSAIDs (meloxicam and nabumetone) or nimesulide ($P < 0.001$).

To avoid a possible bias due to the selective prescription of NSAIDs or variations in GIE costs among the patients belonging to specific risk groups, we defined 4 categories of GI risk based on age (cut-off, 50 years) and a positive GI history, and compared the person-time distribution and costs of the different formulations within and across the 4 groups (Table 6). Almost 60% of the person-time of NSAID

Table 4. Costs of NSAIDs and NSAID-related gastrointestinal events by selected patient characteristics*

	Person-days of NSAID treatment	Total GI cost	NSAID treatment cost	Total GI cost/ NSAID cost %	GI cost per NSAID treatment day	95% CI (GI cost/ day)	Daily cost ratio
Age							
<30	488,529	29,436	236,390	12.5	0.06	0.047–0.074	1†
30–39	680,925	98,639	351,514	28.1	0.15	0.13–0.16	2.4
40–49	1,166,069	263,541	612,322	43.0	0.23	0.20–0.25	3.8
50–59	2,160,170	606,342	1,122,605	54.0	0.28	0.26–0.30	4.7
60–69	2,889,663	967,473	1,521,314	63.6	0.34	0.31–0.36	5.6
70–79	3,267,957	1,169,096	1,765,521	66.2	0.36	0.31–0.41	5.9
>80	1,806,401	694,275	977,868	71.0	0.39	0.33–0.43	6.4
Sex							
Female	8,538,682	2,300,275	4,508,228	51.0	0.27	0.25–0.29	1†
Male	3,921,031	1,528,529	2,079,305	73.5	0.39	0.36–0.42	1.4
Cancer history							
No	12,453,907	3,749,894	6,582,252	57.0	0.30	0.29–0.32	1†
Yes	5,806	78,909	5,281	1,494.1	13.66	5.5–21.7	45.1
GI history							
No	9,427,939	798,215	4,811,598	16.6	0.09	0.074–0.095	1†
Yes	3,031,774	3,030,588	1,775,935	170.6	1.01	0.94–1.06	11.8
Number of prescriptions							
1	5,255,195	1,691,477	2,614,895	64.7	0.32	0.30–0.35	1†
2+	7,204,518	2,137,327	3,972,638	53.8	0.30	0.27–0.32	0.92
Total	12,459,713	3,828,803	6,587,533	58.1	0.31	0.30–0.32	

* Costs in Euros. Sums of the strata may differ due to rounding. NSAIDs = nonsteroidal antiinflammatory drugs. GI = gastrointestinal; CI = confidence interval.
† Reference category

Table 5. Cost of NSAIDs and NSAID-related gastrointestinal events by individual drug and formulation*

	Person-days of NSAID treatment	Person-days of NSAID treatment (%)	Hospitalization cost† (%)	Prescription cost† (%)	Procedure cost† (%)	Total GI cost	NSAID treatment cost	GI cost per NSAID treatment day	95% CI (GI cost/ day)
Oral									
Others‡	1,844,140	14.8	6.7	86.6	6.7	497,123	944,508	0.27	0.25–0.29
Nimesulide	2,510,104	20.1	5.9	85.5	8.6	660,693	1,270,524	0.26	0.25–0.28
Meloxicam/ Nabumetone	602,705	4.8	3.3	87.4	9.3	158,175	486,928	0.26	0.24–0.29
Ibuprofen	492,579	4.0	9.5	82.4	8.0	128,620	222,746	0.26	0.23–0.30
Piroxicam	2,253,732	18.1	16.6	75.7	7.7	542,769	780,959	0.24	0.22–0.27
Diclofenac	2,220,554	17.8	23.7	71.4	4.9	475,913	845,042	0.21	0.18–0.25
Naproxen	894,062	7.2	24.9	70.8	4.3	165,884	276,433	0.19	0.14–0.23
Total oral	10,817,876	86.8	12.7	80.1	7.1	2,629,178	4,827,140	0.24	0.23–0.25
Injectables									
Ketorolac	196,065	1.6	24.0	68.7	7.4	338,773	439,526	1.73	1.50–1.96
Others§	114,866	0.9	12.0	79.4	8.7	122,051	124,093	1.06	0.87–1.26
Diclofenac	289,371	2.3	8.3	84.0	7.7	236,030	234,830	0.82	0.73–0.91
Ketoprofen	311,690	2.5	15.5	74.3	10.1	208,523	277,148	0.67	0.55–0.79
Piroxicam	269,371	2.2	15.8	73.9	10.3	170,919	194,853	0.63	0.55–0.72
Total injectables	1,181,363	9.5	16.2	75.2	8.6	1,076,296	1,270,448	0.91	0.86–0.97
Suppositories¶	95,579	0.8	18.3	75.7	6.0	24,351	31,005	0.25	0.13–0.39
Combinations	364,895	2.9	25.5	73.6	0.9	98,978	458,940	0.27	0.04–0.50
Total	12,459,713	100.0	14.1	78.6	7.4	3,828,803	6,587,533	0.31	0.30–0.32

* Cost in Euros. NSAIDs = nonsteroidal antiinflammatory drugs; GI = gastrointestinal; CI = confidence interval.
† Percentage of total GI costs; row percentages add up to 100%.
‡ Includes: indomethacin, sulindac, fentiazac, acemetacine, proglumetacine, ketorolac, ketoprofen, dicoflenac sodium with misoprostol, tenoxicam, droxicam, cinnoxicam, flurbiprofen, tiaprofenic acid, furprofen, mefenamic acid, niflumic acid, morniflumate, and amtolmetine.
§ Includes tenoxicam, ibuprofen, and naproxen
¶ Includes indomethacin, diclofenac, proglumetacine, cinnoxicam, ibuprofen, naproxen, and ketoprofen.

use was contributed by patients aged more than 50 years and without a history of GI. In a comparison between the highest and lowest risk groups, COX-2 preferential drugs, injectable NSAIDs, and NSAID combinations were prescribed more frequently to elderly patients with a positive history of GI disease than nimesulide, which was used relatively more by low-risk patients ($P < 0.001$). The GIE cost/day of NSAID treatment was 15–20 times higher among elderly patients with a positive GI history (€1.03; 95% CI, 0.96–1.10) than among those aged 50 years or less without such a history (€0.05 per day; 95% CI 0.04–0.06). There were no statistically significant differences between patients treated with COX-2 preferential drugs and nonspecific oral NSAIDs. The GIE costs following treatment with

Table 6. Costs of NSAID-related gastrointestinal events per treatment day by type of formulation, age, and prior GI history*

	No GI history, ≤ 50 years			No GI history, > 50 years			GI history, ≤ 50 years			GI history, > 50 years		
Formulation	% p-days†	GI-cost/ day‡	95% CI (cost/ day)	% p-days†	GI-cost/ day‡	95% CI (cost/ day)	% p-days†	GI-cost/ day‡	95% CI (cost/ day)	% p-days†	GI-cost/ day‡	95% CI (cost/ day)
Oral	15.5	0.037	0.03–0.04	60.8	0.075	0.07–0.08	2.8	0.65	0.60–0.70	20.9	0.83	0.80–0.85
COX-2 preferential§	11.9	0.026	0.02–0.04	60.0	0.053	0.03–0.08	2.7	0.72	0.45–1.00	25.4	0.82	0.73–0.91
Nimesulide	21.5	0.030	0.02–0.04	54.8	0.064	0.05–0.07	3.7	0.73	0.63–0.83	20.0	0.97	0.90–1.05
COX nonselective	13.8	0.042	0.03–0.05	62.7	0.080	0.06–0.10	2.6	0.61	0.54–0.68	20.9	0.78	0.74–0.82
Suppositories	32.6	0.037	0.0–0.15	49.6	0.053	0.03–0.08	3.7	0.72	0.10–1.40	14.1	1.35	0.45–2.26
Injectables	18.7	0.16	0.11–0.21	53.9	0.29	0.23–0.35	3.9	1.73	1.52–1.94	23.5	2.80	2.57–3.03
Combinations	10.7	0.083	0.07–0.10	56.9	0.068	0.04–0.10	3.3	0.47	0.38–0.55	29.0	0.72	0.00–1.51
Total	15.8	0.052	0.04–0.06	59.9	0.093	0.08–0.11	3.0	0.78	0.73–0.83	21.4	1.03	0.96–1.10

* Costs in Euros. NSAID = nonsteroidal antiinflammatory drugs; GI = gastrointestinal; p-days = person-days; CI = confidence interval.
† Percentage of person-days of exposure, calculated using the total person-days for each specific formulation as denominator (row percentages add to 100%).
‡ Ratio of total GI costs/person-days of NSAID treatment, in Euros.
§ Includes meloxicam and nabumetone.

injectable NSAIDs were higher than those related to all of the other formulations for all categories of risk ($P < 0.001$).

DISCUSSION

The main finding of this study is that the iatrogenic costs to the NHS of NSAID treatment add 58% to the cost of the treatment itself, and they amount to €0.31/treatment day, a cost that is generated by 12.4% of NSAID users (mainly elderly subjects and patients with a positive history of GI disease) and particularly during the first prescription of an NSAID. Comparison to baseline GIE costs shows that up to 64.2% of the GIE costs may be directly attributed to NSAID use. Most of the cost originates from the prescription of gastroprotective drugs, whereas hospitalizations and outpatient diagnostic procedures account for a smaller proportion.

Iatrogenic costs vary widely when considered on the basis of the route of NSAID administration and selected patient characteristics; they are 3.7 times higher following treatment with injectable rather than oral NSAIDs, and are especially high for ketorolac. This finding is consistent across different categories of age and GI disease history, and are also in line with the results of an earlier safety study using the same database, which showed that the estimated relative risk of hospitalization for upper GI bleeding in subjects without a history of GI disease was 24.7 for ketorolac and 2.7 for diclofenac (oral) compared with the nonuse of NSAIDs (14). Some clinical studies have suggested that the GI tolerability of nimesulide, meloxicam, and nabumetone is better than that of other NSAIDs (23,26). We estimated a non-statistically significant reduction (35%) in iatrogenic costs when we compared COX-2 preferential drugs with nonselective oral NSAIDs in patients without a history of GI disease, but this difference disappeared in the analysis of subjects with a positive history. One explanation for this finding could simply be that there is no difference in the safety profiles of the currently available NSAIDs (11). Another possible explanation is that there is a preferential prescription of NSAIDs with a perceived better safety profile to patients with more severe GI disease, whereas NSAIDs with a higher perceived risk of GI toxicity would be evenly prescribed to persons without a known risk for GI disease. This may lead to residual confounding, even after stratification. A third interpretation is that gastroprotective drugs are also prescribed for preventive purposes (regardless of the occurrence of adverse GI events) to high-risk patients who take COX-2 preferential drugs, and this adds to their GI costs.

The results of previous studies of the iatrogenic costs of NSAID therapy are generally not comparable with those described here because of differences in study design, health care structures, and/or the type of costs analyzed. Some European researchers have developed models based on the incidence and treatment costs of NSAID-induced gastroduodenal ulcers, suggesting that ulcers add between 8% and 200% to the costs of NSAID treatment with variations relating to the individual NSAIDs (20–22). Our study is more comparable with two US studies. In a 2-year followup study of patients with arthritis covered by Medicaid, approximately 25% of the population experienced NSAID-related adverse events requiring further medical care. The GIE costs added 46% to the mean cost of treatment, but no information was provided regarding individual NSAIDs (17). In a retrospective cohort study of people aged 65 years or more enrolled in the Tennessee Medicaid program, the annual cost per patient for all types of medical care required as a result of GI disease increased with the frequency of use ($244 for frequent users, i.e., $0.67 per day) and dosage of NSAIDs (27).

The contribution of our study to the subject stems from its epidemiologic approach and its use of real computer-based population data rather than data derived from external modelling. We tried to estimate the iatrogenic cost per day of individual NSAIDs in the general population, and to stratify this cost on the basis of some important risk factors that are not always included in safety studies. To this end, and taking advantage of the wealth of information available in the SISR database, we developed a model that at least partially accounts for inadequate compliance, any delays in the provision of elective medical services, and the sequence of medical costs that may be triggered by an upper GI event. Furthermore, we estimated a baseline cost to quantify the burden of GI disorders in the absence of NSAID exposure and provide a better insight into the presented results. Because the characteristics of the population in FVG and its access to health care are representative of the larger population of NSAID users in Italy, and to some extent in other countries with an NHS providing universal coverage, our results may be generalized to the entire Italian population, and (with some caution) to other countries.

However, the study has some limitations relating to the inherent methodologic challenges of an observational study in this field. First, drug-specific costs (and their variations) should not be used to evaluate differences in the GI safety of individual drugs, and even the results of a stratified analysis should be interpreted with caution. Our study design and analyses were not intended to provide an estimate of a causal association between the type of NSAID therapy and GIE costs, and the observed variations involving different NSAIDs may have been due to differences in patient characteristics rather than drug effects. Furthermore, iatrogenic costs can also be generated for preventive purposes and are therefore not, per se, a good marker for drug safety.

Secondly, our cost estimates are based on real population data, but also involve a number of internal modelling assumptions and should therefore be regarded as approximate. Nevertheless, the assumptions seem to hold true and, in many ways, the results are consistent with what is known from the literature. The iatrogenic costs may have been over- or underestimated. Overestimation may have occurred if some medical costs were erroneously attributed to an upper GIE (e.g., inappropriate coding in the SISR records of hospitalizations, prescriptions, or procedures or inappropriate attribution) or related to NSAID exposure (e.g., an overly large risk window or an inappropriate attribution of events occurring outside the risk window). In the first case, a coding error would have a limited

impact on the results, not only because it would be nondifferential and would therefore both add and subtract events for the analysis, but also (and more importantly) because the quality of the SISR records is very high as a result of routine quality control procedures, as has been documented previously in the case of GI-related hospitalizations (14,25). By comparison to baseline GIE costs, we estimated that the overestimation due to inappropriate attribution (use of resources for reasons other than NSAIDs) could be as high as 36%. The magnitude of a distortion related to the second set of possibilities is more difficult to ascertain, although the size of our risk window is in line with that used in the literature concerning the GI safety of NSAIDs (11), and the upper boundaries of a potential overestimate can always be drawn if one chooses the most conservative assumptions.

Underestimation may have occurred for several reasons. First, the main analysis only included hospitalizations with a primary discharge diagnosis of the conditions of interest, and excluded all of the secondary, tertiary, and quarternary diagnoses, some of which may have been the reason for admission. Had we accounted for the cost of hospitalizations with a relevant nonprimary discharge diagnosis, the iatrogenic cost of NSAIDs would have risen from 58% to 65%. Secondly, we could not identify specialist consultations due to GIE from the database, which would cost the NHS €20.7 per visit. The other possible causes of underestimation (an overly short risk window, the missing contribution of high-risk patients meeting the exclusion criteria) appear to be less relevant. It also should be pointed out that, because our study considers the NHS perspective, the analysis only includes reimbursed GI events following a reimbursed prescription for NSAIDs; it therefore does not include the GIE costs following the nonreimbursed use of (prescription or over the counter) NSAIDs because this has not yet been quantified in FVG. Had we been able to account for them, we would have estimated a larger exposure to NSAIDs but not higher NSAID costs to the NHS, whereas we would have estimated higher total GIE costs to the NHS (following nonreimbursed NSAID use). However, the ratio "GIE costs/NSAID treatment cost" would not have changed from the NHS perspective because GIE costs enter the ratio only if generated by relevant NSAID costs. Finally, the study does not include any nonreimbursed GIE costs (regardless of NSAID reimbursement) and, although this was not the object of our analysis and does not affect our results, it is worth pointing out that out-of-pocket medical expenses represent an additional cost to be borne by the patients. All of the above is indirectly supported by the fact that the costs were generated by a smaller proportion of our study cohort (12%) than the proportion described in other studies (30% in the US).

In conclusion, we show that GI events occurring in a relatively small proportion of NSAID users add 58% to the NHS cost for NSAID treatment. Despite the inevitable limitations of studies of this kind, including the inherent risk of over- or underestimating real costs, we feel that this figure is a very reasonable approximation. Iatrogenic costs are mainly generated by coprescription of gastroprotective drugs, and are higher in the elderly, in subjects with a previous history of GI diseases or cancer, and in users of injectable NSAIDs. There is no difference in the iatrogenic costs of COX-2 preferential and COX nonspecific drugs. Recent data from the Celecoxib Long-term Arthritis Safety Study and VIGOR study show that new COX-2 selective agents significantly reduce the incidence of endoscopically detected gastroduodenal ulcers in comparison with ibuprofen and diclofenac or naproxen (30–31). Whether these new compounds are capable of lowering the iatrogenic costs of NSAID treatment remains to be evaluated and will depend on their GI safety under everyday circumstances and the approach of physicians toward the prescription of gastroprotective drugs for NSAID-treated patients at risk.

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