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Upper gastrointestinal symptoms and therapies in elderly out-patients, users of non-selective NSAIDs or coxibs

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SUMMARY

Background: The association between coxib or non-steroidal anti-inflammatory drug use with gastrointestinal symptoms and drug prescriptions in ambulatory elderly patients is not well defined.

Aim: To evaluate the association between non-steroidal anti-inflammatory drug NSAID and coxib use with gastrointestinal symptoms and therapies in elderly subjects managed by their general practitioner.

Materials: The study was carried out by 133 general practitioners in Italy. By using a structured interview, sex, age, physical function, current medications, new drug prescriptions and upper gastrointestinal symptoms were registered from all elderly subjects who were referred to their general practitioners during a 2-week period. The numbers of hospitalizations, gastrointestinal bleeding events and gastrointestinal diagnostic procedures occurring during the last 6-month period were recorded.

Results: Included in this study were 5515 elderly subjects. The overall prevalence of drug use was 92%. Musculo-skeletal drugs were taken by 15% of patients; NSAIDs were taken by 6%, and coxibs by 3% of patients. A significantly higher prevalence of upper gastrointestinal symptoms was observed in elderly NSAID users compared with coxib users and non-users of musculo-skeletal drugs (44% vs. 33% vs. 32% respectively, $P = 0.001$). The prescriptions of drugs for acid-related disorders were significantly higher in patients who were concomitantly taking NSAID rather than coxibs (13% vs. 6%, $P < 0.01$). The prescriptions of drugs for acid-related disorders were significantly associated with the presence of upper gastrointestinal symptoms (OR = 1.7, 95% CI = 1.6–1.9), previous gastrointestinal disorders (OR = 1.1, 95% CI = 1.0–1.3) and NSAID use (OR = 1.5, 95% CI = 1.0–2.2), but no coxib use.

Conclusion: In this elderly population, upper gastrointestinal symptoms and prescriptions for gastroenterological drugs were higher in non-steroidal anti-inflammatory drug users than coxib users and non-users of musculo-skeletal drugs.

INTRODUCTION

The prevalence of drug use as well as adverse drug reactions (ADR) increase with advancing age. Data from the GIFA (Italian Group of Pharmacoepidemiology in the Elderly)[1] on 28.411 patients consecutively admitted to 81

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hospitals throughout Italy reported that gastrointestinal (GI) complaints represented the most common events (19%) of 964 cases of ADR (3.4% of all hospital admissions). In this population, moreover, non-steroidal anti-inflammatory drugs (NSAID), aspirin and antiplatelets were the drugs most frequently responsible of severe ADR included GI bleeding.[1] Another study from all medicare/medicaid certified nursing homes in four states of US carried out on 125.516 newly admitted elderly residents from 1992 to 1996 showed that NSAID exposure increased the GI-related hospitalization rate in both men [rate ratios, RR = 2.64, 95% confidence interval (CI) = 1.17–5.99] and women (RR = 3.3, 95% CI = 1.85–5.65).[2] More recently, a study carried out on 3154 elderly out-patients who were managed by 63 general practitioners (GP) in Italy reported that NSAIDs and/or aspirin use was significantly associated with a greater number of upper GI symptoms and prescriptions of GI drugs than non-users of these classes of drugs.[3]

The cyclo-oxygenase-2 (COX-2) inhibitors, i.e. coxibs, are a new group of agents with anti-inflammatory, pain reducing and quality of life improving effects similar to that of NSAIDs even in elderly people.[4] Clinical and epidemiological trials have reported that coxibs have a lower potential for causing upper GI injury, i.e. upper GI haemorrhage, in elderly patients,[5] compared with NSAIDs. Recently, coxib use was associated with a significantly decreased risk of out-patient physician claims for upper GI symptoms[6] and less GI co-therapy compared with non-selective NSAID use.[7] However no studies have yet evaluated the association between coxib or NSAID use with GI symptoms and GI drug prescriptions specifically in ambulatory elderly patients.

Aim of the study was to evaluate the relationship between NSAID and coxib use with GI symptoms and GI drug prescriptions in elderly patients managed by their GP.

MATERIALS AND METHODS

Selection of GPs

The study was funded by FIRI (Italian Fundation for the Reasearch on Aging) and was carried out by 133 GPs. At the study's conception, 192 GPs were randomly identified from local GP lists, 188 of whom attended a preliminary meeting to receive information about the aim, methods and study design. The meeting was carried out by 24 educated specialists in geriatrics referring to 24 geriatric units in Italy. Of 188 GPs who attended the meeting, 133 GPs agreed to carry out the investigation.

Inclusion criteria

The investigation was performed from March to June 2003. General practitioners included all patients seen during a 2-week period (10 working days) who accepted to participate in the study. All subjects aged 65 years and over who sought their GP for a medical problem during this 2-week period were included in the study. Elderly patients who were visited in their home or in nursing homes were not included.

Data collection

In all elderly subjects, the data were obtained by a structured interview of patients and/or their relatives and where possible, were confirmed by the GPs' medical records. Demographic data (age, gender), physical functions structured according to the activities of daily living (ADL)[8] and the instrumental activities of daily living (IADL)[9] questionnaires, current therapies and new drug prescriptions, GI symptoms according to the Gastrointestinal Symptom Rating Scale (GSRS)[10] and other GI symptoms (vomiting, haematemesis and/or melena) were recorded. Moreover, the presence of previous GI disorders (GI bleeding events and/or GI diagnostic procedures occurred during the last 6-month period) were recorded. Records were computerized and e-mailed to the statistic reference centre for evaluation.

Drug use

Drug use was identified according to the Anatomical Therapeutics Chemical Classification code system (ATC classification).[11] In this system, drugs are divided into 14 main anatomical groups, each being further divided into two sublevels, therapeutical and pharmacological, respectively. During the interview, the names of specific drugs were recorded as well as the doses, the use patterns (acute, chronic, on demand) and the duration of treatment.

Patients were defined as drug users if they took a drug of any of the above-described classes at the moment of the visit. Moreover, the new drug prescriptions, including the doses of drugs, were recorded according to the same ATC classification system.

Non-steroidal anti-inflammatory drug and coxib drugs were included in the M group (musculo-skeletal drugs, reimbursed by Health National System in Italy when prescribed by GPs) of the ATC classification while GI drugs were included in the A group. Upper GI drug use was defined as any treatment with antacids, H_2-blockers, proton pump inhibitors (PPIs), sucralfate, misoprostol, or prokinetics.

Physical functions

Physical functions were assessed with standardized tests evaluating the patient's ability to perform six ADL: bathing, dressing, transferring, walking, toileting and eating.[8] Eight IADL, i.e. managing finances, taking medications, using the telephone, food or clothes shopping, washing, using transportation, preparing meals and doing housework, were also evaluated.[9] We defined 'severe disability' as a loss of three or more functions on the ADL and/or IADL questionnaires, 'moderate disability' as a loss of two functions on the ADL and/or IADL tests, 'mild disability' as a loss of at least one function on the ADL and/or IADL tests and 'no disability' as no loss in ADL/IADL functions.

Upper GI symptoms

Gastrointestinal symptoms were evaluated with the GSRS, modified for patients with upper GI disorders.[10] The questionnaire included 15 items for the description of GI symptoms, however, only the following items were evaluated in the present study:

- abdominal pain syndrome (items 1: stomach ache or pain and 4: hunger pains in the stomach or belly);
- reflux syndrome (items 2: heartburn; 3: acid reflux); and
- indigestion syndromes (items 5: nausea; 6: rumbling in the stomach, i.e. vibrations or noise in the stomach; 7: bloated stomach, i.e. swelling in the stomach; 8: burping, i.e. bringing up air or gas through the mouth) were evaluated.

Items that described diarrhoea and constipation syndromes (items 9–15) were not reported in the study. The GSRS questionnaire included a response scale with seven grades: we defined symptomatic patients those patients who reported mild or moderate or severe discomfort at least in one item.[12]

Moreover, the presence of vomiting, melena and/or haematemesis and the presence of previous GI disorders (GI bleeding events and/or GI diagnostic procedures occurred during the last 6-month period) were recorded.

Statistics

Statistical analysis was performed using SPSS 11.5 statistical package. The Pearson's Chi-squared and the Fisher's exact test or Student's *t*-test for unpaired data were used where appropriate.

In order to summarize many variables by few factors, factor analysis was employed retaining factors with eigenvales >1. Including ADL and IADL scores, GSRS abdominal pain, reflux and indigestion scores, haematemesis, melena, vomiting and previous GI events (occurred during the last 6-month period), factorial analysis resulted in three factors; the first was strongly correlated with GI symptoms (GI symptoms score), the second with ADL and IADL scores (disability score), and the third was correlated with previous GI events (previous GI disorders score). All three components accounted for 67% of the global variance.

Labeling and interpretation of the resulting factors were performed as function of the component matrix. Factor's scores were generated for all patients and used as input for subsequent analysis.

Multiple linear regression analysis was performed to correlate upper GI symptoms factor score with age, sex, disability factor, previous GI disorders factor and specific drug's classes use. Binary logistic regression model was used to compute odds ratio (OR) and relative 95% CI of some independent variables predicting the actual use or the *de novo* prescription of GI protective drugs. The maximum likelihood method was used for entering and removing variables and for calculating variable interaction. All *P* values were two-tailed with statistical significance indicated by a value of $P < 0.05$.

RESULTS

Study population: demographic characteristics and drug use

During the study period, 5533 subjects were observed by 133 GPs; 18 subjects were excluded because they did not fulfill inclusion criteria (age 65 years or over). Thus, the final evaluation was performed in 5515 elderly

subjects (males = 2519, females = 2996, mean age = 74.97 ± 6.2 years, range = 65–100 years). No differences have been found between males and females as regards mean age ($M = 74.9 \pm 6$ vs. $F = 75.2 \pm 6.3$ years, P = ns). However, females had significantly higher disability rates than males both at ADL ($F = 17.3\%$ vs. $M = 13.1\%$, $P < 0.0001$) and IADL scores ($F = 41.1\%$ vs. $M = 31.0$, $P < 0.0001$).

A total of 5053 of 5515 subjects (91.6%) were taking at least one drug, with a statistically significant difference observed between males and females (90.6% vs. 92.5%, $P = 0.017$). Cardiovascular drugs (71.7%) were those most frequently taken by the elderly. Other pharmacological classes used with great frequency were low-dose aspirin (20.6% of subjects), GI drugs (19.7%), nervous system drugs (17.2%) and musculo-skeletal drugs (15.4%).

The prevalence of anti-inflammatory and antirheumatic drug use was 9%; non-selective NSAIDs accounted for 6.11% (337 subjects) and the prevalence of coxib use was 2.9% (162 subjects). Table 1 illustrates the demographic and functional characteristics in the study population divided into NSAID and/or coxib users vs. non-users. Results showed that NSAID and/or coxib users were significantly more females and were taking an higher mean number of drugs than non-users. Moreover, patients who were taking NSAIDs and/or coxibs had a significantly higher disability, as evaluated by ADL, particularly of grade moderate or severe. No differences were found in demographic and functional characteristics between NSAID users and coxib users. Table 2 illustrates specific NSAID and coxib use in this population, classified according to gender. Results showed that nimesulide (26.2%), diclofenac (16.6%) and piroxicam (7.4%) were the most frequent non-selective NSAIDs taken, while celecoxib and rofecoxib were the only two coxibs taken (18.6% and 13.8% of the total anti-inflammatory and antirheumatics, respectively). Women took more NSAIDs (7.9% vs. 3.9%, $P < 0.0001$) and coxibs (3.7% vs. 2.02%, $P < 0.0001$) than men. No significantly modifications in NSAID and coxib use was observed with increasing age.

NSAID, coxib use and GI symptoms

A total of 1764 subjects of 5387 who completed the GSRS questionnaire (32.7%) presented at least one mild and/or moderate and/or severe upper GI symptom; the prevalence of upper GI symptoms was significantly higher in females than males (34.2% vs. 30.9%, $P = 0.011$). In detail, women had a significantly higher prevalence of abdominal pain (17.7% vs. 14.5%, $P = 0.002$) and reflux syndrome (15.1% vs. 13.0% $P = 0.027$) than men, while no differences in the prevalence of indigestion syndrome were observed between the two sexes (males = 23.8% vs. females = 26.0, $P > 0.05$).

A significantly higher prevalence of upper GI symptoms was observed in elderly NSAID users than coxib users (43.7% vs. 32.7%, $P = 0.02$) or no-users of

Table 1. Demographic and functional characteristics of elderly subjects divided according to NSAID and/or coxib use vs. non-use

	Non-users of NSAIDs and/or coxibs (No = 5016)	NSAID and/or coxib use (No = 499)	NSAID use (No = 337)***	Coxib use (No = 162)***
Males (No, %)	2369 (47.2)*	150 (30.1)*	99 (29.4)	51 (31.5)
Females (No, %)	2647 (52.8)*	349 (69.9)*	238 (70.6)	111 (68.5)
Mean age ± s.d.	75.1 ± 6.2	74.9 ± 6.3	74.8 ± 6.4	74.9 ± 6.2
Total number drugs ± s.d.	2.8 ± 1.9*	3.8 ± 2.0*	3.8 ± 2.1	3.7 ± 1.8
Physical function#	No = 4826	No = 483	No = 328	No = 155
ADL				
No disability	4102 (88.3)*	390 (80.7)*	263 (80.2)	127 (81.9)
Mild disability	473 (9.8)	57 (11.8)	36 (11.0)	21 (13.5)
Mod/severe disability	251 (5.2)**	36 (7.4)**	29 (8.8)	7 (4.5)
IADL				
No disability	3100 (64.2)	313 (64.8)	206 (62.8)	107 (69.0)
Mild disability	915 (18.2)	90 (18.6)	65 (19.8)	25 (16.1)
Mod/severe disability	811 (16.8)	80 (16.5)	57 (17.4)	23 (14.8)

* $P < 0.0001$; ** $P = 0.05$; *** P = not significant: # ADL and IADL data were missing in 190 non-users and 16 NSAID/coxib users.

Table 2. Specific NSAIDs and coxibs taken by elderly subjects divided according to gender

	No. of patients (%) ($n = 499$)	No. of females (%) ($n = 349$)	No. of males (%) ($n = 150$)
M01AB. Acetic acid derivates			
Amtolmetin	3 (0.60)	2 (0.57)	1 (0.67)
Indomethacin	1 (0.20)	1 (0.29)	0 (0.00)
Diclofenac	83 (16.63)	52 (14.89)	31 (20.66)
Proglumetacin	1 (0.20)	1 (0.29)	0 (0.00)
Ketorolac	4 (0.80)	3 (0.85)	1 (0.67)
Aceclofenac	4 (0.80)	4 (1.15)	0 (0.00)
M01AC. Oxicams			
Piroxicam	37 (7.41)	28 (8.02)	9 (6.00)
Tenoxicam	5 (1.00)	2 (0.57)	3 (2.00)
Meloxicam	16 (4.01)	13 (3.72)	3 (2.00)
M01AE. Propionic acid derivates			
Ibuprofen	23 (4.60)	14 (4.01)	9 (6.00)
Naproxen	14 (2.80)	8 (2.29)	6 (4.00)
Ketoprofen	28 (5.61)	18 (5.16)	10 (6.67)
Flurbiprofen	1 (0.20)	1 (0.29)	0 (0.00)
M01AX. Others NSAID			
Benzidamina	1 (0.20)	1 (0.29)	0 (0.00)
Glucosamina	8 (1.60)	5 (1.43)	3 (2.00)
Nabumetone	2 (0.40)	2 (0.57)	0 (0.00)
Ac. Niflumico	1 (0.20)	1 (0.29)	0 (0.00)
Nimesulide	131 (26.25)	102 (29.22)	29 (19.33)**
M01CB. Gold			
Auranofin	5 (1.00)	4 (1.15)	1 (0.67)
M01AH. Coxibs			
Celecoxib	93 (18.64)	70 (20.06)	23 (15.33)
Rofecoxib	69 (13.83)	41 (11.75)	28 (18.67)*
Total	530	373	157

Thirteen patients took two NSAIDs concomitantly and 19 patients took one NSAID and one coxib concomitantly.
* $P = 0.056$.
** $P = 0.028$.

musculo-skeletal drugs (43.7% vs. 32.1%, $P = 0.001$). In particular, NSAID users had a significantly higher prevalence of abdominal pain (23.1% vs. 16.2%, $P = 0.002$), reflux syndrome (19.2% vs. 13.9%, $P = 0.011$), indigestion syndrome (32.6% vs. 24.4%, $P = 0.001$) and vomiting (6.9% vs. 2.4%, $P = 0.0001$) than non-users of musculo-skeletal drugs. In contrast, no differences in the prevalence of upper GI symptoms were observed between coxib users and non-users of musculo-skeletal drugs (Figure 1).

Multiple linear regression analysis demonstrated that upper GI symptoms were significantly associated with NSAID use ($P < 0.002$) and no with coxib or other drug use. Moreover, regression logistic analysis confirmed that vomiting was significantly associated with NSAID use (OR = 2.6, 95% CI = 1.7–3.9) and no with coxib or other drug use.

NSAID, coxib use and prescriptions of GI drugs

As reported in Table 3, 1929/5515 patients (35%) received at least one new prescription of drug. The most prescribed were musculo-skeletal drugs (29.3%), anti-infective drugs for systemic use (20.6%) and gastroenterological drugs (15.2%). Among the musculo-skeletal drugs, NSAIDs were prescribed in 19.2% and coxibs in 9.4% of patients. Among the gastroenterological drugs, those for acid-related disorders were prescribed in 9.02% of patients: PPIs (4.7%) were more prescribed than antacids (2.1%), sucralfate (1.34%), H_2-blockers (0.62%) or misoprostol (0.05%). The new prescriptions of drugs for acid-related disorders were significantly higher in patients who concomitantly were taking NSAIDs than coxibs (13.1% vs. 6.0%, $P < 0.01$).

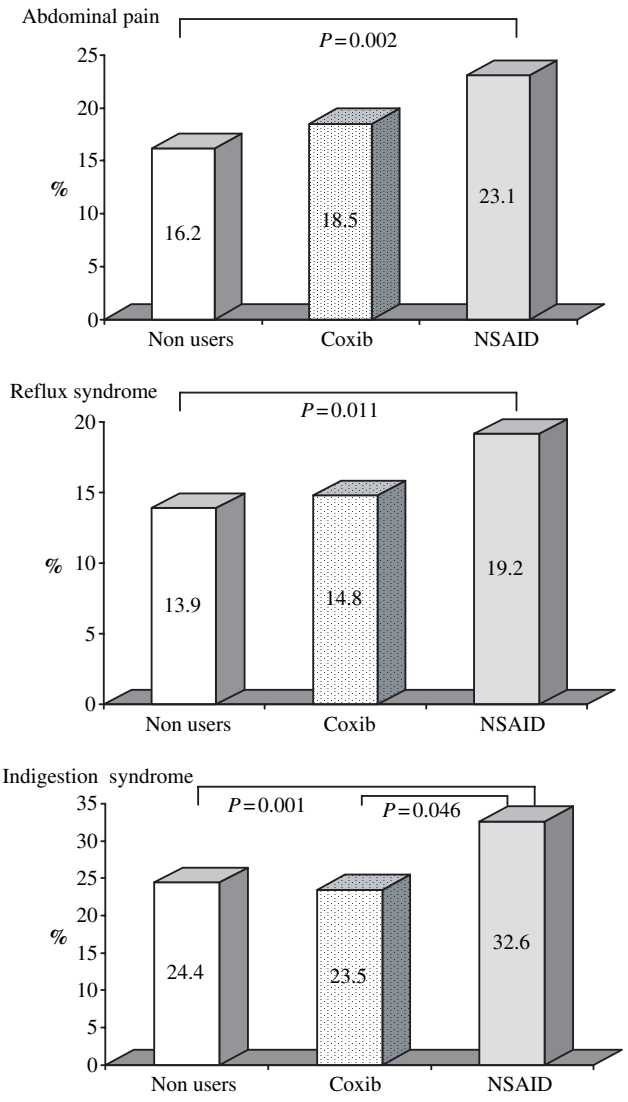

Figure 1. Prevalence of abdominal pain, reflux and indigestion syndromes in elderly NSAID users vs. coxib users and vs no-users musculo-skeletal drugs.

Multivariate analysis demonstrated that the new prescriptions of drugs for acid-related disorders were significantly associated with the presence of upper GI symptoms (OR = 1.7, 95% CI = 1.6–1.9), previous GI disorders (OR = 1.1, 95% CI = 1.0–1.3) and NSAID use (OR = 1.5, 95% CI = 1.0–2.2), but no coxib or other drug use.

DISCUSSION

This study demonstrated in a large out-patient population that over 15% of the elderly people were taking a musculo-skeletal medication, and that the use of these drugs was higher in females than males (19% vs. 11.1%, $P < 0.0001$). The use of non-selective NSAIDs (6.1%) and coxibs (2.9%) accounted for almost 10% of patients. This high prevalence of musculo-skeletal use in the elderly confirms previous data[1–3, 13–15] and certainly reflects the prevalence of rheumatic disorders in old age.[16]

In this elderly population, over 30% of patients reported at least one symptom related to the upper GI tract, as evaluated by means of the GSRS. The GSRS has been administered in the interview format in 5387 patients (97.6% of total population). No problems were encountered with patients understanding or questionnaire administration confirming that the GSRS has also in the elderly people a good reliability and acceptable validity and responsiveness.[12]

This study reported that elderly NSAID users had a significant higher prevalence of epigastric and/or abdominal pain, reflux symptoms and indigestion syndrome than non-users of musculo-skeletal drugs. This finding is in agreement with a previous study carried out in 1375 residents of Minnesota aged 65 years and older reporting that non-aspirin NSAIDs were significantly associated (OR = 1.8, 95% CI = 1.3–2.6) with dyspepsia (defined as pain located in the upper abdomen or nausea) and/or heartburn.[17] More recently, a telephone survey of a US random sample of 1600 persons at least 40 year old reported that NSAID users were twice as likely an non-users to report GI side effects,[18] while an epidemiological study from Italy carried out in 3154 elderly out-patients demonstrated a significantly higher prevalence of upper GI symptoms in NSAID and low-dose aspirin users than non-users (25% vs. 28% vs. 16.6% respectively, $P < 0.0001$).[3]

In this study, elderly NSAID users reported a higher prevalence of upper GI symptoms than those reported by subjects who were treated with coxibs (43.7% vs. 32.7%, $P < 0.05$). The results were very similar to the percentages of 43.3% and 35.5% dyspepsia-like events ($P < 0.001$) recently reported in a randomized double-blind trial by over 3600 diclofenac and celecoxib users, respectively.[19] Indeed, the data of our study confirm in a 'real-world' setting the results of double-blind trials carried-out in patients with osteoarthritis or rheumatoid arthritis that reported fewer incidence of abdominal pain and dyspepsia in patients treated with coxib than with other non-selective NSAIDs.[20, 21] The data are also in agreement with a recent analysis of an insurance claims database of approximately 1.8 million persons in

Table 3. The six classes of drugs more frequently prescribed in elderly out-patients divided according to gender

ATC codes	Drug classes	All patients ($n = 1929$) (%)	Females ($n = 1117$) (%)	Males ($n = 812$) (%)	P
M.	Musculo-skeletal system	578 (29.29)	362 (32.40)	216 (26.60)	0.007
M01.	Anti-inflammatory and antirheumatics				
M01A	NSAID	366 (18.97)	215 (19.24)	151 (18.59)	ns
M01AH	COXIB	182 (9.43)	124 (11.10)	62 (7.63)	0.011
I.	Anti-infective drugs for systemic use	398 (20.63)	196 (17.54)	202 (24.87)	0.0001
A.	Gastroenterological apparatus	293 (15.18)	172 (15.39)	812 (14.9)	ns
A02	Drugs for acid related disorders				
A02A.	Antacids	40 (2.07)	21 (1.88)	19 (2.33)	ns
A02BA.	Anti-H2	12 (0.62)	9 (0.80)	3 (0.36)	ns
A02BB.	Misoprostol	1 (0.05)	1 (0.05)	0 (0.0)	ns
A02BC.	PPIs	91 (4.71)	50 (4.47)	41 (5.04)	ns
A02BX.	Sucralfate	26 (1.34)	21 (1.88)	5 (0.61)	ns
C.	Cardiovascular system	239 (12.39)	149 (13.33)	90 (11.08)	ns
N.	Nervous system	195 (10.11)	133 (11.9)	62 (7.63)	0.003
R.	Respiratory system	194 (10.06)	96 (8.59)	98 (12.06)	0.006

United States: coxib use was associated with a significantly decreased risk of out-patient physician claims for upper GI symptoms compared with non-selective NSAIDs.[6] As the study design was cross-sectional, however, no conclusions about the cause and effect of NSAID use and GI symptoms can be made.

In this study, NSAID users were shown to receive significantly more prescriptions of GI drugs than coxib users (13.1% vs. 6.0%, $P = 0.01$). This finding is in agreement with a recent analysis of a US administrative claims database of >8 milion lives in which less GI co-therapy was reported in patients 1 year after switching from chronic NSAID therapy to coxib therapy (OR in coxib vs. NSAID period was 0.89, 95% CI = 0.69–0.97).[7] However, the percentage of elderly NSAID users co-treated to prevent damage to the upper GI tract was surprisingly low (13%), considering that it is well established that older people are at very high risk for uncomplicated peptic ulcer[22] as well as for upper GI bleeding[23] and that antisecretory drugs are very effective in the prevention of such drug-related complications.[22, 23] Thus, GPs were found to undertreat for prevention of upper GI damage in elderly out-patients who were prescribed NSAIDs. Of course, these data did not include the gastroprotective prescription rate for the elderly who were living in nursing homes and/or who had a more severe disability and co-morbidity than out-patients. Indeed, in a recent American study, geriatricians reported that 68% of elderly nursing-home residents who needed NSAID therapy were co-treated with gastroprotective drugs.[24]

In conclusion, in this elderly out-patient population, upper GI symptoms and prescriptions for gastroenterological drugs were higher in NSAID users than coxib users and non-users of musculo-skeletal drugs. Educational and clinical strategies need to be implemented in order to reduce the GI impact of NSAID use in elderly people.

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APPENDIX I

The SOFIA project investigators

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