NSAIDs Increase Risk of Gastrointestinal Bleeding in Primary Care Patients with Dyspepsia

John H. Kurata, PhD, MPH; Aki N. Nogawa, MS; and Dean Noritake, MD
Los Angeles, San Bernardino, Irvine, and Sylmar, California

BACKGROUND. A 1-year prospective study of 545 patients with dyspepsia examined the natural history of dyspepsia in a primary care population. Predictors of gastrointestinal bleeding and other related utilization-of-service indicators were identified.

METHODS. Subjects were adult primary care patients seen at a southern California county medical center. Data were collected by means of a patient questionnaire as well as from medical charts and a computerized hospital billing system. Chi-square, *t* test, and stepwise multiple logistic regression analyses were used to analyze the data. Outcome events were follow-up visits for any gastrointestinal event and follow-up visits for gastrointestinal bleeding specifically.

RESULTS. Prior exposure to nonsteroidal anti-inflammatory drugs doubled the odds for any follow-up gastrointestinal event (odds ratio = 1.9; 95% CI = 1.4 to 2.8). Nonsteroidal anti-inflammatory drugs increased the risk for gastrointestinal bleeding by a factor of 7 (odds ratio = 7.1; 95% CI = 1.3 to 50.0).

CONCLUSIONS. In a cohort of primary care patients with dyspepsia, use of nonsteroidal anti-inflammatory drugs was the most important predictor of a follow-up gastrointestinal event, both for any gastrointestinal event and gastrointestinal bleeding specifically.

KEY WORDS. Dyspepsia; anti-inflammatory agents, non-steroidal; gastrointestinal hemorrhage; primary health care; physicians, family; prospective study. *(J Fam Pract 1997; 45:227-235)*

Approximately one in 18 visits to general and family practice physicians are for symptoms referable to the digestive system, while stomach pain is the sixth most common principal reason for visit.[1] Large-scale community studies of patients with dyspeptic symptoms have reported prevalence rates of 25% to 38%.[2-4] Despite the high prevalence of this condition, information on the natural history of dyspepsia based on documentation of the complete clinical course in patients is lacking. Most prospective studies of primary care patients focus either on the evaluation of disease management strategies[5-7] or on symptom-based scoring algorithms that predict underlying organic pathologic conditions.[8-10] This is the first prospective study of dyspepsia in a primary care population to examine treatment outcomes and the risk factors associated with those outcomes.

This prospective study of the natural history of dyspepsia used baseline[11] and 1-year follow-up data on family medicine clinic patients with dyspepsia to identify predictors of gastrointestinal (GI) bleeding and utilization of medical services for GI-related conditions. Independent variables used in these analyses were patient demographic characteristics; exposure to risk factors such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, and cigarette smoke; prior GI problems; and presence of chronic conditions such as arthritis, heart disease, cancer, and chronic obstructive pulmonary disease (COPD).

Submitted, revised, March 31, 1997.
From San Bernardino County Medical Center, Research and Policy Analysis, San Bernardino (J.H.K. and A.N.N.); the Division of Family Medicine, UCLA School of Medicine, Los Angeles (J.H.K.); the Department of Family Medicine, University of California, Irvine (A.N.N.); and the Department of Medicine, Oliveview-UCLA Medical Center, Sylmar (D.N.), California. Requests for reprints should be addressed to John H. Kurata, PhD, MPH, Research and Policy Analysis, San Bernardino County Medical Center, 755 E Gilbert St, San Bernardino, CA 92404.

METHODS

Patient Population and Data Collection

Five hundred forty-five adult primary care patients with dyspepsia were enrolled in this 1-year follow-up study of medical services utilized for GI-related conditions. (The patient's enrollment visit is referred to as the "index GI visit.") Subjects were selected from the ambulatory patient population at San Bernardino County Medical Center (SBCMC) in southern California. The baseline study consisted of chart abstracts and surveys from adults (18 years of age or older) seen at Family Medicine outpatient clinics for GI-related conditions (ICD-9-CM diagnosis codes 530 to 537, 564, 787, or 789.0) between January and June 1993. Of the 693 adult patients representing 932 eligible GI visits, 545 patients were enrolled in the baseline chart abstract component. These patients reported proximal alimentary tract symptoms (eg, pain, discomfort, heartburn, vomiting, or nausea); or signs or symptoms resulting in an antiulcer medication prescription. Complaints related to gynecologic conditions or other underlying factors such as injury, influenza, and food poisoning were excluded. The baseline survey component consisted of mailed questionnaires or telephone interviews of enrolled patients who were English-speaking and who had no underlying psychosocial impairment. There were 428 patients contacted, and 288 who responded. Detailed descriptions of the baseline study and selection criteria have been presented elsewhere.[11]

For the follow-up study, computerized hospital billing data on utilization of SBCMC inpatient and outpatient services, including diagnosis codes, were collected for all 545 patients for 1 year following their index visits. The index GI visit to the Family Medicine clinics was excluded, but all other services utilized on the index visit date were included. In addition to services utilized, data were also collected on use of the following NSAIDs: aspirin, fenoprofen calcium, ibuprofen, indomethacin, naproxen, phenylbutazone, piroxicam, sulindac, and tolmetin sodium.

An overview of the relationship between the baseline study[11] and the current follow-up study can be seen in the Figure. Data collection protocols were reviewed and approved by the SBCMC Institutional Review Board.

Independent Variables

Independent variables included baseline demographics (ie, sex, age, race/ethnicity) and index GI visit diagnosis. The index visit diagnosis categories were abdominal pain (eg, epigastric pain, right upper quadrant pain, dyspepsia); gastroesophageal reflux disease (GERD) (eg, reflux, hiatal hernia, heartburn); peptic ulcer disease (PUD) (eg, gastric ulcer, duodenal lesions); gastritis; and other (eg, irritable bowel syndrome, diarrhea, nausea and vomiting, gas).

Risk factors of current cigarette smoking, alcohol use, and NSAID use comprised additional independent variables. Information on current cigarette smoking status and alcohol use was obtained from patient charts (ie, major problem lists, clinic visit notes) and self-reports. Alcohol abuse was defined as a report from the subject of an alcohol-related medical problem or a physician note in the medical chart of alcohol abuse or high consumption. Patients were identified as current NSAID users based on a combination of medical chart information, survey responses, and pharmacy utilization data. The specific items from each of these sources that were used to determine current exposure to NSAIDs are as follows:

1. Charted records that NSAIDs were ordered at the time of the index visit or during the 3 months prior to the index visit
2. Charted GI visit notes that gastropathy was NSAIDs-induced
3. Baseline survey responses indicating that NSAIDs were used currently (at the time of the survey) and regularly (often or nearly every day)
4. Self-reports that NSAIDs had caused GI problems
5. Pharmacy utilization data that indicated NSAIDs were ordered prior to a follow-up GI event.

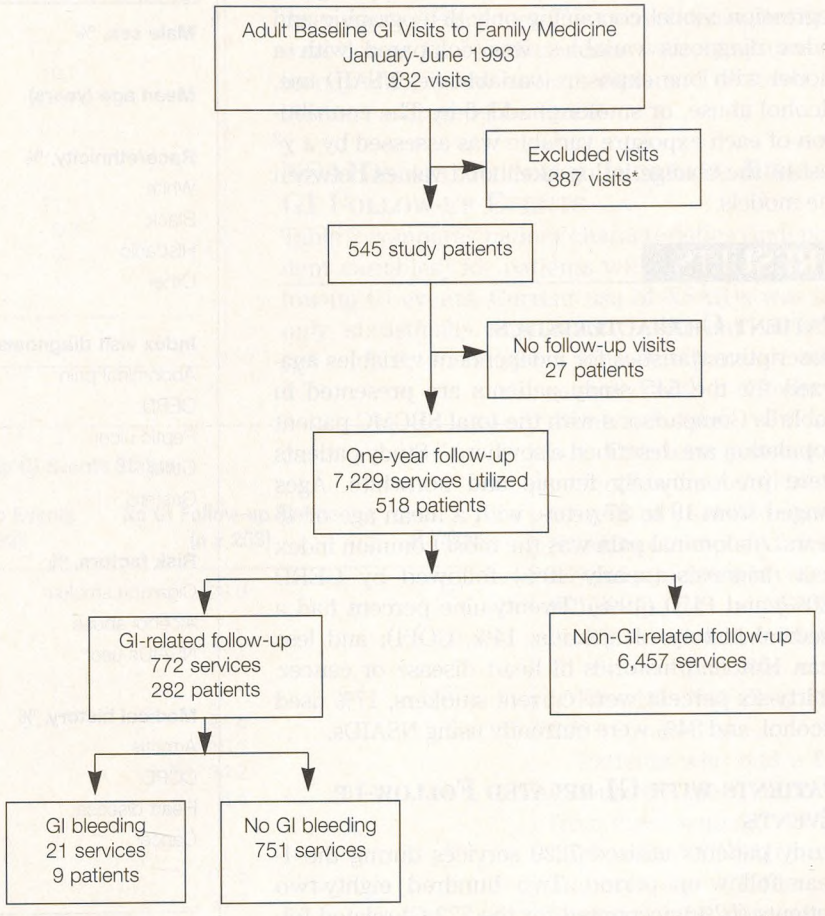
The last group of independent variables were indicator variables derived from the patient's history of selected conditions: arthritis, COPD, heart disease, and cancer. These variables and the preceding independent variables were selected because they are considered to be the most important risk factors for peptic ulcer and other subgroups of dyspeptic patients. Medical history of arthritis was obtained from two sources. Patients' charts (ie, problem lists or clinical notes) were examined for mention of rheumatoid arthritis (RA), osteoarthritis (OA)

including degenerative joint disease, or other arthropathy such as bursitis. Additional arthritic patients were identified from follow-up–year service utilization data by identifying study patients seen for RA (ICD-9-CM 714), OA (ICD-9-CM 715), or other arthropathy (ICD-9-CM 716). Patients could be classified into more than one arthritis category.

Patients with COPD, heart disease, or cancer were identified using ICD-9-CM diagnosis codes for these conditions adapted from a National Center for Health Statistics (NCHS) report.[12] They are ICD-9-CM 490–496 for COPD; ICD-9-CM 390–398, 402, 404–429 for heart disease; and ICD-9-CM 140–239 for cancer. Utilization data were the sole means of identifying study patients with heart disease or COPD. Cancer cases were identified using a combination of chart and utilization data.

FIGURE

Flow diagram of the 1-year prospective study of GI outcomes for 545 primary care patients with dyspepsia.



* There were 211 repeat visits by enrolled study patients. The remaining 176 visits represent GI symptoms attributable to, for example, gynecologic conditions; gallbladder, liver, or kidney problems; accidents, injury, or allergic reactions; or infectious diseases.[11]

Dependent Variables

Study patients having follow-up GI-related events (ICD-9-CM codes 530–537, 564, 578, 787, 789.0), including GI bleeding visits (ICD-9-CM codes 456.0, 578.0, 578.1, 578.9, and fourth-digit hemorrhage codes for PUD, 531–533), were identified from utilization data. The ICD-9-CM diagnoses for GI bleeding were adapted from Cutler and Mendeloff.[13] Three GI follow-up variables were created. One variable counted the number of GI-related services used by each patient; other variables indicated the presence or absence of either a follow-up GI service or GI bleeding. Chart, survey, and hospital record data relevant to the patients with GI bleeding were carefully reviewed to verify bleeding history. Gastrointestinal bleeding was selected for study because it is one of the most serious GI complications associated with acid-peptic diseases.

Statistical Methods

A level of significance of $P=.05$ was selected for all statistical tests. The χ^2 statistic (for categorical variables) and t test (for continuous data) were calculated. Odds ratios and 95% confidence intervals (CI) estimated risk for follow-up GI outcomes associated with exposure variables. For bleeding and NSAID use, an exact 95% CI was calculated using the

approximation procedure described by Cornfield.[14]

Logistic regression analysis was used to examine the relationship between the independent variables and the presence or absence of a follow-up GI-related event as the dependent variable. The logistic regression model containing only demographic and index diagnosis variables was compared with a model with one exposure variable (ie, NSAID use, alcohol abuse, or smoking) added in. The contribution of each exposure variable was assessed by a χ^2 test of the change in log likelihood values between the models.

RESULTS

Patient Characteristics

Descriptive statistics for independent variables analyzed for the 545 study patients are presented in Table 1. Comparisons with the total SBCMC patient population are described elsewhere.[11] Study patients were predominately female and nonwhite. Ages ranged from 19 to 87 years, with a mean age of 46 years. Abdominal pain was the most common index visit diagnosis (nearly 40%) followed by GERD (20%) and PUD (19%). Twenty-nine percent had a medical history of arthritis; 14%, COPD; and less than 10% had histories of heart disease or cancer. Thirty-six percent were current smokers, 17% used alcohol, and 34% were currently using NSAIDs.

Patients with GI-related Follow-up Events

Study patients utilized 7229 services during the 1-year follow-up period. Two hundred eighty-two patients (52%) accounted for the 772 GI-related follow-up events that represented 11% of all follow-up services (Table 2). (The only GI-related service for 263 of the 545 study patients was the index visit to the Family Medicine clinics.) The mean number of GI-related services was 1.4; there was a maximum of 21 GI-related services used (one patient).

The 21 GI-bleeding–related events were: two for bleeding esophageal varices (ICD-9-CM 456.0); one for gastric ulcer (GU) hemorrhage (ICD-9-CM 531.4); two for duodenal ulcer (DU) hemorrhage (ICD-9-CM 532.4); six for hematemesis (ICD-9-CM 578.0); and 10 for unspecified GI hemorrhage (ICD-9-CM 578.9).

Nine patients (1.7% of the study population) accounted for the 21 events (Table 2). Bleeding was observed at endoscopy for four cases: one case of DU; one case of GU; one case of stomal ulcer; and one case of esophageal and gastric varices. These four patients had 14 visits for GI bleeding during the follow-up year: two for bleeding varices; two for peptic ulcer hemorrhages; two for hematemesis; and eight for unspecified GI hemorrhages. All four patients whose diagnoses were verified by endoscopy had used NSAIDs prior to the follow-up GI event. Three of the five bleeders in the remaining categories were NSAID users.

Three patients were categorized as upper GI bleeding cases based on diagnoses of bleeding pep-

TABLE 1

Characteristics of Patients with Dyspepsia

Independent Variables	Study Patients (n = 545)
Male sex, %	30.3
Mean age (years)	46.3
Race/ethnicity, %	
White	43.9
Black	13.9
Hispanic	34.9
Other	7.3
Index visit diagnosis, %	
Abdominal pain	39.3
GERD	19.6
Peptic ulcer	18.9
Other	11.8
Gastritis	10.5
Risk factors, %	
Cigarette smoker	36.3
Alcohol abuse	16.7
NSAIDs user	33.8
Medical history, %	
Arthritis	28.8
COPD	14.1
Heart disease	5.5
Cancer	8.4

GERD denotes gastroesophageal reflux disease; NSAIDs, nonsteroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease.

TABLE 2

GI-Related Patient Outcomes and Utilization of Services

Dependent Variables	Study Patients
Follow-up GI-related services	
No. of services	772
% of services (base = 7229)	10.7
No. of patients	282
% of patients (base = 545)	51.7
GI bleeding	
No. of services	21
% of services (base = 7229)	0.3
No. of patients	9
% of patients (base = 545)	1.7

GI denotes gastrointestinal.

tic ulcer (one case) and vomiting blood (two cases). The upper GI bleeders were high utilizers of medical services for GI-related events. The mean number of GI-related services utilized was 11.3 for the four endoscopy-verified cases and 6.7 for the remaining three upper GI bleeders. The two remaining patients were lower GI bleeding cases with symptoms of bloody stool, tarry stool, or melena. The lower GI bleeders averaged 1.5 services.

NSAIDs and Alcohol Increase Risk of GI Follow-up Events

Table 3 compares patient characteristics (independent variables) for patients with and without follow-up GI events. Current use of NSAIDs was the only statistically significantly different variable (χ^2 = 12.9; P = .0003) between patients who returned with a GI-related event and those who did not. Forty-one percent of patients with a follow-up GI-related service used NSAIDs, compared with 26% of patients with no GI follow-up. Use of NSAIDs nearly doubled the risk for GI follow-up (odds ratio [OR] = 1.9; 95% CI =1.3 to 2.8).

Patients who had a follow-up GI bleed differed from those who did not for current use of NSAIDs and alcohol use (Table 4). Seventy-eight percent of bleeders used NSAIDs compared with 33% of nonbleeders (χ^2 = 7.9; P = .005). The risk for bleeding among NSAID users was seven times that for nonusers (OR = 7.1; 95% CI = 1.3 to 50.0). There was moderate association between alcohol use and bleeding; 44% of bleeders were classified as alcohol users compared with 16% of nonbleeders (χ^2 = 5.1; P = .02).

TABLE 3

Patient Characteristics by Follow-up GI Events Status

Characteristic	GI Follow-up Events (n = 282)	No GI Follow-up Events (n = 263)	*P* Value
Male sex, %	31.6	28.9	.50
Mean age (years)	46.7	45.9	.50
Race/ethnicity,%			.52
White	45.7	41.8	
Black	12.4	15.6	
Hispanic	35.5	34.2	
Other	6.4	8.4	
Index visit diagnosis, %			.71
Abdominal pain	41.8	36.5	
GERD	17.7	21.7	
Peptic ulcer	18.8	19.0	
Other	11.3	12.2	
Gastritis	10.3	10.6	
Risk factors, %			
Cigarette smoker	39.7	32.7	.09
Alcohol abuse	18.1	15.2	.37
NSAIDs user	40.8	26.2	.0003*
Medical history, %			
Arthritis	30.5	27.0	.37
COPD	14.9	13.3	.60
Heart disease	5.0	6.1	.57
Cancer	9.9	6.8	.20

* Statistically significant.
GI denotes gastrointestinal; GERD, gastroesophageal reflux disease; NSAIDs, nonsteroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease.

TABLE 4

Patient Characteristics by GI Bleeding Status

Characteristic	GI Bleeders (n = 9)	Non-bleeders (n = 536)	*P* Value
Male sex, %	22.2	30.4	.60
Mean age (years)	48.4	46.3	.63
Race/ethnicity, %			.61
White	55.6	43.7	
Black	22.2	13.8	
Hispanic	22.2	35.1	
Other	0	7.5	
Index visit diagnosis, %			.54
Abdominal pain	44.4	39.2	
GERD	0	20.0	
Peptic ulcer	22.2	18.8	
Other	11.1	11.8	
Gastritis	22.2	10.3	
Risk factors, %			
Cigarette smoker	55.6	36.0	.23
Alcohol abuse	44.4	16.2	.02*
NSAIDs user	77.8	33.0	.005*
Medical history, %			
Arthritis	44.4	28.5	.30
COPD	11.1	14.2	.79
Heart disease	0	5.6	.47
Cancer	0	8.6	.36

* Statistically significant.
GI denotes gastrointestinal; GERD, gastroesophageal reflux disease; NSAIDs, nonsteroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease.

The logistic regression model containing demographic and index diagnosis variables was compared with the model with NSAID exposure added in. The change in log likelihoods was statistically significant (χ^2 = 12.5; P <.001). Exposure to NSAIDs nearly doubled the odds for any type of follow-up GI event (OR= 1.9; 95% CI = 1.3 to 2.8), even when controlling for sex, race, age, and index diagnosis. There were no statistically significant improvements with the addition of either alcohol or smoking exposures to the logistic regression model.

DISCUSSION

In the present study, NSAID use was the most important predictor of a follow-up GI event, for both any GI event and GI bleeding specifically. We focused on GI bleeding because it is one of the most serious GI complications associated with acid-peptic diseases. Perforation is another serious GI complication; however, there were no perforation cases in this study cohort. Prior exposure to NSAIDs doubled the odds for any follow-up GI event; use of NSAIDs also increased odds for bleeding by a factor of 7. These risks are similar to pooled risk estimates of 2.7 to 4.7 from meta-analyses of NSAID-induced gastropathy.[15-17] The estimate of attributable risk for GI follow-up related to NSAID use in this population is 23%, within the range of 3% to 29% reported in the literature for the general population.[17]

Study Strengths

Findings here were derived from a prospective study of GI events. The timing of outcomes (either follow-up GI events or follow-up GI bleeding) and of exposure to NSAIDs was assessed. Thus, the natural history of dyspepsia (what predicts serious GI complications for dyspeptic patients) could be examined. Knowledge of the timing of NSAID use contributed to conclusions concerning the link between NSAID use and GI bleeding. For example, analyses of study data confirmed that NSAIDs were prescribed and used prior to endoscopy in the four GI bleeding cases with endoscopic verification. Multivariate analyses allowed determination of potential predictors of follow-up GI events and controlled for covariate effects.

Outpatient charts, hospital records, and survey data for the nine patients with GI bleeding were carefully reviewed to verify bleeding history. Four patients had the bleeding site endoscopically veri-

fied. In addition, two patients had reported bloody vomit; while another, who had a history of peptic ulcer verified by upper GI radiography and endoscopy, made an outpatient visit for bleeding DU. Subsequent endoscopy 3 months later indicated that the DU had healed. The remaining two patients were probable lower GI bleeding cases; they reported having bloody stool, tarry stool, or melena.

Study Limitations

The SBCMC Family Medicine population is not representative of the general US population. It does, however, represent a population of low socioeconomic status (Medicaid).[11] Furthermore, the proportion of visits for digestive disease problems in the SBCMC population (4%) is similar to the 4.4% of office visits for symptoms referable to the digestive system from the 1994 National Ambulatory Medical Care Survey.[18]

Completeness of data for exposure variables is an issue, as is amount of exposure, especially with regard to alcohol abuse and smoking. Since both of these are unhealthy behaviors, patients may not be forthcoming about these habits, especially to physicians. While there is a section of the major problem list that requests information on substance use, and specifically mentions tobacco and alcohol, we do not know whether providers always asked patients about these behaviors, or whether they just noted them if the patient happened to mention them.

We examined the use of NSAIDs among patients with arthritis to assess the validity of the data on exposure to NSAIDs. In this study, 56% of RA and 63% of OA patients had current exposure to NSAIDs, and 86% of RA and OA patients had current or past exposure to NSAIDs. Just 16 RA/OA patients (14%) had no documentation of NSAID use in SBCMC hospital and clinic records. This is not unexpected since patients may purchase NSAIDs over the counter or use an outside pharmacy. In comparison, Pincus and Griffin[19] reported that 71% of RA patients in the ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System) population were using NSAIDs.

Implications for GI Treatment in Family Practice

In the present study, the best predictor of GI follow-up visits was the use of NSAIDs. Many of the patients were taking NSAIDs to treat arthritis and other musculoskeletal problems. Because NSAIDs are the mainstay treatment for rheumatic and musculoskeletal conditions, we examined the differences between patients with arthritis and those without arthritis for follow-up GI events. Patients with arthritis had twice the risk for a follow-up GI bleed as did those without it (OR = 2.0; 95% CI = 0.5 to 7.6). For the 108 OA patients, the bleeding risk was three times that of nonarthritic patients (OR = 2.9; 95% CI = 0.8 to 11.2). This finding is consistent with previous studies in which a strong association was found between NSAID use and GI damage,[15-17] especially among patients with arthritis and other musculoskeletal problems.[20-22]

As managed care expands, primary care physicians are likely to treat an increasing proportion of patients with musculoskeletal conditions. Even today, according to data from an NCHS survey, primary care physicians treat 28% of patients for musculoskeletal symptoms, which account for nearly one third of drug orders for pain relief medications.[1] In this study, only 22 of the 157 patients with arthritis were seen in rheumatology or orthopedics clinics. Most of these patients were treated solely by family physicians.

What are the implications of this greater reliance on primary care physicians? It is important for the primary physician to recognize the risk of NSAID use and to be able to identify those patients at greatest risk for GI complications. Our multivariate analysis showed that NSAID therapy was the major predictor of higher risk for gastropathy. Furthermore, the proportion of visits for bleeding was three times higher in the study sample than in the overall SBCMC patient population: 0.3% vs 0.1% ($P<.0001$). This finding suggests that patients with dypepsia are at higher risk of developing GI bleeding than the overall ambulatory patient population. In addition to the findings from the present study, the epidemiologic and clinical literature indicates that the elderly, patients with prior history of upper GI bleeding or PUD, or those on concomitant corticosteroid or anticoagulant therapies are among the higher risk groups.[15,17,23] Since information on corticosteroids and anticoagulants was not collected in this study, we were unable to assess the effect of these drug exposures on risk estimates.

Family physicians may do well to assume a more proactive role in the management of patient populations with dyspepsia to reduce the rate of serious complications. Results of this study suggest that patients with dyspepsia being treated concomitantly with NSAIDs should be reassessed for their need to continue such agents. Some patients might be appropriately treated with lower doses of NSAIDs for their analgesic effects or, alternatively, pure analgesics might provide equally beneficial results, especially for noninflammatory conditions.

Another alternative for patients who need to continue NSAID therapy might be prophylactic therapy to prevent NSAID-induced injury. Three classes of drugs are currently used: the histamine-receptor antagonists (eg, ranitidine, famotidine, nizatidine); the gastric acid-pump inhibitor (omeprazole); and the prostaglandin analogue (misoprostol). Although all of these drugs have been proven to be effective in reducing endoscopic lesions,[24-29] only misoprostol has been shown to reduce the rate of serious gastrointestinal complications attributed to NSAIDs.[28] A recent literature review has recommended that clinicians co-administer misoprostol to prevent NSAID-induced gastric ulcer, especially for patients at high risk of complications.[30]

It may be important to involve such specialists as gastroenterologists and rheumatologists when treating certain types of patients with dyspepsia. Gastroenterologists may need to perform diagnostic tests on dyspeptic patients who require continuous NSAID therapy to determine the presence of ulcer or esophagitis. For dyspeptic patients who also have chronic musculoskeletal or rheumatic conditions, rheumatologists may be helpful in optimizing NSAID treatment regimens.

Another approach might be to have other specialists participate in training and education programs with primary care physicians. With the aging of the population, numbers of patients with musculoskeletal conditions are likely to increase, while at the same time, with the expansion of managed care, fewer of these patients will be referred to specialists. This conjunction of factors makes it imperative for primary care physicians and other specialists to collaborate in providing an efficient and seamless system of care for their patients.

ACKNOWLEDGMENTS

This work was supported in part by funding from the Agency for Health Care Policy and Research, US Public Health Service, Department of Health Services, National Institutes of Health (#RO3 HS07257), and from G. D. Searle Pharmacoeconomics.

REFERENCES

1. Schappert SM. National Ambulatory Medical Care Survey, 1991 summary. Hyattsville, Md: National Center for Health Statistics, Vital and Health Statistics, series 13, No. 116, 1994. DHHS publication No. (PHS) 94-1777.
2. Doll R, Avery Jones F, Buckatzsch MM. Occupational factors in the aetiology of gastric and duodenal ulcers with an estimate of their incidence in the general population. London: His Majesty's Stationery Office; 1951. Medical Research Council Special Report Series No. 276.
3. Jones R, Lydeard S. Prevalence of symptoms of dyspepsia in the community. BMJ 1989; 298:30-2.
4. Weir RD, Backett EM. Studies of the epidemiology of peptic ulcer in a rural community: prevalence and natural history of dyspepsia and peptic ulcer. Gut 1968; 9:75-83.
5. Bytzer P, Hansen JM, Schaffalitzky de Muckadell OB. Empirical H_2-blocker therapy or prompt endoscopy in management of dyspepsia. Lancet 1994; 343:811-6.
6. Goodson JD, Richter JM, Lane RS, Beckett TF, Pingree RG. Empiric antacids and reassurance for acute dyspepsia. J Gen Intern Med 1986; 1:90-3.
7. Nyren O, Adami HO, Bates S, Bergstrom R, Gustavsson S, Loof L, et al. Absence of therapeutic benefit from antacids or cimetidine in non-ulcer dyspepsia. N Engl J Med 1986; 314: 339-43.
8. Bytzer P, Schaffalitzky de Muckadell OB. Prediction of major pathologic conditions in dyspeptic patients referred for endoscopy. A prospective validation study of a scoring system. Scand J Gastroenterol 1992; 27: 987-92.
9. Holdstock G, Harman M, Machin D, Patel C, Lloyd RS. Prospective testing of a scoring system designed to improve case selection for upper gastrointestinal investigation. Gastroenterology 1986; 90:1164-9.
10. Mansi C, Mela GS, Pasini D, Grosso M, Corti L, Moretti M, Celle G. Patterns of dyspepsia in patients with no clinical evidence of organic disease. Dig Dis Sci 1990; 35:1452-8.
11. Kurata JH, Nogawa AN, Chen YK, Parker CE. Dyspepsia in primary care: perceived causes, reasons for improvement, and satisfaction with care. J Fam Pract 1997; 44:281-8.
12. National Center for Health Statistics. Births, marriages, divorces, and deaths for June 1995. Monthly vital statistics report, vol 44, No. 6. Hyattsville, Md: Public Health Service, 1995. DHHS publication No. (PHS) 96-1120.
13. Cutler JA, Mendeloff AI. Upper gastrointestinal bleeding. Nature and magnitude of the problem in the US. Dig Dis Sci 1981; 26(July suppl): 90s-5s.
14. Kleinbaum DG, Kupper LL, Morgenstern L. Epidemiologic research. New York, NY: Van Nostrand Reinhold, 1982:302-6.
15. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med 1991; 115:787-96.
16. Hawkey CJ. Non-steroidal anti-inflammatory drugs and peptic ulcers. Facts and figures multiply, but do they add up? BMJ 1990; 300:278-84.
17. Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer. Nonsteroidal antiinflammatory drugs, *Helicobacter pylori*, and smoking. J Clin Gastroenterol 1997; 24:2-17.
18. Schappert SM. National Ambulatory Medical Care Survey: 1994 summary. Advance data from vital and health statistics, No. 273. Hyattsville, Md: National Center for Health Statistics, 1996. DHHS publication No. (PHS) 96-1250.

19. Pincus T, Griffin M. Gastrointestinal disease associated with nonsteroidal anti-inflammatory drugs: new insights from observational studies and functional status questionnaires [editorial]. Am J Med 1991; 91:209-12.
20. Bloom BS. Direct medical costs of disease and gastrointestinal side effects during treatment for arthritis. Am J Med 1988; 84(suppl 2A):20-4.
21. Fries JF, Williams CA, Bloch DA, Michel BA. Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. Am J Med 1991; 91:213-22.
22. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. Arch Intern Med 1996; 156:1530-6.
23. Amadio P Jr, Cummings DM, Amadio PB. NSAIDs revisited—selection, monitoring, and safe use. Postgrad Med 1997; 101:257-71.
24. Graham DY, White RH, Moreland LW, Schubert TT, Katz R, Jaszewski R, et al. Duodenal and gastric ulcer prevention with misoprostol in arthritis patients taking NSAIDs. Ann Intern Med 1993; 119: 257-62.
25. Hawkey CJ, Swannell AJ, Eriksson S, Walan A, Bjersing M, Jalinder M, et al. Lower frequency of gastroduodenal ulcers and erosions and dyspeptic symptoms in NSAID users during maintenance with omeprazole compared to ranitidine [abstract]. Gastroenterology 1996; 110:A131.
26. Levine LR, Cloud ML, Enas NH. Nizantidine prevents peptic ulceration in high-risk patients taking nonsteroidal anti-inflammatory drugs. Arch Intern Med 1993; 153:2449-54.
27. Raskin JB, White RH, Jaszewski R, Korsten MA, Schubert TT, Fort JG. Misoprostol and ranitidine in the prevention of NSAID-induced ulcers: a prospective, double-blind, multicenter study. Am J Gastroenterol 1996; 91:223-7.
28. Silverstein FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. Ann Intern Med 1995; 123:241-9.
29. Taha AS, Hudson N, Hawkey CJ, Swannell AJ, Trye P, Cottrell J, et al. Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. N Engl J Med 1996; 334:1435-9.
30. Gerritz S, Newton WP. Prevention of NSAID-induced GI mucosal injury [journal club review]. J Fam Pract 1997; 44:130-1.