American Journal of Epidemiology

Vol. 141, No. 6
Printed in U.S.A.

Nonsteroidal Anti-inflammatory Drugs and the Incidence of Hospitalizations for Peptic Ulcer Disease in Elderly Persons

Walter E. Smalley,[1,2] Wayne A. Ray,[2] James R. Daugherty,[2] and Marie R. Griffin[2,3]

To determine the incidence rate of serious ulcer disease among users and nonusers of nonsteroidal anti-inflammatory drugs (NSAIDs), a retrospective cohort study was done on 103,954 elderly Tennessee Medicaid recipients with 209,068 person-years of follow-up from 1984 to 1986. There were 1,371 patients hospitalized with peptic ulcer disease or upper gastrointestinal hemorrhage identified by Medicaid hospital claims and verified by review of the medical record. Ulcer hospitalization rates by NSAID exposure category, duration of use, and daily dose were determined. The rates of ulcer hospitalization among nonusers and current users of NSAIDs were 4.2 and 16.7 per 1,000 person-years, respectively, an excess rate among current users of 12.5 (95% confidence interval (CI) 11.4–13.6) per 1,000 person-years. Among new users, the ulcer hospitalization rates were 26.3 per 1,000 person-years during the first 30 days of use and 20.9 per 1,000 person-years over the next 31–180 days, representing excess ulcer hospitalization rates of 22.1 (95% CI 18.6–25.6) and 16.7 (95% CI 13.1–20.1) per 1,000 person-years, respectively. For long-term users (180 days or more of continuous NSAID use), the ulcer hospitalization rate remained elevated at 15.3, an excess of 12.0 (95% CI 10.3–13.6) hospitalizations per 1,000 person-years. The excess hospitalization rates per 1,000 person-years increased with increasing dose from 6.0 (95% CI 4.0–8.0) for the lowest dose category to 17.8 (95% CI 15.5–20.1) for the highest. The excess rate of ulcer hospitalization for elderly NSAID users is high. These drugs should be used with caution in elderly persons, and alternatives to NSAID therapy should be strongly considered. *Am J Epidemiol* 1995;141:539–45.

anti-inflammatory agents, non-steroidal; cohort studies; gastrointestinal hemorrhage; Medicaid; peptic ulcer

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used drugs in the United States. Approximately 75 million NSAID prescriptions are dispensed annually (4.5 percent of all prescriptions) at a cost of about $2.5 billion (1–3). NSAID use increases with age so that the point prevalence of prescription NSAID use is between 10 and 15 percent for persons aged 65 years or older (4–7).

The frequent use of NSAIDs by elderly patients is of concern because evidence is mounting that NSAID use is an important risk factor for peptic ulcer disease in this population. A recent meta-analysis that combined the results from eight studies of nonaspirin NSAIDs and serious gastrointestinal complications reported a summary relative risk estimate of 5.5 for persons aged 65 years or older (8). However, most of the evidence linking NSAIDs to peptic ulcer disease comes from case-control studies that do not provide absolute rates of disease in users and nonusers of NSAIDs. In addition, the focus of most cohort studies published to date has also been on relative risks rather than on absolute rates (9–13). There have been several cohort studies of serious gastrointestinal side effects associated with NSAID use. However, these studies have been limited by the lack of specific information regarding the absolute rates in the elderly (9, 12, 14, 15), the use of a select population (16), or the use of a limited number of outcomes such as death (11), perforation (14), or upper gastrointestinal hemorrhage (10, 15). In addition, there is little information regarding how the risk of these outcomes varies with dose and duration of therapy. This information is crucial for clinical and policy decision making. Lacking such data, the clinician treating an elderly patient with osteoarthritis (the primary reason for NSAID use in the elderly) (6, 17) cannot quantify the risks and benefits of NSAID therapy. Similarly, policy analyses such as the value of

Received for publication January 10, 1994, and in final form December 19, 1994.

Abbreviations: CI, confidence interval; ICD-9-CM, *International Classification of Diseases*, 9th revision, clinical modification; NSAID, nonsteroidal anti-inflammatory drug.

[1] Department of Medicine, Division of Gastroenterology, Vanderbilt University, Nashville, TN.
[2] Department of Preventive Medicine, Vanderbilt University, Nashville, TN.
[3] Department of Medicine, Division of General Internal Medicine, Vanderbilt University, Nashville, TN.
Reprint requests to Dr. Walter E. Smalley, MCN-A-1128 VUMC, Nashville, TN 37208.

therapeutic alternatives to NSAIDs (18–21) or the cost-effectiveness of prophylactic agents (22–24) are hampered by the lack of data on incidence rates of clinically important ulcer disease among users and nonusers of NSAIDs.

The objective of this study was to calculate rates of hospitalization for confirmed peptic ulcer disease by NSAID use status in a large cohort of persons aged 65 years and older. We determined how age, sex, duration, and dose of NSAID use influenced these rates and examined rates of disease associated with NSAID use by type of ulcer disease.

MATERIALS AND METHODS

Study design

We conducted a retrospective cohort study of hospitalization for peptic ulcer disease between 1984 and 1986 among 103,954 persons aged 65 years or older who were Tennessee Medicaid enrollees. The Medicaid cohort provided a well-defined population for which computerized pharmacy claims provided indicators of non-aspirin NSAID use, and hospital claims provided starting points for case identification. This cohort was the study base for a previously reported nested case-control study (5). In our analysis, we classified all person-time among cohort members by NSAID use status and calculated incidence rates of hospitalization for peptic ulcer disease in each of the resulting groups.

Sources of data

The study population was drawn from the Tennessee Medicaid program, which, at the time of the study, had an annual enrollment of approximately 85,000 persons aged 65 years or older, accounting for 15 percent of the state's elderly population. The Medicaid enrollment file identifies persons who are eligible to receive Medicaid benefits; the specific dates of Medicaid coverage; and the sex, race, date of birth, and the county of residence of the enrollees. Linked Medicare-Medicaid files include admission and discharge dates for hospitalizations and are coded by diagnosis according to the *International Classification of Diseases*, Version 9, Clinical Modification (ICD-9-CM) (25) (up to two diagnoses in Medicaid and up to six in Medicare). The pharmacy file contains reimbursed prescriptions for outpatients and nursing home residents. During the study, most prescription drugs were included on the Medicaid formulary. This file identifies when the prescription was filled, which drug was dispensed, how much of the drug was dispensed, and the number of days the drug supply should last. The nursing home file includes the beginning and ending dates of each nursing home stay that was reimbursed by Medicaid. Tennessee state death certificate files, which include the ICD-9-CM-coded underlying cause of death, have been linked with the Medicaid enrollment file.

Cohort

The study cohort consisted of all Tennessee Medicaid enrollees aged 65 years or older during the study period with at least 1 year of Medicaid enrollment. Persons entered the cohort on the last of the following dates: January 1, 1984, attainment of age 65 years, and attainment of 365 days of Medicaid enrollment. For each cohort member, person-time ended on the first of the following dates: December 31, 1986, termination of Medicaid enrollment, a potential study event, or death. Person-time in the hospital and within 30 days after hospitalization was excluded because Medicaid data do not identify drugs given in the hospital.

NSAID exposure

Exposure to non-aspirin NSAIDs was determined using computerized Medicaid pharmacy files. Aspirin was not studied because most aspirin exposure in this cohort was "over the counter" use (5) and, thus, was not present in Medicaid files. With the date of prescription and the days supply, person-time was classified as follows: *Current use* of NSAIDs extended from the day the prescription was filled through the end of the days of supply of drug as recorded by the pharmacist (usually 30 days, the maximum days supply allowed in the Tennessee Medicaid program); *indeterminate use* included days 1–60 after the last day of current use; *former use* included days 61–365 after the last day of current use; and *nonuse* days were those with no preceding NSAID prescription or those more than 365 days after current use. To determine the validity of our exposure categories, we compared them with NSAID use as recorded in the medical record, a source of exposure information that likely is incomplete. Among patients with a study event who were classified as current, indeterminate, former, and nonusers of NSAIDs by this definition, 64, 45, 20, and 5 percent, respectively, were noted to be NSAID users in the hospital record.

Current use time was categorized by the duration of continuous NSAID use, defined as the sum of consecutive days of current use (with no lapses between NSAID refills of use of greater than 14 days). New use was defined as current use of 180 days or less preceded by a period of at least 180 days without an NSAID prescription. Long-term use was defined as at least 180 days of continuous use. The remainder of person-time was defined as intermittent use, that is,

180 days or less of continuous use with one or more NSAID prescriptions in the 180 days prior to the current period of use.

"Standard doses" for each individual NSAID were defined by the manufacturer's lowest recommended daily dose for treating rheumatoid arthritis (26). The NSAID standard doses were ibuprofen (1,800 mg), indomethacin (75 mg), sulindac (300 mg), naproxen (500 mg), fenoprofen (900 mg), piroxicam (20 mg), tolmetin (600 mg), and meclofenamate (200 mg). Dosage categories associated with similar ulcer rates were combined to yield three categories: less than 0.75, 0.75–1.75, and more than 1.75 standard doses per day, termed low, moderate, and high dose.

Study events

Peptic ulcer disease included hospitalization for gastric or duodenal ulcer as confirmed by surgery, endoscopy, roentgenogram, or autopsy as well as hospitalization for upper gastrointestinal hemorrhage with no other identified cause, defined by hematemesis, the presence of blood in a nasogastric aspirate, or melena. Hospitalizations for other causes of upper gastrointestinal hemorrhage, such as esophageal varices, gastric cancer, or gastritis were excluded. The first qualifying hospitalization in the study period was identified by reviewing the medical records of cohort members with a diagnosis on hospital discharge or an underlying cause of death on a death certificate, indicating gastric, duodenal, peptic or gastrojejunal ulcer (ICD-9-CM codes 531–534), other disorders of the stomach and duodenum (codes 536 and 537), or gastrointestinal hemorrhage (code 578). Cases of duodenal and pyloric ulcer were classified as "duodenal ulcer." Cases of gastric, gastrojejunal, and gastric and duodenal ulcer occurring simultaneously were classified as "gastric ulcer."

Of the 4,195 cohort members initially screened, 503 were excluded because the ulcer had been found incidentally, hospital records were not located, or the events did not meet enrollment, date, or age criteria (5). Of the remaining 3,692 patients, persons who did not meet the case definition with a past history of ulcer disease only (n = 102), lower gastrointestinal hemorrhage (n = 458), gastrointestinal hemorrhage of unknown origin (n = 327), other upper gastrointestinal disease only (n = 307) (such as gastritis or malignancy), or other diagnoses (n = 421) were excluded from the study. Persons with events that occurred within the hospital or within 30 days of a hospital discharge (n = 662) were excluded. The remaining 1,415 patients with peptic ulcer disease were the cases for the previous study using this database (5). However, upon reexamination of these hospitalizations, we excluded 44 additional patients whose events occurred within 30 days of a previous hospital discharge, leaving a total of 1,371 patients with events of interest for this study.

Analysis

Unadjusted hospitalization rates for each category were calculated by dividing the number of events by person-time at risk. To control for potential differences in subject characteristics by exposure, we determined adjusted rates from Poisson regression models (27) using the method of marginal prediction (28). The models included terms for age, sex, race, nursing home status, any hospitalization in the prior year, and NSAID use. To measure the effect of NSAID use, we calculated the difference between adjusted rates of current users and nonusers of NSAIDs; 95 percent confidence intervals for rate differences were calculated with a test-based method (29).

RESULTS

The cohort included 103,954 Medicaid enrollees with 209,068 person-years of follow-up. This study population was predominately female (74 percent of person-time) and had substantial proportions of blacks (28 percent), persons residing in nursing homes (20 percent), and the very old (18 percent older than age 85 years, 44 percent aged 75–84, and 41 percent aged 65–74). Cohort members were prescribed NSAIDs for 13 percent of person-time (current use), while an additional 23 percent of person-time occurred within 1 year after an NSAID prescription (indeterminate and former use).

In the 209,068 person-years of follow-up, 1,371 cohort members were hospitalized for peptic ulcer disease, or 6.6 hospitalizations per 1,000 person-years (table 1). These 1,371 patients experienced an in-hospital mortality of 7.9 percent. Among cohort members not exposed to NSAIDs, the ulcer hospitalization rate was 4.2 per 1,000 person-years, while among current users of NSAIDs the rate was 16.8 per 1,000 person-years. Rates for former and indeterminate users were 5.5 and 10.0 per 1,000 person-years, respectively. The adjusted rates from the multivariate model were similar to the unadjusted rates. The adjusted rate difference between current users and nonusers of NSAIDs was 12.5 (95 percent confidence interval (CI) 11.4–13.6) excess ulcer hospitalizations per 1,000 person-years of NSAID use.

In each age and sex group, current users of NSAIDs had ulcer hospitalization rates substantially greater than those for comparable nonusers (table 2). The excess ulcer hospitalization rate for women (13.0 hos-

TABLE 1. Ulcer hospitalization rates (per 1,000 person-years) by NSAID* exposure category, Tennessee Medicaid enrollees aged 65 years or older, 1984–1986

NSAID exposure	Person-years	No. of hospitalizations	Unadjusted rate	Adjusted rate†	Adjusted rate difference‡	95% CI*
Nonuse	134,560	569	4.2	4.2	0	Reference
Former	28,446	157	5.5	5.3	1.1	0.3–2.0
Indeterminate	18,995	189	10.0	10.6	6.4	5.3–7.6
Current	27,067	456	16.8	16.7	12.5	11.4–13.6
Total	209,068	1,371	6.6			

* NSAIDs, nonsteroidal anti-inflammatory drugs; CI, confidence interval.
† Adjusted for age, sex, race, nursing home status, and hospitalization in the previous year by Poisson regression models using the method of marginal prediction.
‡ Difference between adjusted rate in the group using NSAID and that in nonusers.

TABLE 2. Age- and sex-specific ulcer hospitalization rates* (per 1,000 person-years), Tennessee Medicaid enrollees aged 65 years or older, 1984–1986

Sex and age (years)	NSAID† exposure category		Rate difference‡	95% CI†
	Nonuse	Current use		
Men				
65–74	4.4	14.3	9.9	6.4 to 13.3
75–84	5.9	15.4	9.5	5.7 to 13.1
≥85	8.4	14.1	5.7	−1.7 to 13.3
Total	5.6	14.8	9.2	6.8 to 11.5
Women				
65–74	3.0	10.5	7.5	5.9 to 9.2
75–84	3.7	17.9	14.2	12.1 to 16.1
≥85	5.3	28.5	23.2	19.6 to 26.8
Total	3.7	16.7	13.0	11.7 to 14.3

* Adjusted for race, nursing home status, and hospitalization in the previous year by Poisson regression models using the method of marginal prediction.
† NSAID, nonsteroidal anti-inflammatory drug; CI, confidence interval.
‡ Difference between adjusted rate in the group using NSAID and that in nonusers.

TABLE 3. Diagnosis-specific ulcer hospitalization rates* (per 1,000 person-years) for nonusers and current users of NSAIDs†, Tennessee Medicaid enrollees aged 65 years or older, 1984–1986

Specific diagnosis	Nonuser	Current user	Rate difference‡	95% CI†
Gastric ulcer	1.2	6.5	5.3	4.7–6.0
Duodenal ulcer	1.8	7.3	5.5	4.7–6.2
Gastrointestinal hemorrhage	1.2	2.9	1.7	1.1–2.2

* Adjusted for age, sex, race, nursing home status, and hospitalization in the previous year by Poisson regression models using the method of marginal prediction.
† NSAIDs, nonsteroidal anti-inflammatory drugs; CI, confidence interval.
‡ Difference between adjusted rate in the group using NSAIDs and that in nonusers.

pitalizations per 1,000 person-years) was greater than that for men (9.2 per 1,000 person-years, $p < 0.05$). Among women, the excess rate among current NSAID users increased with age ($p < 0.05$), so that women aged 85 years or older who were current NSAID users had 23.2 (19.6–26.8) more hospitalizations per 1,000 person-years than did comparable nonusers of NSAIDs.

For the entire cohort, the hospitalization rates for gastric and duodenal ulcer and upper gastrointestinal hemorrhage were 6.5, 7.3, and 2.9 per 1,000 person-years, respectively. In each diagnostic category, current NSAID users had a substantial excess rate of ulcer hospitalizations (table 3). Five percent of the ulcer patients in this cohort presented with perforation, a serious complication of ulcer disease that was associated with an in-hospital mortality of 26 percent. The hospitalization rate for ulcer perforation among current NSAID users was 1.5 per 1,000 person-years, which was an excess of 1.3 (95 percent CI 1.0–1.6) hospitalizations over that of nonusers.

Regardless of the duration of therapy, current users had a substantial excess rate of ulcer hospitalization (table 4). For "new users" (current use of 180 days or less preceded by a period of at least 180 days without an NSAID prescription), the excess rates for the first 30 days and the subsequent 31–180 days were 22.1 (95 percent CI 18.6–25.6) and 16.7 (95 percent CI 13.1–20.1) per 1,000 person-years, respectively. For "long-term users" (more than 180 days of continuous use), the excess rate of ulcer hospitalization was 12.0 (95 percent CI 10.3–13.6). For "intermittent users" (180 days or less of continuous use with one or more NSAID prescriptions in the 180 days prior to the current period of use), the excess rate of ulcer hospitalization was 11.1 (95 percent CI 9.8–12.4), similar to the excess rate among long-term users.

The adjusted rate of ulcer hospitalization increased with increasing dose of NSAID. The excess rate among those current users who received low, moder-

TABLE 4. Ulcer hospitalization rates per 1,000 person-years among current NSAID* users by duration of use and daily dosage, Tennessee Medicaid enrollees aged 65 years or older, 1984–1986

Current NSAID use category	Person-years		Adjusted rate†	Rate difference‡	95% CI*
	No.	%			
Duration of continuous use					
New§ (<30 days)	2,020	7.5	26.3	22.10	18.6–25.6
New§ (31–180 days)	1,527	5.6	20.9	16.70	13.1–20.1
Intermittent‖	15,674	58.0	15.3	11.10	9.8–12.4
Long-term¶	7,846	29.0	16.2	12.00	10.3–13.6
Daily dose#					
Low	4,328	16.0	10.2	6.00	4.0–8.0
Moderate	18,027	66.6	17.1	12.90	11.5–14.3
High	4,712	17.4	22.0	17.80	15.5–20.1

* NSAID, nonsteroidal anti-inflammatory drug; CI, confidence interval.
† Adjusted for age, sex, race, nursing home status, and hospitalization in the previous year by Poisson regression models.
‡ Difference between adjusted rate in the group using NSAIDs and that in nonusers (4.2 per 1,000 person-years).
§ "New" users received no prescription for NSAIDs for at least 180 days prior to the current course of therapy.
‖ "Intermittent" users received at least one NSAID prescription in the 180 days preceding the current course of therapy.
¶ "Long-term" users had received NSAIDs continuously for at least 180 days.
# Standard doses based upon the manufacturer's lowest recommended daily dose for treating rheumatoid arthritis: low = <0.75, moderate = 0.75–1.75, and high = ≥1.75 standard doses per day.

ate, and high doses were 6.0 (95 percent CI 4.0–8.0), 12.9 (95 percent CI 11.5–14.3), and 17.8 (95 percent CI 15.5–20.1) per 1,000 person-years, respectively.

For both new and long-term users of NSAIDs, the excess rate of ulcer hospitalizations increased with increasing daily dose (figure 1). New users taking high doses had the highest excess ulcer hospitalization rate of 26.3 (95 percent CI 19.7–32.9) per 1,000 person years, while long-term users on low doses had the lowest excess ulcer hospitalization rate of 5.8 (95 percent CI 2.4–9.2) per 1,000 person-years.

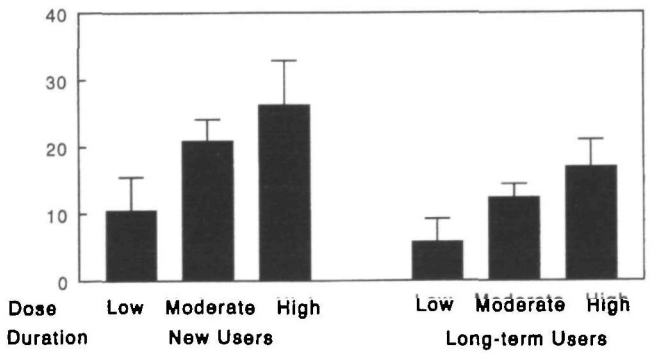

FIGURE 1. Effect of duration and dose of NSAIDs on ulcer hospitalization rates in elderly Tennessee Medicaid enrollees, 1984–1986. *Y-axis: rate difference per 1,000 person-years (95 percent confidence interval);* difference between adjusted rate in NSAID use group and that in nonusers. (Adjusted rate in nonusers, 4.2 per 1,000 person-years). Standard doses based upon the manufacturer's lowest recommended daily dose for treating rheumatoid arthritis: low = <0.75, moderate = 0.75–1.75, and high >1.75 standard doses per day. New users had used NSAIDs for less than 180 days and had received no prescription for NSAIDs for at least 180 days prior to becoming a user. Long-term users had used NSAIDs continuously for 180 days or more.

DISCUSSION

NSAID use was associated with a substantial rate of hospitalization for peptic ulcer disease in this cohort of elderly Medicaid patients. Among current users of NSAIDs, the adjusted rate of hospitalization for ulcer disease was 16.7 per 1,000 person-years, in contrast to a rate of 4.2 among nonusers, an attributable rate of 12.5 excess hospitalizations for ulcer disease per 1,000 person-years among users. The excess risk was highest for women aged 85 years or older. Those who were current NSAID users had a rate of 28.5 per 1,000 person-years, substantially in excess of that of 5.3 for comparable nonusers. Although the increased risk among older women was not demonstrated in the large meta-analysis (8), it was present in some other studies (12, 13) and was not accounted for by dose (13).

Although the excess risk of ulcer disease was highest for new users of NSAIDs, it remained elevated throughout therapy: Long-term users who received NSAIDs continuously for 180 days or more had an excess rate of 12.0 (95 percent CI 10.3–13.6) per 1,000 person years. Even the lowest risk group, long-term users of low-dose NSAIDs, had an excess ulcer hospitalization rate of 5.6 per 1,000 person-years compared with that of nonusers. An excess rate was present for all disease types—gastric ulcer, duodenal ulcer, gastrointestinal hemorrhage—and for perfora-

tion, a serious complication that should nearly always be associated with hospitalization.

The evidence from this and other studies suggests that increased rates of peptic ulcer disease in NSAID users represent an effect of the drugs per se. The cohort design of the study, in which all qualifying ulcer cases were identified for a defined population and ascertainment of drug use was prior to the onset of disease, minimizes the chances for selection or information bias. Although we did not have information on compliance, previous studies have shown that pharmacy claims are good indicators of prescription drug use (30–32). Furthermore, nondifferential exposure misclassification would underestimate the association between NSAIDs and peptic ulcer disease. Physicians caring for patients on NSAIDs may have a lower threshold for admitting patients and performing diagnostic evaluations to diagnose peptic ulcer disease. However, among NSAID users, the admissions for ulcer disease were associated with perforation, obstruction, transfusion, or surgery in over 50 percent of cases (5) and thus were not elective in nature. The multivariate analysis that controlled for indicators of frailty, including nursing home status and prior hospitalization, yielded rates that were very similar to the unadjusted rates, indicating that the effect of NSAIDs was not confounded by these factors. Our previous case-control study, conducted in the same population, demonstrated that other drug use, a prior history of peptic ulcer disease, aspirin use, smoking, and ethanol use also were not confounding factors within this population (5).

The elderly Medicaid population has unique demographic characteristics that may limit the generalizability of these results to other populations. However, the rate of ulcer disease among NSAID users in this study was four times that among nonusers, consistent with the relative risks reported from other elderly populations (8) and, by virtue of the study design, was nearly identical with the results from the prior nested case-control study conducted in this population (5). The overall ulcer hospitalization rate in this cohort of 6.6 per 1,000 person-years is also similar to the rate of 4.4 hospitalizations with peptic ulcer disease as the first listed diagnoses per 1,000 persons aged 65 years and over reported from the National Hospital Discharge Survey (33). The incidence rates of ulcer and gastrointestinal hemorrhage hospitalizations among nonusers of NSAIDs reported here were also similar to those reported for elderly Saskatchewan residents, for whom rates ranged from 2 to 8 per 1,000 person-years in men and women aged 65–85 years (12).

The findings of this study emphasize the need for caution in prescribing NSAIDs for elderly patients. Complications of peptic ulcer pose a serious risk to frail elderly patients: In this cohort, patients with ulcer hospitalizations had a 8 percent in-hospital mortality. The risks of hospitalization associated with NSAID use in this population are comparable with the risks of hospitalization for bleeding complications of low-dose oral anticoagulant therapy for atrial fibrillation as reported in recent trials (about 10–20 per 1,000 person-years) (34, 35), therapy that generally has been regarded as much more dangerous than NSAID therapy (36).

The initial use of NSAIDs in uncomplicated osteoarthritis should be reconsidered in the context of other potentially effective alternatives such as acetaminophen (18, 19, 37), weight loss (21), and physical activity (20). Such caution is particularly important for patients with other risk factors for peptic ulcer disease, such as other medical illness, past ulcer history, ethanol and tobacco use, or for those receiving corticosteroids or anticoagulants (38, 39).

ACKNOWLEDGMENTS

Supported in part by FDA Cooperative Agreement FDU-0000073.

Dr. Smalley was a Ciba-Geigy fellow in Pharmacoepidemiology during the preparation of this manuscript.

REFERENCES

1. Tomita DK, Baum C, Kennedy DL, et al. Drug utilization in the United States-1987, ninth annual review. Washington, DC: Department of Health and Human Services, 1988. (DHHS publication no. PB89–143325).
2. Tomita DK, Kennedy DL, Baum C, et al. Drug utilization in the United States-1988, tenth annual review. Washington, DC: Department of Health and Human Services, 1988. (DHHS publication no. PB90–15921).
3. Burke LB, Baum C, Jolson HM, et al. Drug utilization in the United States-1989, eleventh annual review. Washington, DC: Department of Health and Human Services, 1991. (DHHS publication no. PB91–198838).
4. Griffin MR, Ray WA, Schaffner W. Nonsteroidal anti-inflammatory drug use and death from peptic ulcer in elderly persons. Ann Intern Med 1988;109:359–63.
5. Griffin MR, Piper JM, Daugherty JR, et al. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med 1991;114:257–63.
6. Somerville K, Faulkner G, Langmen M. Nonsteroidal anti-inflammatory drugs and bleeding peptic ulcer. Lancet 1986; 1:462–4.
7. Chrischilles EA, Lemke JH, Wallace RB, et al. Prevalence and characteristics of multiple analgesic drug use in an elderly study group. J Am Geriatr Soc 1990;38:979–84.
8. 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.
9. Beardon PHG, Brown SV, McDevitt DG. Gastrointestinal events in patients prescribed nonsteroidal anti-inflammatory

drugs: a controlled study using record linkage in Tayside. Q J Med 1989;266:497–505.
10. Beard K, Walker AM, Perera DR, et al. Nonsteroidal anti-inflammatory drugs and hospitalization for gastroesophageal bleeding in the elderly. Arch Intern Med 1987;147:1621–3.
11. Guess HA, West R, Strand LM, et al. Fatal upper gastrointestinal hemorrhage or perforation among users and nonusers of nonsteroidal anti-inflammatory drugs in Saskatchewan, Canada 1983. J Clin Epidemiol 1988;41:35–45.
12. Garcia Rodriguez LA, Walker AM, Gutthann SP. Nonsteroidal antiinflammatory drugs and gastrointestinal hospitalizations in Saskatchewan: a cohort study. Epidemiology 1992;3: 337–42.
13. Henry D, Dobson A, Turner C. Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs. Gastroenterology 1993;105:1078–88.
14. Jick SS, Perera DR, Walker AM, et al. Nonsteroidal anti-inflammatory drugs and perforated peptic ulcer. (Letter). Lancet 1987;2:1398.
15. Carson JL, Strom BL, Soper KA, et al. The association of nonsteroidal anti-inflammatory drugs with upper gastrointestinal tract bleeding. Arch Intern Med 1987;147:85–8.
16. Fries JF, Miller SR, Spitz PW, et al. Toward an epidemiology of gastropathy associated with nonsteroidal antiinflammatory drug use. Gastroenterology 1989;96:647–55.
17. Jones AC, Berman P, Doherty M. Non-steroidal anti-inflammatory drug usage and requirement in elderly acute hospital admissions. Br J Rheumatol 1992;31:45–8.
18. Amadio P Jr, Cummings DM. Evaluation of acetaminophen in the management of osteoarthritis of the knee. Curr Ther Res 1983;34:59–66.
19. Bradley JD, Brandt KD, Katz BP, et al. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 1991;325:87–91.
20. Kovar PA, Allegrante JP, MacKenzie CR, et al. Supervised fitness walking in patients with osteoarthritis of the knee. A randomized, controlled trial. Ann Intern Med 1992;116: 529–34.
21. Felson DT, Zhang Y, Anthony JM, et al. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. Ann Intern Med 1992;116:535–9.
22. Graham DY, Agrawal NM, Roth SH. Prevention of NSAID-induced gastric ulcer with misoprostol: multicentre, double-blind, placebo-controlled trial. Lancet 1988;2:1277–80.
23. Edelson JT, Tosteson ANA, Sax P. Cost-effectiveness of misoprostol for prophylaxis against nonsteroidal anti-inflammatory drug-induced gastrointestinal tract bleeding. JAMA 1990;264:41–7.
24. Hillman AL, Bloom BS. Economic effects of prophylactic use of misoprostol to prevent gastric ulcer in patients taking nonsteroidal anti-inflammatory drugs. Arch Intern Med 1989;149: 2061–5.
25. US Department of Health and Human Services. International Classification of Diseases, 9th Revision, Clinical Modification. 2nd ed. Washington, DC: US GPO, 1980.
26. Anonymous. Drugs for rheumatoid arthritis. Med Lett Drugs Ther 1993;33:65–70.
27. McCullagh P, Nelder JA. Generalized linear models. 2nd ed. New York, NY: Chapman and Hall, 1989:193–208.
28. Wilcosky TC, Chambless LE. A comparison of direct adjustment and regression adjustment of epidemiologic measures. J Chronic Dis 1985;10:849–56.
29. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research principles and quantitative methods. New York, NY: Van Nostrand Reinhold Co., Inc., 1982:1–529.
30. Lessler JT, Harris BSH. Medicaid data as a source of post-marketing surveillance information. Final report. Vol. I. Technical report. Research Triangle Park, NC: Research Triangle Institute, 1984.
31. Landry JA, Smyer MA. Home visit medicine use validation study. In: Anonymous. Medicine, health, and aging: enrollment in Pennsylvania's Pharmaceutical Assistance Contract for the Elderly (PACE) Program. Philadelphia, PA: The Pennsylvania State University, 1986:1–37.
32. Leister KA, Edwards WA, Christensen DB, et al. A comparison of patient drug regimens as viewed by the physician, pharmacist and patient. Med Care 1981;19:658–64.
33. Graves EJ, Kozak LJ. National hospital discharge survey: annual summary, 1990. Hyattsville, MD: National Center for Health Statistics, 1992. (Vital and health statistics, Series 13: No. 112). (DHHS publication no. (PHS) 92–1773).
34. The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 1990;323:1505–11.
35. Stroke prevention in atrial fibrillation investigators. Stroke prevention in atrial fibrillation study: final results. Circulation 1991;84:527–39.
36. Kutner M, Nixon G, Silverstone F. Physicians' attitudes toward oral anticoagulants and antiplatelet agents for stroke prevention in elderly patients with atrial fibrillation. Arch Intern Med 1991;151:1950–3.
37. Calin A. Pain and inflammation. Am J Med 1984; 77(Suppl.3A):9–15.
38. Shorr RI, Ray WA, Daugherty JR, et al. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. Arch Intern Med 1993;153:1665–70.
39. Piper JM, Ray WA, Daugherty JR, et al. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991;114:735–40.