Excess Costs from Gastrointestinal Disease Associated with Nonsteroidal Anti-inflammatory Drugs

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OBJECTIVE: **To quantify medical care costs for the diagnosis and treatment of gastrointestinal disorders attributable to use of nonsteroidal anti-inflammatory drugs (NSAIDs) other than aspirin in elderly persons.**

DESIGN AND SETTING: **Retrospective cohort study of 75,350 Tennessee Medicaid enrollees at least 65 years of age.**

MEASUREMENTS: **The cohort was classified by baseline NSAID use as nonusers (no use preceding 1988), occasional users (< 75% of days) or regular users (≥ 75% of days). For the follow-up year (1989), we calculated annual rates of utilization of and Medicare/Medicaid payments for: medical care for NSAID-associated gastrointestinal disorders; hospitalizations/emergency department visits for peptic ulcers, gastritis/duodenitis, and gastrointestinal bleeding; outpatient upper and lower gastrointestinal tract radiologic and endoscopic examinations; and histamine$_2$ (H_2)-receptor antagonist, sucralfate, and antacid prescriptions. Rates were adjusted for demographic characteristics and baseline health care utilization.**

RESULTS: **Among nonusers of NSAIDs, the adjusted mean annual payment for all types of medical care for study gastrointestinal disorders was $134. This increased to $180 among occasional users, an excess of $46 ($p < .001$); and to $244 among regular users, an excess of $111 ($p < .001$, comparison with both nonusers and occasional users). Cohort members with any baseline year NSAID use had an adjusted mean annual payment of $191, $57 ($p < .001$) higher than that for nonusers. In both users and nonusers of NSAIDs, medications and inpatient care accounted for the largest component of costs. Among regular NSAID users, excess payments increased with baseline NSAID dose: $56, $120, and $157 for less than 1, 1 to 2, and more than 2 standard units per day, respectively ($p < .01$, linear trend).**

CONCLUSIONS: **Nonsteroidal anti-inflammatory drug (NSAID) use in elderly patients was associated with substantial excess costs and utilization of medical care for gastrointestinal disorders.**

KEY WORDS: **nonsteroidal anti-inflammatory drugs (NSAIDs); adverse effects; gastrointestinal disorders; misoprostol; cost identification.**

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most frequently used medications by persons 65 years of age or older. Between 10% and 15% of elderly persons use a prescription NSAID on any given day.[1–3] A common and potentially serious adverse effect of NSAIDs is gastrointestinal mucosal injury.[4,5] Among older NSAID users, between 10% and 50% have abdominal pain,[6,7] 10% to 30% have gastroduodenal lesions,[6–9] and during 1 year of use 1% to 3% develop complications resulting in hospitalization or death.[10] Because of the high prevalence of NSAID use, approximately 30% of ulcer-related hospitalizations and deaths in this population are attributable to NSAIDs.[1,11]

The increasing emphasis on evaluating the cost-effectiveness of drugs,[12] and other medical care interventions,[13] suggests the need to consider the economic as well as the clinical consequences of NSAID use. Economic analysis is particularly important for NSAID use in the elderly because of the high prevalence of drug use,[1–3] the frequency and potential high costs of adverse effects, and the availability of several alternative therapeutic strategies for management of musculoskeletal symptoms (the primary reason for NSAID use). These include concomitant prophylaxis with misoprostol or other synthetic prostaglandin E_1 analogues,[9,14] use of analgesic (i.e., lower) doses rather than anti-inflammatory doses of NSAIDs,[15,16] acetaminophen,[15] physical therapy and exercise,[17] topical medications,[18] and weight reduction.[19]

Because the gastrointestinal side effects of NSAIDs are so frequent, quantification of medical care resource utilization for these disorders is central to the economic evaluation of these drugs. However, we are not aware of epidemiologic studies of the costs of NSAID-associated gastrointestinal disorders in an elderly population. We thus conducted a cost-identification, retrospective cohort study among Tennessee Medicaid enrollees age 65 years or older that quantified utilization of and costs for medical care for treatment of gastrointestinal disease attributable to NSAID use.

METHODS

Sources of Data

The computerized files of the Tennessee Medicaid program were the primary study data source[1,11,20]; these files

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enabled us to identify a cohort with computerized records of both NSAID use and treatment for gastrointestinal disorders. At the time of the study, the Medicaid program had an annual enrollment of 90,000 persons 65 years of age or older, or 15% of the state's elderly population.

All Medicaid files included a unique recipient number, and for medical care claims this included dates of the services and Medicaid/Medicare (when applicable) payments to providers.[20] The *enrollment file* included dates of Medicaid enrollment, the demographic characteristics of the enrollees, and, through linkage with death certificates, date of death. The *inpatient file* of claims for hospitalizations (linked to Medicare claims) included the dates of admission and discharge, diagnoses (admitting and up to five discharge diagnoses) coded according to the International Classification of Diseases; Version 9, Clinical Modification (ICD-9-CM),[21] and the Diagnosis-Related Group (DRG) code.[22] Comparable files identified visits to hospital emergency departments and stays in skilled nursing facilities. The *physician file* of claims for outpatient visits identified the specific service performed with *Physicians' Current Procedural Terminology* fourth edition (CPT4) codes,[23] but at the time of this study did not reliably include diagnoses. The *clinic file* identified the institutional component of Medicaid and Medicare payments for services provided in hospital outpatient departments and outpatient surgical facilities. The *pharmacy file* of claims for reimbursed prescriptions for outpatients and nursing home residents identified the drug dispensed, strength, and days of medication supply.

Cohort

The cohort consisted of all enrollees of Tennessee Medicaid 65 years of age or older on January 1, 1989, who were enrolled in Medicaid throughout 1988, the baseline year. Each cohort member was followed from January 1, 1989, through the first of the following dates: end of the study (December 31, 1989), termination of Medicaid enrollment, or death. Nonusers of NSAIDs in the baseline year who subsequently began use during follow-up were censored on the day before such use began.

NSAID Use

Because Medicaid only reimburses for drugs obtained with a prescription, we studied only nonaspirin NSAIDs. Those on the Medicaid formulary during the baseline year were sodium thiosalicylate, magnesium salicylate, salsalate, salicylamide combinations, ibuprofen, indomethacin, phenylbutazone, fenoprofen, naproxen, tolmetin, sulindac, meclofenamate, diflunisal, piroxicam, mefenamic acid, and ketoprofen; diclofenac and flurbiprofen were added to the formulary in 1989.

Each cohort member was classified according to NSAID use in the baseline year. The proportion of days with NSAID use during the baseline year was estimated as the total days of supply for NSAID prescriptions during that year divided by 366. *Nonusers* had no NSAID use in the baseline year, *occasional users* had fewer than 75% of days with NSAID use, and *regular users* had 75% or more of days with NSAID use. During follow-up, the latter two groups had prescription NSAID use on 22% and 67% of days, respectively. NSAID users also were classified by the average daily dose for prescriptions filled in the baseline year. Doses for different agents were expressed as standard units, using the manufacturers' minimum recommended daily doses for the treatment of rheumatoid arthritis as conversion factors (as previously described,[24] but with 1,800 mg/d ibuprofen = 1 standard unit).

Medical Care for Study Gastrointestinal Disorders

Study outcomes were the utilization and cost of medical care provided during follow-up for the diagnosis and treatment of gastrointestinal disorders potentially related to the use of NSAIDs. Study disorders included gastric and duodenal ulcers, gastritis, duodenitis, other gastrointestinal bleeding disorders, and abdominal pain, but excluded gastrointestinal malignancies, esophageal strictures, or variceal bleeding—conditions with little evidence of association with NSAID exposure. Medical care studied included hospital admissions, outpatient visits, and medication prescriptions, with costs defined as payments by Medicaid and Medicare.

Hospital Admissions

Study hospitalizations (admission during follow-up) satisfied one of two diagnostic criteria. The first was a primary (first-listed) discharge diagnosis of gastroduodenal ulcer disease (ICD-9-CM codes 531–534), gastritis/duodenitis (code 535), or gastrointestinal hemorrhage (code 578) in the absence of secondary discharge diagnoses (gastrointestinal malignancy or esophageal strictures/varices) that potentially explained such bleeding. The second criterion included other hospitalizations with one of the above codes for both the admission diagnosis and one of the secondary discharge diagnoses, with the presence of a DRG code indicating nonneoplastic gastrointestinal disease (codes 146–171, 174–190),[22] and the absence of any discharge diagnosis indicating gastrointestinal malignancy or esophageal strictures or varices. Hospitalizations in the latter category were primarily for gastrointestinal bleeding associated with a diagnosis of diverticulosis. For qualifying hospitalizations, the length of stay included the index hospitalization as well as subsequent transfers to another hospital. The cost for each hospitalization was calculated as the sum of three types of Medicare/Medicaid payments: (1) to hospitals for the entire hospital stay as well as for emergency department or outpatient department visits on the date of admission, (2) to physicians and other outpatient providers for services performed during the hospital stay, and

(3) to skilled nursing facilities for up to 30 days of stay following hospital discharge.

Outpatient Visits

Study outpatient care included physician and emergency department visits. Physician visits were restricted to those with procedures because at the time of the study physician claims generally did not include diagnostic codes. Qualifying CPT4 procedure codes were those for upper or lower gastrointestinal tract endoscopy (colonoscopy as well as sigmoidoscopy), or upper or lower gastrointestinal tract barium radiologic studies. The few procedures associated with conditions unlikely to be related to NSAID use (< 5%), such as sclerotherapy, percutaneous feeding tube placement, or esophageal dilation, were excluded. Qualifying emergency department visits had codes for one of these procedures or met the first diagnostic criterion for hospital admissions. Outpatient visit costs included payments (both professional and institutional components) for the primary encounter as well as those for all other physician, laboratory, radiology, and ambulance services on the visit day. Analysis of a sample of Medicaid profiles suggested that at least 95% of such payments were related to the primary encounter.

Medication Prescriptions

These drugs included histamine$_2$ (H_2)-receptor antagonists, sucralfate, and antacids. Omeprazole and misoprostol were not on the Tennessee Medicaid formulary at the time of this study.

Analysis

The analysis estimated annual mean utilization of and payment for medical care for study gastrointestinal disorders within each NSAID use group. The analysis adjusted the means for baseline differences among these groups and tested the null hypothesis of no difference among the adjusted means. Univariate means were calculated by dividing total utilization or payments during follow-up by total person-years of follow-up.

Multivariate Analysis

The utilization or payment outcome variables contain both values that are zero (persons with no care) and values that are positive continuous (utilization/payments for persons with one or more episodes of care). Hence, standard multivariate techniques for discrete or continuous variables could not be used. We thus used *two-part models*, which separately model the number of episodes of care received and the (utilization/payments) per episode. These models were developed by Duan and colleagues to analyze expenditure data from the RAND Health Insurance Experiment,[25] and have been applied in other health care utilization analyses.[26] The model for number of episodes assumed this variable was Poisson, which accounted for person-time of follow-up for each cohort member. Standard Poisson regression techniques,[27] with correction when appropriate for overdispersion, were used to estimate rate-ratio parameters for each covariate. The model for payments per episode was lognormal, with parameters estimated by taking the log transform of payments per episode (among cohort members with one or more episodes), applying standard linear model techniques,[27] and retransforming parameters accounting for the lognormal distribution,[28] using the smearing estimate.[29]

Estimation and Hypothesis Testing

Given the parameter estimates from the two-part model, we then estimated the mean payments for each NSAID use group by the method of marginal prediction.[30] Hypothesis testing is complex because there are two parameters that could differ with NSAID use—one related to the number of episodes per person and the other to payments per episode. Although separate tests for each of these parameters could be performed, the primary hypotheses of interest pertains to overall differences in payments. This null hypothesis can be expressed as

$$E_1(\text{Payments}) = E_0(\text{Payments}),$$

where E_i denotes the expected value among a group of NSAID users and E_0 that among nonusers. The two-part model formulation permits calculations of the expected value for payments as the product of the expected number of episodes and the expected value of payments per episode, given that one or more episodes occurred.[31] Thus, the null hypothesis is

$$E_1(\text{Episodes/person})\,E_1(\text{Payments/episode}) =$$
$$E_0(\text{Episodes/person})\,E_0(\text{Payments/episode}).$$

This is equivalent to

$$\ln(E_1(\text{Episodes/person})/E_0(\text{Episodes/person})) +$$
$$\ln(E_1(\text{Payments/episode})/E_0(\text{Payments/episode})) = 0.$$

The first term is the regression coefficient for the NSAID user group from the Poisson regression and the second is that from the linear model. This expression thus defines a test statistic and an associated variance estimate (assuming independence of estimates from the two models), which we used for all hypothesis testing.

Model Construction

To control for possible confounding by poor health, we constructed several surrogate indices of illness at baseline. These included nursing home residence at start of follow-up (no/yes), baseline-year hospital admission (no/yes), baseline-year emergency department visit (no/yes), and number of major classes of other prescription medications (antihypertensive, other cardiovascular, antimicrobial, psychotropic, other) received in the baseline year (0 to 5). All multivariate models included these terms as well as terms for age (< 85/≥ 85), gender, race (Afri-

Table 1. Characteristics of the Cohort in Baseline Year, by NSAID Use Status*

	Nonuser	Occasional User	Regular User	p Value†
N	45,795	24,633	4,922	
Age, mean (SD)	78.0 (8.1)	76.5 (7.5)	77.6 (7.7)	< .001
Female (%)	73.0	80.4	81.2	< .001
African-American (%)	23.3	27.0	19.1	< .001
Residence in SMSA‡ (%)	54.4	48.2	45.2	< .001
In nursing home (%)	26.6	12.0	31.6	< .001
Hospitalization (%)	24.1	33.1	25.4	< .001
Emergency dept. visit (%)	16.9	27.4	19.3	< .001
No. of major drug classes prescribed, mean (SD)	2.4 (1.6)	3.2 (1.2)	3.3 (1.1)	< .001

Occasional users used NSAIDs < 75% days in the baseline year; regular users ≥ 75% of days.
†p values are for test of the hypothesis that characteristic does not vary by NSAID use.
‡SMSA indicates Standard Metropolitan Statistical Area.

can-American/not African-American), and residence in a Standard Metropolitan Statistical Area (SMSA). Alternative models that included baseline use of other drugs associated with gastrointestinal bleeding (oral corticosteroids, anticoagulants, antineoplastic agents) and more detailed surrogate indices of health (e.g., number of emergency department visits, use of individual categories of drugs) and demographic covariates did not materially change any parameter estimates. Means for total payments were estimated as the sum of means for each type of medical care. All analyses used software from SAS for Poisson regression and linear regression.[32]

Within-Subjects Analysis and Exclusions

We further assessed the contribution of NSAID use *per se* to medical care for study gastrointestinal disorders in a secondary within-subjects analysis of nonusers of NSAIDs at baseline who began NSAID use during follow-up (in the primary analysis, follow-up ceased at this time). This analysis contrasted payments (expressed as mean payments per person-year of follow-up) for the periods before and after NSAID use began. The null hypothesis that payments did not change after NSAID use began was tested by calculating Δ = payments after − payments before (annualized) for each subject and performing a z test. Although the Δs are not Gaussian, the large sample size insures normality of the z statistic.

As a further check of confounding, we also compared payments by NSAID use status for gastrointestinal disorders excluded from the primary analysis. This was done using univariate analysis because of the small sample size.

RESULTS

The study cohort included 75,350 Medicaid enrollees 65 years of age or older with 67,576 person-years of follow-up. The mean age of the study population (SD) was 77 (7.9), 76% were female, 24% were African-American, 52% resided in a SMSA, and 22% were nursing home residents. In the baseline year, cohort members used medications from a mean (SD) of 2.7 (1.5) of the five major drug classes, and 27% had been hospitalized. There were 24,633 (33%) occasional NSAID users and 4,922 (6%) regular users. When compared with nonusers, NSAID users were younger, more likely to be female, white, and reside in a non-SMSA country (Table 1). In the baseline year, NSAID users had more hospitalizations, emergency department visits, and prescriptions for other medications. Occasional users were less likely and regular users were more likely than nonusers to be residing in a nursing home at baseline.

The cohort had Medicaid/Medicare payments of $10,992,792 for study gastrointestinal disorders during follow-up (Table 2). Of these payments, 38% were for hospitalizations, 14% for outpatient visits, and 48% prescribed medications. Of study hospitalizations, 38% were for peptic ulcers, 22% for gastritis/duodenitis, and 40% for other gastrointestinal bleeding. Study outpatient visits were most commonly for upper (32%) or lower (23%) gastrointestinal tract barium radiologic studies, and study prescriptions were most commonly for H_2-receptor antagonists (81%).

Utilization of and payments for all types of medical care for study gastrointestinal disorders increased with increased baseline frequency of NSAID use (Table 3). Among nonusers of NSAIDs, the adjusted mean annual payment for all types of medical care for study gastrointestinal disorders was $134. This increased to $180 among occasional users, an excess of $46 ($p < .001$); and to $244 among regular users, an excess of $111 ($p < .001$, comparison with both nonusers and occasional users). Cohort members with any baseline year NSAID use had an adjusted mean annual payment of $191, $57 ($p < .001$) higher than that for nonusers. For both users and nonusers of NSAIDs, medications and hospitalizations accounted for the largest component of costs.

Among regular NSAID users, total Medicare/Medicaid payments for study gastrointestinal disorders increased with increasing baseline dose of NASAIDs (Fig. 1). Regular users who at baseline received less than 1 standard unit per day had an adjusted mean annual study

Table 2. Utilization of and Medicaid/Medicare Payments for Medical Care for Study of Gastrointestinal Disorders

Disorder	No. of Medical Care Encounters (%)	Payments in Dollars (%)
Hospital admissions	1,082 (100)	$4,140,823 (100)
Gastric ulcer	176 (16)	$838,873 (20)
Duodenal ulcer/peptic ulcer	240 (22)	$1,023,094 (25)
Gastritis/duodenitis	236 (22)	$568,827 (14)
Other gastrointestinal bleeding disorders	430 (40)	$1,710,029 (41)
Outpatient visits	6,639 (100)	$1,517,385 (100)
Upper gastrointestinal endoscopy	1,068 (16)	$451,579 (22)
Lower gastrointestinal endoscopy	1,473 (22)	$441,900 (29)
Upper gastrointestinal barium x-ray	2,128 (32)	$339,428 (22)
Barium enema	1,523 (23)	$204,330 (13)
Emergency dept. visits with no procedure performed	447 (7)	$80,148 (5)
Medication prescriptions	109,968 (100)	$5,334,584 (100)
H_2-receptor antagonists	88,892 (81)	$4,551,568 (85)
Sucralfate	16,220 (15)	$742,144 (14)
Antacids	4,856 (4)	$40,872 (1)
All study medical care		$10,992,792

payment $56 greater than that for nonusers ($p < .001$). Excess payments increased to $120 for those receiving between 1 and 2 standard units and $157 among those using more than 2 standard units ($p < .001$ for both). A significant ($p < .01$) dose-response trend was present. Similar trends were present for hospital ($p = .239$), outpatient ($p < .005$), and medication ($p < .001$) payments.

Within each subgroup defined by cohort member characteristics, Medicare/Medicaid payments for study gastrointestinal disorders were significantly increased among NSAID users (Table 4). Although payments were substantially higher for persons who were hospitalized, made emergency department visits, or received other medications in the baseline year, within each of these

Table 3. Annual Adjusted Mean Utilization of and Medicaid/Medicare Payments for Study of Gastrointestinal Disorders, by Baseline NSAID Use Status*

Utilization	Nonuser	Occasional User†	Regular User
Hospital admissions			
Admissions per 100 person-years (*N*)	1.319	1.823	2.568‡
Stay per 100 person-years, days	13.09	16.62	25.17‡
Payments per person-year ($)	50.42	66.43	105.05‡
Payments per person-year attributable to NSAID use ($)		16.01	54.63‡
Outpatient visits			
Visits per 100 person-years (*N*)	8.105	11.567	11.311†
Payments per person-year ($)	18.39	26.44	26.53†
Payments per person-year attributable to NSAID use ($)		8.04	8.13†
Medication prescriptions			
Prescriptions per 100 person-years (*N*)	136.50	182.74	233.34‡
Payments per person-year ($)	64.96	86.76	112.73‡
Payments per person-year attributable to NSAID use ($)		21.80	47.77‡
All study medical care			
Payments per person-year ($)	133.78	179.63	244.31‡
Payments per person-year attributable to NSAID use ($)		45.86	110.53‡

**Adjusted for age, gender, race, residence in a Standard Metropolitan Statistical Area, nursing home status, hospitalization or emergency department use in the baseline year, and number of major drug classes used in the baseline year. Occasional users used NSAIDs < 75% days in the baseline year; regular users ≥75% of days.*

†Denotes significantly different from value for nonusers of NSAIDs, p < .001.

‡Denotes significantly different from values for both nonusers and occasional users of NSAIDs, p < .001.

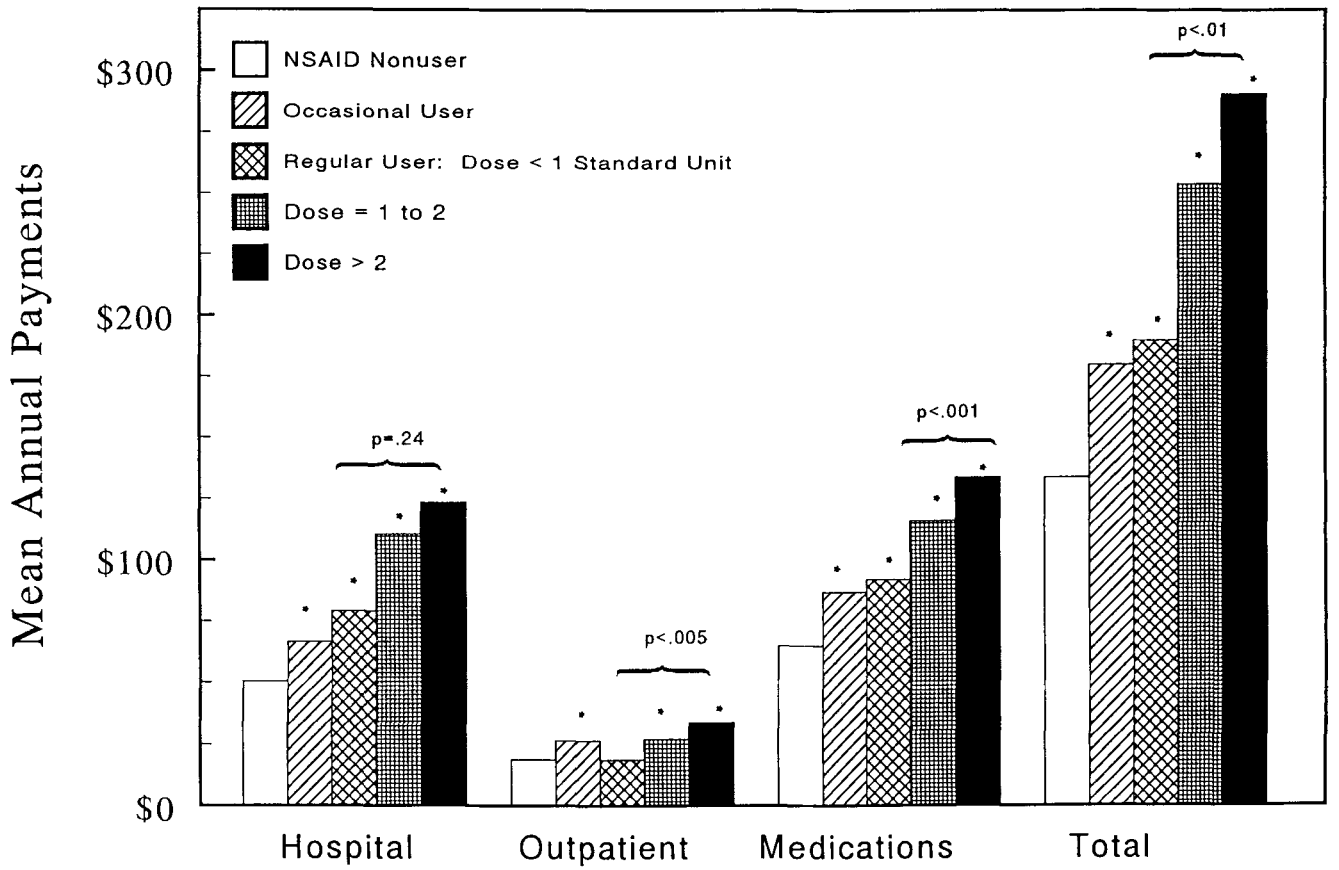

FIGURE 1. Adjusted (for demographic characteristics and health care utilization) mean annual Medicaid/Medicare payments for study of gastrointestinal disorders, by baseline NSAID use group, and for regular users, by baseline NSAID daily dose. Doses are expressed in standard units, where 1 unit is 1,800 mg of ibuprofen or its equivalent. Payments are presented for hospital admissions, out patient visits, prescribed medications, and total services. An asterisk (*) above a bar denotes a value significantly different from that for nonusers at $p \leq .05$. The braces denote the p value for test for trend with increasing dose among regular NSAID users.

subgroups NSAID users had payments consistently higher than those among nonusers.

The within-subjects analysis of new NSAID users identified 6,372 persons with no NSAID use during the baseline year who began use during follow-up. This group had mean annual Medicare/Medicaid payments for study gastrointestinal disorders during follow-up of $136 before versus $227 after NSAID use began, an increase of $91 ($p < .001$). This resulted from increases in payments for hospital admissions ($74), outpatient visits ($4), and medications ($13).

In the analysis of excluded gastrointestinal disorders, there were 20 hospitalizations with payments of $107,901 and 280 outpatient visits with payments of $120,879. For nonusers, occasional users, and regular NSAID users, there were mean annual payments of $3.78, $2.90, and $2.48 per person-year, respectively.

DISCUSSION

In this large cohort of elderly Medicaid enrollees, persons with a prescribed nonaspirin NSAID in the baseline year had excess annual Medicare/Medicaid payments for treatment of peptic ulcer disease, gastritis/duodenitis, abdominal pain, and other gastrointestinal bleeding disorders of $57, even after adjustment for differences between NSAID users and nonusers. The excess increased to $111 with regular NSAID use and to $157 with high-dose, regular use. In this population, NSAID use accounted for 15% of payments for the gastrointestinal disorders studied. In interpreting these findings, several limitations of the study methods must be considered.

NSAID exposure was defined by Medicaid claims for prescription NSAIDs in the baseline year. There were several sources of potential misclassification. Baseline NSAID users had periods of nonuse during the follow-up year. To avoid the resultant misclassification, we considered defining exposure in terms of person-time with NSAID use during follow-up. However, this method could considerably underestimate costs, as NSAID-related gastrointestinal disorders may lead to both discontinuation of NSAID and long-term medical treatment costs. We did not attempt to study aspirin use because it is widely obtained without a prescription, nor could we identify over-the-counter use of ibuprofen. Further misclassification could be induced by noncompliance and obtaining prescription NSAIDs from

Table 4. Annual Adjusted Mean Utilization of Medicaid/Medicare Payments for Study of Gastrointestinal Disorders, All Types of Medical Care, by Baseline NSAID Use Status and Other Cohort Characteristics in Baseline Year*

Characteristic	Nonuser	Occasional User	Regular User
Gender			
Male	$159.85	$191.44†	$236.04†
Female	$124.74	$175.31†	$245.13‡
Age, years			
< 85	$138.14	$178.63†	$250.17‡
≥85	$117.92	$182.80†	$211.79†
Race			
White	$140.87	$190.08†	$262.54†
African-American	$111.18	$146.07†	$184.14†
Residence county type			
SMSA§	$133.20	$177.92†	$230.26‡
Not SMSA	$135.35	$182.80†	$256.05‡
Home			
Community	$135.27	$169.06†	$236.32‡
Nursing home	$136.42	$232.81†	$274.74†
Hospitalized			
No	$107.11	$154.62†	$205.57‡
Yes	$209.27	$252.42†	$343.63‡
Emergency dept. visit			
No	$118.67	$170.34†	$223.12‡
Yes	$193.71	$220.41†	$324.83‡
No. of drug units received			
< 1	$55.91	$123.96†	$151.61†
1–2	$127.19	$164.02†	$236.90‡
3–5	$194.16	$258.77‡	$346.42‡

**Adjusted for age, gender, race, residence in a Standard Metropolitan Statistical Area, nursing home status, hospitalization or emergency department use in the baseline year, and number of major drug classes used in the baseline year. Occasional users used NSAIDs < 75% days in the baseline year; regular users ≥ 75% of days.*

†Denotes significantly different from value for nonusers of NSAIDs, p ≤ .05.

‡Denotes significantly different from value for nonusers and occasional users of NSAIDs, p ≤ .05.

§SMSA indicates Standard Metropolitan Statistical Area.

other sources. However, the most probable effect of each of these sources of misclassification is conservative, causing our study to underestimate the true costs of gastrointestinal disease attributable to NSAIDs.

We limited our study to gastrointestinal disorders related to mucosal injury or bleeding linked with NSAID use. These included abdominal pain,[6,7] gastritis/duodenitis,[33] complications of gastroduodenal ulcers,[1,2,11,36,37] and other types of gastrointestinal bleeding,[38–41] but excluded several disorders less likely to be associated with NSAID use (esophageal strictures, bleeding varices, gastrointestinal malignancies, and lower gastrointestinal disorders absent bleeding). Effects of NSAIDs on other health outcomes and associated costs (e.g., kidney disease, colon cancer) were beyond the scope of this study. We identified medical care for the target disorders from Medicaid/Medicare hospital, outpatient, and pharmacy claims, but did not further verify the presence of a study gastrointestinal disorder. Because claims from Medicaid and Medicare providers are routinely audited,[20] these data accurately record utilization of medical care. Previous studies in this population show that frank miscoding of diagnoses is rare.[1,11] However, our definition includes medical care for prophylaxis, diagnostic assessment, and nonstudy gastrointestinal disease and symptoms. Thus, some fraction of the increased costs among NSAID users may be due to increased surveillance by both patients and providers because of concerns over gastrointestinal effects. Although such use of medical care is not a consequence of physiologic NSAID effects, it nevertheless seems reasonable to attribute the cost of this care to the decision to use NSAIDs. If nondifferential, the remaining misclassification would not affect the rate difference estimates of utilization and payments attributable to NSAID use.[42]

Does the excess utilization of medical care in the NSAID group reflect the effects of these drugs per se, or is it attributable to other characteristics of these patients? The major potential confounders are other risk factors for gastrointestinal disease, propensity to seek treatment for symptoms, association of NSAID use with the utilization of medical care, and opportunities to obtain medical care during provider encounters. Although our study could not measure all of these variables, four lines of evidence suggest a causal role for the drugs. First, previous studies have clearly established that NSAIDs increase the risk of the gastrointestinal disorders studied[1,2,6–9,11,34–41]; the

present study seeks to better quantify the associated costs. Second, our estimates of excess costs control for patient demographics, surrogate measures of health, and frequency of previous medical care utilization. Stratified analyses found that even among cohort members with poor health or high levels of medical care utilization, NSAID users had similar excess payments for study gastrointestinal disorders. Third, there were significant frequency- and dose-response effects. Regular NSAID users had excess payments greater than those for occasional users, and among regular users, there was a linear trend of increasing payments with increasing dose. Fourth, a separate within-subjects analysis of the smaller cohort beginning NSAID use during follow-up, which would control for the effects of many difficult-to-measure patient and provider characteristics, showed an increase in payments after the onset of NSAID use consistent with the primary study finding.

We excluded hospitalizations for gastrointestinal bleeding when there was evidence of malignancy or varices and diagnostic visits when there was evidence of malignancy, varices, or stricture because there was less of an a priori concern that these conditions were caused (or prevented) by NSAID use. The excluded gastrointestinal events were relatively rare, and a univariate analysis of the effects of NSAID use on the occurrence of these events suggests that the impact of NSAID use is specific and not due to uncontrolled selection bias. Including these cases in the analysis would have had no material impact on our summary outcome measures.

Because costs were defined as Medicare/Medicaid payments to vendors, which generally are substantially lower than reimbursement from other third-party payers or charges to patients,[43] our findings may underestimate the impact of NSAIDs on cost of treatment of gastrointestinal disease in other populations. Another source of underestimation was that our study identified only those physician visits during which specific diagnostic procedures were performed. We could not identify other types of visits for study disorders because, at the time of the study, Medicare did not require providers to submit diagnoses for most outpatient visits. Current costs for drug treatment of study conditions may have change with the introduction of misoprostol and omeprazole.

Previous economic analyses of the adverse gastrointestinal effects of NSAIDs have had a narrower scope than the present study, utilizing decision models to evaluate the cost-effectiveness of misoprostol prophylaxis for prevention of gastric ulcers.[44-49] Cost estimates (annualized) have varied substantially, ranging from Edelson and colleagues' figure of $211 for treatment of upper gastrointestinal bleeding in NSAID users,[45] to the $1,206 Hillman and Bloom estimated for treatment of gastric ulcer in osteoarthritis patients who are receiving NSAIDs and have abdominal pain.[46] This heterogeneity stems from differences in the populations considered as well as from the many assumptions made in evaluating the decision models, including the rate of clinically apparent ulcers in NSAID users, the proportions treated in ambulatory or inpatient settings, and the costs of treatment. Our estimate of $246 for a much wider range of gastrointestinal disorders, based on direct measurements of utilization and payments, is most consistent with the lower estimates, which suggests the findings of some studies that misoprostol is cost-saving[44,46-49] hold only in very-high-risk populations.

The applicability of these findings to other populations depends on several parameters, including the prevalence of NSAID use, rates of gastrointestinal disorders attributable to NSAIDs, treatment practices, and reimbursement rates. The limited data available suggest that among the 33 million persons in the United States 65 years of age or older, the patterns of NSAID use[3,50] and gastrointestinal disorders[35,51] are very similar to those in this study; that utilization of outpatient diagnostic procedures is higher than in Medicaid practice[52] whereas rates of medication use are lower.[53,54] Extrapolation of our findings to all Medicaid enrollees 65 years of age or older (an estimated 6 million) and to all U.S. residents in this age group (with adjustment for utilization differences) yields estimates of excess medical care costs for NSAID-associated acute gastrointestinal disorders of $150 million and $500 million, respectively. Despite the uncertainty in the values of many critical parameters, the magnitude of these estimates suggests that reduced use of NSAIDs, by increasing the use of alternative therapies for management of musculoskeletal pain, would have substantial economic as well as clinical benefits.

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