The Effect of Nonsteroidal Anti-Inflammatory Drugs on the Use of Gastroprotective Medication in People with Arthritis

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Objective: To estimate the incidence of gastroprotective medication use among users and nonusers of prescription nonsteroidal anti-inflammatory drugs (NSAIDs) who have arthritis.

Study Design: A retrospective cohort study.

Patients and Methods: We used the Protocare Sciences proprietary Managed Care Organization database, which contains data on more than 3 million lives, to identify 57,136 patients given an initial diagnosis of osteoarthritis (OA; *International Classification of Disease, Ninth Revision, Clinical Modification* [ICD-9-CM] codes: 715, 721.0, 721.3, or 721.9) or rheumatoid arthritis (RA; ICD-9-CM codes: 714.0, 714.1, 714.2, or 714.9); the diagnoses were made during inpatient or outpatient medical encounters occurring between October 1, 1993, and September 30, 1997. The duration of therapy was calculated as the sum of the total number of days of receipt of all prescriptions during the year. The prescribed daily dose was determined by multiplying the drug dose by the number of pills dispensed and then dividing the product by the number of days supplied, as noted in the pharmacy records.

Results: During the year after NSAID initiation, 27% of people with RA and 12% of those with OA were chronic NSAID users. NSAID users with RA were 4 times as likely as NSAID nonusers with RA to begin using a gastroprotective agent within the first year; NSAID users with OA were twice as likely as nonusers with OA to do so.

Conclusion: The use of gastroprotective agents during the first year after NSAID initiation for the treatment of arthritis was greater than their use by those who did not take NSAIDs.

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Arthritis, which affects nearly 43 million people in the United States[1] and cost an estimated $64.8 billion in 1992,[2] is one of the most prevalent conditions in the country. Half the cost of the disease is due to expenditures for medical care and the other half to lost wages.[3] According to one study, in health maintenance organizations prescription medications accounted for 62% and 32% of the total cost of care for rheumatoid arthritis (RA) and osteoarthritis (OA), respectively.[4]

Pain is the major symptom that leads patients with arthritis to visit a physician for relief. Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used classes of medications for general pain relief.[5] They exert their beneficial effects largely through the inhibition of cyclo-oxygenase at the site of inflammation. The drug's action, however, may also result in gastrointestinal (GI) and platelet toxicity.[6] GI toxicity has a wide array of clinical manifestations that ranges from dyspeptic symptoms to life-threatening intestinal bleeding or perforation of gastroduodenal mucosa.[7] The economic impact of these GI side effects is substantial. Management of GI toxicity in NSAID users may increase the cost of arthritis treatment by as much as 46%, raising the cost of arthritis management in the United States by nearly $4 billion annually.[8]

Recently introduced cyclo-oxygenase-2 (COX-2) inhibitors, such as celecoxib and rofecoxib, may decrease GI toxicity,[9,10] thereby reducing the need for concomitant GI medication. Data on the

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use of NSAIDS in patients with arthritis and estimates of the incidence of gastroprotective medication use by prescription NSAID users and nonusers should help to evaluate the potential role of newer NSAIDs.

··· METHODS ···

We obtained approval to perform this study from the Institutional Review Board of Brown University. We derived our study sample from the Protocare Sciences (Santa Monica, CA) proprietary Managed Care Organization database, which contains the annual medical data for approximately 3 milliion members of an unidentified managed care organization (MCO). The members of this MCO receive comprehensive prepaid health insurance for inpatient and outpatient medical services.

Unique identifiers assigned to each member permit cross-linkage of eligibility files and outpatient, inpatient, and pharmacy claims. Eligibility files contained sociodemographic information (ie, date of birth, sex, state, and date of death) and enrollment information (ie, the start and cancellation dates of coverage). Overall, approximately 33% of the members disenroll each year; 21% of those with arthritis do so. Inpatient and outpatient claims contain diagnosis information coded by the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).[11] Pharmacy claims include the dispensing date, quantity of drugs supplied, number of days supplied, and drug type according to the National Drug Code (NDC) system. To translate NDCs into therapeutic classes and subclasses, we used the Master Drug Data Base (MediSpan Inc., Indianapolis, IN), achieving a match rate exceeding 95%.

We identified 65,163 patients who received an initial diagnosis during inpatient or outpatient medical encounters occurring between October 1, 1993, and September 30, 1997, of OA (ICD-9-CM codes 715, 721.0, 721.3, or 721.9) or RA (ICD-9-CM codes: 714.0, 714.1, 714.2, or 714.9). The date of the first arthritis claim served as the index date. To establish that the claim was an initial diagnosis for arthritis, enrollees had to have had at least 12 months of continuous health coverage before their initial arthritis diagnosis. We did not include 1103 patients who lacked continuous health coverage or people who died (n = 185) or disenrolled (n = 6739) during the 6 months after the initial diagnosis. Patients who died or disenrolled after this period were censored on the date of the event; all other patients were followed for 1 year postdiagnosis. The remaining 57,136 patients comprised the study sample.

We classified patients according to their NSAID use. NSAID users were those who had at least 1 pharmacy claim for an NSAID within 6 months before or after the index date. Nonusers had no claims for any NSAID during the observation period. We used the days' supply of drug prescribed, from the pharmacy claim record, to estimate the number of days of therapy. The duration of therapy (defined as the use of any NSAID within the year) was calculated as the sum of the total number of days of receipt of all prescriptions during the observation period. The percentage of time receiving therapy was calculated as the duration of therapy divided by the number of days of observation. NSAID use was classified on the basis of the percentage of time receiving therapy: (1) single prescription (only 1 prescription filled, no refills); (2) infrequent intermittent use (multiple prescriptions filled and refilled but accounts for less than 30% of the time); (3) frequent intermittent use (multiple prescriptions filled and refilled but accounts for 30% to 60% of the time); and (4) chronic use (multiple prescriptions filled and refilled and accounts for more than 60% of the time). The prescribed daily dose was determined by multiplying the drug dose by the number of pills dispensed and dividing the product by the number of days supplied as recorded in the pharmacy records.

For people with no history of use of gastroprotective drug use at the time of NSAID therapy initiation, we estimated the incidence of use of any gastroprotective drug, and the incidence of use by type of drug (H_2-receptor antagonists, proton pump inhibitors, and prostaglandins). We used the dates of disenrollment or death to censor the estimates. Estimates of concurrent initiation of NSAIDs and gastroprotective drugs and estimates of initiation of a gastroprotective agent within 3, 6, and 12 months of the index date were calculated stratified by type of arthritis and NSAID use (single prescription, infrequent intermittent use, frequent intermittent use, and chronic use).

··· RESULTS ···

Table 1 shows the patient demographic data for the 57,136 patients in the sample with arthritis. The majority of people were diagnosed with OA. Patients with arthritis were more likely to be female (62%)

and older than 60 years (65%). Approximately 50% were diagnosed with arthritis in 1994 or 1995. The median length of plan enrollment was 71 months (the inclusion criteria specified a minimum of 18 months) and did not vary by type of arthritis. Women comprised 71% of patients with RA and 61% of those with OA. Patients with RA were younger than those with OA: 29% of RA patients but only 17% of OA patients were younger than 50 years of age. Nine percent of arthritis patients had a history of gastroprotective drug use prior to receiving a diagnosis of arthritis.

Approximately one fourth of the patients initiated NSAID therapy 6 months preceding or subsequent to their date of diagnosis (OA, 23%; RA, 26%). NSAID users and non-NSAID users did not differ with respect to age, sex, or state of residence.

The characteristics of initial NSAID therapy in patients with arthritis are shown in **Table 2**. The most commonly prescribed NSAID for initial treatment of arthritis was ibuprofen (OA, 28.8%; RA, 19.7%), followed by naproxen (OA, 21.3%; RA, 19.0%) and diclofenac (OA, 6.3%; RA, 10.0%). The 3 branded NSAID products (etodolac, nabumetone, and oxaprozin) initially were used 17.6% of the time in OA patients and 21.5% of the time in RA patients. We evaluated these trends by year and found considerable variation in the choice of NSAIDs for initial treatment (data not shown). A consistent increase in oxaprozin use (from 0% in 1992 to 20% in 1997) corresponded to a decrease in ibuprofen use (from 31% in 1992 to 18.2% in 1997). The use of all other single-source products remained constant.

Table 2 also shows the average daily dose (as well as median and maximum dosages), by type of NSAID and type of arthritis. Patients with RA had much higher average daily doses of aspirin-containing drugs and of ibuprofen (aspirin, 2970 mg; ibuprofen, 2078 mg) than did patients with OA (aspirin, 887 mg; ibuprofen, 1976 mg). The initial starting doses of naproxen and diclofenac did not vary by type of arthritis.

The average duration of NSAID therapy, by type of arthritis, is presented in **Table 3**. Patients with RA who initiated NSAID therapy within 6 months before or after receiving their diagnosis were more likely to be chronic NSAID users than were patients with OA who initiated NSAID therapy during this period (26.9% and 12.1%, respectively).

Table 1. Sociodemographic Characteristics of People with Arthritis

Characteristic	Osteoarthritis* (N = 51,771)	Rheumatoid Arthritis* (N = 5365)
	Percentage	
Female	61	71
Age (y)		
18-29	1	2
30-39	4	8
40-49	12	19
50-59	17	19
60-69	20	19
70-79	30	24
80+	15	10
State of residence		
Florida	45	36
Kentucky	14	20
Texas	9	9
Other	32	35
Year of diagnosis		
1992-1993	16	24
1994-1995	54	48
1996-1997	30	28
History of previous gastroprotective medication use	9	10
Median months of enrollment (range)	71 (18-281)	70 (18-240)

*Percentages may not total to 100% because of rounding.

During the first year of therapy, patients with RA filled an average of 4.8 NSAID prescriptions (standard deviation [SD], 3.7), whereas those with OA filled an average of 3.5 (SD, 3.0). Nearly 70% of patients with OA and 50% of patients with RA used NSAIDs for less than one third of the year.

To estimate the effect of NSAID use on the addition of a gastroprotective drug to the medication regimen, we show the estimates of incidence, by type of arthritis in NSAID users and in NSAID nonusers, in **Table 4**. The initiation of gastroprotective medications by nonusers of NSAIDS was uncommon; among NSAID users, however, RA patients were twice as likely as OA patients to be coprescribed one of these agents (5.1% and 2.5%, respectively). Although the incidence increased correspondingly with the duration of the follow-up period, the increases were more pronounced among patients with RA. Nearly one third of these patients began taking a gastroprotective medication within 1 year of NSAID initiation, compared with 17% of NSAID users with OA and compared with only 7% of nonusers of NSAIDS with either OA or RA. The gastroprotective medications used most frequently by

Table 2. Use and Average Daily Dose per Day, by NSAID

	% Use by Population		Daily Dose (mg)*					
			Average		Median		Maximum	
	OA (n = 12,060)	RA (n = 1396)	OA	RA	OA	RA	OA	RA
	Percentage							
Salicylates								
Aspirin-containing drugs	1.0	1.3	887	2970	325	3077	2925	4875
Choline magnesium	0.7	1.2	2346	2000	2250	2250	4500	3000
Diflunisal	0.5	0.7	1026	1050	1000	1000	3000	1500
Salsalate	3.3	4.1	2212	2484	2250	2500	4500	5769
Propionic acids								
Fenoprofen	0.7	0.2	1538	1400	1765	1200	2400	1800
Flurbiprofen	1.3	1.2	226	232	200	200	417	303
Ibuprofen	28.8	19.7	1976	2078	1800	2000	6667	5000
Ketoprofen	2.1	2.9	197	200	200	200	450	375
Naproxen/naproxen sodium	21.3	19.0	1010	1010	1000	1000	3025	2000
Oxaprozin	8.2	8.6	1193	1216	1200	1200	3000	2000
Acetic acids								
Diclofenac	6.3	10.0	143	148	150	150	367	300
Etodolac	3.3	4.0	792	806	800	800	1565	1333
Indomethacin	7.0	6.9	109	118	100	100	283	250
Ketorolac	2.0	1.6	39	39	38	38	120	80
Sulindac	0.1	0.1	363	400	400	400	400	400
Tolmetin	4.2	5.3	454	585	400	400	1800	1800
Enolic acids								
Phenylbutazone	0.1	0.1	341	400	300	400	560	400
Piroxicam	2.1	3.4	20	20	20	20	40	40
Other								
Meclofenamate	1.1	0.7	220	219	200	200	625	333
Nabumetone	6.1	8.9	1122	1176	1000	1000	3000	2500

NSAID = nonsteroidal anti-inflammatory agent; OA = osteoarthritis; RA = rheumatoid arthritis.
*Outliers were considered to be values exceeding the 99th percentile and were not included in the analysis.

patients with OA and by those with RA were the H_2-receptor antagonists. Proton pump inhibitors, prostaglandins and H_2-receptor antagonists were used more frequently by patients with RA than by patients with OA.

··· DISCUSSION ···

In 1996, Smalley et al[12] used Tennessee Medicaid data to estimate the cost of diagnosis and treatment of GI disease attributable to the use of nonaspirin NSAIDs in elderly people. According to these researchers, the adjusted mean annual per capita payment for all types of medical care for GI disease was highest for regular users of NSAIDs ($244). This amount was greater than the mean cost of $180 for occasional users, and the mean cost of $134 for non-NSAID users. Drug treatment costs examined in that study did not reflect modern use of H_2-receptor antagonists, proton pump inhibitors, or prostaglandins, however, and development of these NSAIDs has underscored the importance of obtaining data on the use of NSAIDS by patients with arthritis, as well as estimates of the incidence of gastroprotective medication use by NSAID users and nonusers.

The present findings document that a substantial proportion of people with arthritis initiates NSAID therapy within 6 months of the initial diagnosis. Although some of these patients continue with NSAID therapy, many more discontinue it. Seventy percent of people with OA and 50% of people with RA use NSAIDS for less than 30% of the year after the initial diagnosis. Nonetheless, within 1 year after beginning therapy, NSAID users with RA were 4 times more likely to initiate taking a gastroprotective drug than were nonusers. Similarly, NSAID users with OA were twice as likely as their non–NSAID-using counterparts to begin taking a gastroprotective drug within the year of NSAID initiation.

In our study, nearly one third of OA patients used only 1 NSAID prescription during the first year after diagnosis. The average duration of total NSAID therapy by arthritis type is consistent with findings reported in the literature and with current clinical perception. Scholes et al[13] reported median times to discontinuance of ibuprofen and naproxen in an OA population of 53 and 51 days, respectively. Medical practitioners generally perceive RA therapy to be more chronic and to consume more healthcare resources than OA therapy. In our study, the duration of NSAID therapy did not appear to be age related among patients with a diagnosis of RA. The continuation rates for OA patients

Table 3. Average Duration* of NSAID Therapy Within 1 Year of Initiation

	OA (N = 12,060)	RA (N = 1396)
NSAID scripts (n)		
Mean	3.5	4.8
Standard deviation	3.0	3.7
Duration of NSAID therapy (d)		
Mean	82.7	125.1
Standard deviation	81.5	103.3
Percentage of time receiving NSAID therapy†		
Mean	22.6	34.3
Standard deviation	22.3	28.3
NSAID use‡		
Chronic use	12.1	26.9
Frequent intermittent use	18.3	23.4
Infrequent intermittent use	37.7	27.7
Single prescription	31.9	22.1

NSAID = nonsteroidal anti-inflammatory agent; OA = osteoarthritis; RA = rheumatoid arthritis.
*Calculated from any NSAID use within the follow-up period for users defined as NSAID user within 6 months before or after the date of diagnosis and no initial NSAID.
†Calculated as the duration of therapy divided by the number of days of observation.
‡Classified on the basis of the percentage of follow-up time receiving therapy: (1) single prescription (only 1 prescription filled, no refills); (2) infrequent intermittent use (multiple prescriptions filled and refilled but accounts for <30% of the time); (3) frequent intermittent use (multiple prescriptions filled and refilled but accounts for 30% to 60% of the time); and (4) chronic use (multiple prescriptions filled and refilled and accounts for >60% of the time).

in our study were somewhat higher than the 15% to 20% reported by Scholes et al. The researchers' estimate reflects only the first NSAID prescribed, however, whereas our study includes all NSAID therapy for the year, including NSAID switches. A comparison of total NSAID therapy time versus initial therapy time demonstrated that the former was approximately 25% to 30% longer, indicating that switching of NSAIDS was a common phenomenon in the managed care population we studied.

The average dosages of NSAIDs reported in this analysis suggest that most drugs were used at high doses. However, the most commonly prescribed NSAID, ibuprofen, was used at a dose that was 25% less than the maximal dose for the product.[14] Anecdotal reports on the use of over-the-counter (OTC) products suggest that people may use OTC NSAIDs in addition to a "background" prescription agent. We have no information on OTC NSAID use and therefore were unable to evaluate this hypothesis. Prescription ibuprofen remained the most widely used NSAID for initial therapy for arthritis. This finding suggests that patients may be less likely to use multiple tablets of low-dose OTC medications.

Use of gastroprotective agents post-NSAID initiation may represent a proxy for undocumented dyspepsia or increased GI risk.[15] Only 2.5% and 5% of patients with OA and RA, respectively, were concurrently prescribed a gastroprotective medication and their initial NSAID prescription. Within 1 year of NSAID initiation, 17% of NSAID users with OA and 29% of NSAID users with RA received H_2-receptor antagonists, proton pump inhibitors, or prostaglandins, compared with 7% of nonusers of NSAIDs. Singh et al[16] observed GI medication use of 29.4% over 2.5 years in the Arthritis, Rheumatism, and Aging Medical Infor-mation System (ARAMIS, Palo Alto, CA) database. Although our estimates differ from those derived from the ARAMIS database, the estimates of the risk of additional use of a gastroprotective medication from either study are considerable.

Furthermore, within the 6 months after beginning gastroprotective therapy, patients in our study continued to take gastroprotective agents 46% to 52% of the time, receiving medications for average durations that approached or exceeded the time required for mere ulcer healing. These results imply that a considerable number of patients required chronic,

Table 4. Incident Gastroprotective Medication Use in People Without History of Use of Gastroprotective Agents*

	OA		RA	
	NSAID User (n = 10,435)	NSAID Nonuser (n = 24,525)	NSAID User (n = 1205)	NSAID Nonuser (n = 2425)
At time of initial NSAID				
Gastroprotective agent	2.5	0.1	5.1	0.2
H_2-receptor antagonist	1.8	0.1	3.5	0.2
Proton pump inhibitor	0.2	0.0	0.2	0.0
Prostaglandins	0.6	0.0	1.6	0.0
Within 3 mo of initial NSAID†				
Gastroprotective agent	6.9	1.7	13.9	2.0
H_2-receptor antagonist	5.6	1.5	9.9	1.7
Proton pump inhibitor	0.8	0.3	0.9	0.5
Prostaglandins	0.8	0.0	4.1	0.1
Within 6 mo of initial NSAID†				
Gastroprotective agent	9.6	3.3	19.0	3.4
H_2-receptor antagonist	8.0	2.8	14.2	2.8
Proton pump inhibitor	1.3	0.6	2.4	0.7
Prostaglandins	1.1	0.0	4.9	0.2
Within 1 year of initial NSAID†				
Gastroprotective agent	17.1	7.0	29.3	7.0
H_2-receptor antagonist	14.5	6.1	22.7	5.8
Proton pump inhibitor	3.0	1.4	5.6	1.4
Prostaglandins	1.5	0.2	6.4	0.6

NSAID = nonsteroidal anti-inflammatory agent; OA = osteoarthritis; RA = rheumatoid arthritis.
*Time 0 was the date of the first NSAID prescription regardless of the date of initial diagnosis of arthritis.
†NSAID users/nonusers censored on the date of disenrollment or death at 6 months (n = 339/1630) and at 1 year (n = 2264/2999).

as opposed to acute, therapy, which may reflect therapy for preventive purposes. In future research, the nature of the medical encounter that occurred prior to the initiation of the gastroprotective agent warrants evaluation.

We interpret these data with some caution. First, we recognize the limitations of analyses based on claims databases. We could not capture the use of OTC medications, even though many NSAIDs and gastroprotective medications were widely available over the counter during the study period. Therefore, we may have underestimated not only the proportion of NSAID users, but the incidence of gastroprotective agent use as well. In addition, the claims database did not capture the use of drug samples. Moreover, because we based our study on data in a claims database, we were unable to evaluate actual use and adherence. Furthermore, because claims data do not contain clinical information, such as indices of severity of arthritis, we were unable to analytically adjust for these factors. As a result, we cannot rule out the possibility that confounding by these unmeasured factors may have explained the findings.

··· CONCLUSION ···

Management of pain is the principal concern in the pharmacologic treatment of patients with arthritis, as the risk/benefit ratio of disease-modifying therapies is high in patients most likely to present with arthritis. Arthritis patients do not receive continuous NSAID therapy during their first year postdiagnosis. Despite the low use of NSAIDs, however, use of gastroprotective medications within this population is considerable and may be continuous, as opposed to intermittent for managing symptomatic disease.

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