Trends in Medication Use for Osteoarthritis Treatment

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ABSTRACT. ***Objective.*** To investigate recent national trends in nonsteroidal antiinflammatory drug (NSAID) and acetaminophen use for osteoarthritis (OA).

Methods. Using data from the 1989-98 National Ambulatory Medical Care Survey, a representative sample of US office based physician visits, we assessed 4471 visits by patients 45 years or older with a diagnosis of OA. We examined cross sectional and longitudinal patterns of OA pharmacotherapy. The independent effects of patient and physician characteristics on NSAID and acetaminophen use were examined using multiple logistic regression analysis.

Results. Pharmacological treatment for OA (either NSAID, acetaminophen, or both) has steadily decreased from 49% of visits (1989-91) to 46% (1992-94) to 40% (1995-98) (p = 0.001). Reduced NSAID use over this time period (46% to 33%; p = 0.001) was partially offset by a modest increase in acetaminophen use (5% to 10%; p = 0.001). Among individual NSAID, ibuprofen (5.7% of OA visits), nabumetone (4.9%), naproxen (4.6%), and aspirin (4.4%) were the most frequently reported in 1995-98. For patient visits in 1995-98, 45 to 59-year-olds (38%) received NSAID more often than 60 to 74-year-olds (34%) or patients older than 75 (28%; p = 0.029). Other possible predictors of OA therapy included patient race and physician specialty.

Conclusion. The decline in the use of NSAID from 1989 to 1998, especially among elderly patients, and the frequent selection of safer medications may reflect awareness of the literature citing the risks of nonsteroidals for OA. However, variations in prescribing patterns among different patient populations and the modest use of acetaminophen, despite evidence supporting its efficacy, suggest that better assimilation of the literature into medical practice is needed to optimize OA therapy. (J Rheumatol 2002;29:999–1005)

Key Indexing Terms:
OSTEOARTHRITIS
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TIME TRENDS

Osteoarthritis (OA) has a profound impact on both individuals and society. The prevalence of symptomatic knee and hip OA among adults has been reported to be as high as 6.1% and 4.4%, respectively[1]. Together, these 2 forms of OA account for more lower extremity disability in elderly patients than any other condition; nearly half of all elderly patients with OA report experiencing symptoms every day[2,3]. This debilitation, in turn, results in increased utilization of medical resources and substantial financial costs. OA patients' average direct medical expenses are twice as high as patients without OA and they experience a 3-fold increase in the number of days of home healthcare needed[4,5]. The total lost earnings due to OA has been estimated at $6.6 billion[6]. The societal impact also is substantial; it was estimated in 1994 that the total cost for OA was $15.5 billion[7].

Various treatment options have proven to be effective for relief of OA symptoms, particularly nonsteroidal antiinflammatory drugs (NSAID) and acetaminophen[8]. Among these 2 choices, historically, NSAID have been considered the primary therapy for OA, resulting in an estimated 8 million people using NSAID each year for OA and other conditions[9]. Serious side effects, however, particularly an increased risk of peptic ulcers and gastrointestinal (GI) bleeding, can result from prolonged NSAID use[10-12]. While the one-year incidence rate of serious GI events for all NSAID users is low (about 1/1000 people), the prevalent use of NSAID gives rise to a substantial number of complications[9,12]. Roughly 76,000 hospitalizations and 7600 deaths result from NSAID use annually[9]. The drug misoprostol, when prescribed with NSAID, can effectively reduce the risk of GI complications, but it does not completely eradicate the risks of nonsteroidals[10,11,13]. Additionally, omeprazole, a proton pump inhibitor, and ranitidine, a histamine-2 receptor blocker, are effective in treating NSAID induced bleeds and they help prevent the formation of future ulcers[14,15]. While more recently released cyclooxygenase-2 (COX-2) inhibitors have reduced risk of GI side-effects[16], concerns regarding adverse cardiovascular events have been raised[17].

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An increased awareness of NSAID side effects has spawned the publication of numerous articles critically assessing existing OA management. In 1991, Bradley and colleagues published a randomized controlled trial comparing ibuprofen to acetaminophen in the treatment of knee OA[18]. They found few differences in the efficacy of the 2 drugs, raising doubts about the comparative advantage of NSAID. Other publications also have stressed caution in the use of NSAID, especially among elderly patients for whom the risk of GI complications is greatest[12,19-22]. These concerns were summarized in the American College of Rheumatology (ACR) publication of guidelines for knee and hip OA that promoted acetaminophen as a first-line pharmacological agent[23,24]. While some studies suggest the superiority of NSAID[25], such assessments may not account fully for differing side effect profiles. Even with the availability of COX-2 inhibitors, acetaminophen continues to be considered the drug of first choice for OA[26-29]. Questions also have been raised concerning the selection of specific NSAID for use in OA treatment[21,30]. While each NSAID can affect individual patients quite differently[31], there is little evidence of systematic differences in effectiveness between subclasses of NSAID, despite vastly varying costs[21,32]. There is, however, evidence supporting significant differences in the risk of GI toxicity between NSAID[33,34], with some less expensive NSAID (particularly ibuprofen and aspirin) showing less GI toxicity. Consequently, when NSAID are required, physicians should consider the safety profile and relative cost of each individual nonsteroidal[31,32].

As with other chronic diseases where multiple pharmacological treatment options exist, nonclinical factors might be expected to play a role in OA treatment. Mazucca, *et al* found that 65% of primary care physicians prescribed NSAID in suboptimal antiinflammatory doses for uncomplicated OA of the hip compared to 24% of rheumatologists. Further, rheumatologists were more likely than primary care physicians to choose a therapeutic program that did not affect prostaglandin synthesis for OA complicated by gastropathy or renal insufficiency[35]. Brandt, *et al* reported that US patients with Medicare might not receive optimal treatment because their insurance does not cover outpatient pharmacy expenses[36].

The current literature raises important concerns about OA treatment. Little is known about the influence of this literature, however, since few studies have documented how OA is actually treated[35,37,38]. Using data from the National Ambulatory Medical Care Survey (NAMCS), we investigated the treatment of OA from 1989 to 1998. In particular, we evaluated what effects important publications, including the ACR guidelines, have had on the use of acetaminophen and NSAID and whether age, sex, race, insurance type, or physician specialty influenced OA pharmacotherapy.

MATERIALS AND METHODS

The data for this study came from the 1989-98 NAMCS conducted by the National Center for Health Statistics, Hyattsville, Maryland[39]. This survey provides assessments over time of US office based physician practices. Drawing from the master lists of all US patient care physicians maintained by the American Medical Association (AMA), Chicago, Illinois, and the American Osteopathic Association, Chicago, Illinois, a random stratified sample of US patient care physicians was selected by geographic region and specialty. Participation rates of eligible physicians ranged from 68% in 1998 to 74% in 1989. In each year, doctors kept logs of patient visits during a randomly selected week, from which a systematic sample of visits was assessed.

For each selected visit, physicians completed a detailed form listing diagnoses, medications (continued or new, over-the-counter or prescribed), and clinical services that they provided. Each record contained patient demographic information, including age, sex, race, ethnicity, and source of payment. The National Center for Health Statistics provided a visit weight for each record, calculated from the physician and visit sampling rates, adjusted for nonresponse. These weights enabled us to extrapolate the results to national practice patterns. We modified these weights to obtain effective sample sizes for use in statistical testing[40]. In the past, studies have validated the general accuracy of NAMCS data[41].

We identified OA visits using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) diagnostic codes of 715.0–715.9 for any of the 3 possible diagnoses reported on the patient visit form[42]. These codes include OA that is generalized, localized (primary, secondary, or unspecified), involving more than one site (but not generalized), and unspecified. We restricted our sample to visits by patients over the age of 45 years. To increase the power of our statistical comparisons and to better assess the influence of the salient studies and guidelines published in the early to mid 1990s, we divided the 10 years of data into 3 groups: 1989–91, 1992–94, and 1995–98. These methods identified 4471 OA visits: 1429 in 1989–91, 1314 in 1992–94, and 1728 in 1995–98. For these visits, we identified key medications by coding for generic and proprietary names of all NSAID, including aspirin, as well as acetaminophen, misoprostol, proton pump inhibitors, and histamine-2 receptor blockers.

We examined several potential predictors of OA treatment patterns including age, sex, race, patient insurance type, and physician specialty. Physician specialty was defined using categories established by the AMA, with family practitioners and general practitioners grouped together. To avoid small cell sizes, we collapsed payment source options into 3 categories: "Medicare," "Private/health maintenance organization (HMO)," and "Other." Chi-square tests for trend are reported for univariate intertemporal comparisons and standard chi-square tests for bivariate results, with p values ≤ 0.05 considered statistically significant. We developed 3 multivariable logistic regression models to assess the extent to which these 5 characteristics predicted OA therapy in 1995–98[43,44]. The dependent variables in these regression models were NSAID treatment (Model 1), acetaminophen treatment (Model 2), and any pharmacological treatment (Model 3).

RESULTS

In 1995-98, an estimated 50.9 million visits, or 3.5% of all office based visits by patients 45 years of age and older, were associated with a diagnosis of OA. For these patients, 76.7% were 60 years of age or older, 68.8% were female, and 81.0% were white. Of all OA visits in 1995-98, 32% were to internists, 28% to general practitioners/family practitioners (GP/FP), 22% to orthopedic surgeons, and 9% to rheumatologists (Table 1). In 1992-94, there were an estimated 36.7 million OA visits accounting for 3.8% of all

Table 1. Patient and physician characteristics of OA visits by patients 45 years or older for 1995–98.

Visit Characteristic	NAMCS Records	National Estimates of OA Visits (in millions)	Percentage of OA Visits
Age			
45–59	403	11.8	23.3
60–74	732	21.5	42.1
75+	593	17.6	34.6
Sex			
Female	1123	35.0	68.8
Male	605	15.9	31.2
Race			
Non-white	295	9.7	19.0
White	1433	41.3	81.0
Physician specialty			
GP/FP	344	14.4	28.2
Orthopedic surgery	618	10.9	21.5
Rheumatology	118	4.3	8.5
Other	210	4.8	9.4
Internal medicine	438	16.5	32.4
Payment Source			
Medicare	969	28.5	55.9
Other	255	6.7	13.2
Private/HMO	504	15.7	30.8
Totals	1728	50.9	100.0

office based visits within this age group. Of these OA visits, 38% were to internists, 23% to GP/FP, 21% to orthopedic surgeons, and 8% to rheumatologists. In 1989-91, 3.4% of all office based visits by patients 45 years of age and older were associated with OA (30.6 million OA visits). During this time period, internists saw 34% of the OA visits, GP/FP 33%, orthopedic surgeons 16%, and rheumatologists 8%. For OA visits in 1995-98, 39.8% were associated with pharmacological treatment. Physicians reported using acetaminophen for 10.0% of OA visits, while NSAID were reported in 32.6%. Among individual NSAID, ibuprofen (5.7% of OA visits) and nabumetone (4.9%) were the most commonly reported, followed by naproxen (4.6%), aspirin (4.4%), and diclofenac (3.5%) (Table 2). The report of aspirin in OA was associated with coexisting coronary artery disease 23.3% of the time in 1995-98.

The percentage of OA visits with some form of medicinal therapy (39.8%) decreased from 48.6% in 1989-91 ($p = 0.001$). This decrease in pharmacological therapy reflects a 13.6% drop in NSAID usage over this time period ($p = 0.001$). Partially offsetting this decrease in NSAID was an increase in acetaminophen use from 4.6% of visits in 1989-91 (Table 2).

Certain patient characteristics influenced the treatment of OA. In 1995-98, age was associated with medication use. For 45 to 59-year-olds, NSAID or acetaminophen use was reported in 45.4% of the visits. Among older age groups, pharmacological treatment was less likely: 39.8% of visits for 60 to 74-year-olds and 36.4% of visits for patients 75 years and older ($p = 0.071$). NSAID use in particular was less likely among elderly patients, while acetaminophen use fluctuated by age (Tables 3 and 4). This pattern of age related NSAID use was confirmed and was statistically significant within a multiple logistic regression analysis (Model 1, Table 5). Comparisons across time revealed a substantial, statistically significant decline in NSAID use within all 3 age groups. For patients older than 75, this decline was accompanied by a statistically significant increase in acetaminophen usage (Table 3 and 4).

Assessing the influence of race on medication use, we did not find any consistent patterns. Both NSAID and acetaminophen rates were similar for white and nonwhite patients in 1995-98 (Table 3 and 4) and these similarities were confirmed by the logistic regression analysis (Models 1 and 2). The decline in rates of NSAID use between 1989-91 and 1992-94, however, was slightly more substan-

Table 2. Percentage of OA visits by patients 45 years or older with the specified treatment reported.

Drugs	1989–91	1992–1994	1995–98	p
Acetaminophen	4.6	7.7	10.0	≤ 0.001
NSAID	46.2	40.8	32.6	≤ 0.001
Ibuprofen	9.3	7.0	5.7	0.006
Nabumetone	0.0	4.0	4.9	≤ 0.001
Naproxen	8.4	5.9	4.6	0.002
Aspirin	3.8	4.3	4.4	0.736
Diclofenac	8.4	3.7	3.5	≤ 0.001
Etodolac	0.0	4.6	3.3	≤ 0.001
Piroxicam	5.8	3.9	1.1	≤ 0.001
All other NSAID	12.2	9.2	6.8	≤ 0.001
Any pharmacological treatment	48.6	46.1	39.8	≤ 0.001

Table 3. Predictors of NSAID use for OA visits by patients 45 years or older. Data are percentages.

Factors	1989–91	p*	1992–94	p*	1995–98	p*	p** (time trend)
Age		0.060		0.104		0.029	
45–59	51.6		46.5		37.6		0.016
60–74	48.2		41.8		33.9		≤ 0.001
75+	41.5		36.7		28.0		0.001
Sex		0.206		0.686		0.441	
Female	47.6		41.3		33.3		≤ 0.001
Male	43.1		39.8		31.0		0.004
Race		0.153		0.013		0.177	
Non-white	50.9		48.9		36.5		0.007
White	45.1		38.7		31.7		≤ 0.001
Physician specialty		≤ 0.001		≤ 0.001		≤ 0.001	
GP/FP	46.5		50.5		37.1		0.005
Orthopedic surgery	29.6		25.4		18.4		0.029
Rheumatology	69.1		37.1		52.4		≤ 0.001
Other	39.2		36.3		32.5		0.636
Internal medicine	50.0		45.6		34.1		≤ 0.001
Payment source		0.065		0.390		0.531	
Medicare	43.3		39.0		31.6		≤ 0.001
Other	48.4		41.9		31.8		0.008
Private/HMO	52.4		44.8		35.1		≤ 0.001
Totals	46.2		40.8		32.6		≤ 0.001

* p value for association of selected factors with NSAID by chi-square. ** p value for time trend in NSAID use for each particular subpopulation.

Table 4. Predictors of acetaminophen use for OA visits by patients 45 years or older. Data are percentages.

Factors	1989–91	p*	1992–94	p*	1995–98	p*	p** (time trend)
Age		0.672		0.399		0.682	
45–59	4.3		5.9		10.2		0.059
60–74	5.3		7.4		9.1		0.087
75+	4.0		9.2		10.9		0.002
Sex		0.268		0.136		0.749	
Female	5.1		8.6		9.8		0.004
Male	3.5		5.7		10.4		0.002
Race		0.152		0.732		0.811	
Non-white	2.7		8.3		10.4		0.010
White	5.1		7.6		9.9		≤ 0.001
Physician specialty		0.400		0.671		0.024	
GP/FP	3.4		5.8		9.1		0.011
Orthopedic surgery	5.6		7.7		7.4		0.721
Rheumatology	8.2		11.2		19.9		0.080
Other	5.3		7.4		8.5		0.702
Internal medicine	4.3		8.4		10.8		0.007
Payment source		0.800		0.639		0.302	
Medicare	4.3		7.7		10.1		≤ 0.001
Other	5.4		9.2		6.9		0.381
Private/HMO	4.8		6.5		11.4		0.019
Totals	4.6		7.7		10.0		≤ 0.001

*p value for association of selected factors with acetaminophen by chi-square. ** p value for time trend in acetaminophen use for each particular subpopulation.

tial for white patients, resulting in statistically significant differences in NSAID usage between racial groups in 1992-94. For this time period, white patients received NSAID in 38.7% of their OA visits, while nonwhite patients received them in 48.9% of their visits (p = 0.013; Table 3).

Besides patient characteristics, physician specialty influenced OA treatment. For OA visits to rheumatologists in 1995-98, NSAID were reported 52.4% of the time (Table 3), while only 18.4% of OA visits to orthopedic surgeons resulted in NSAID use. Internists (34.1%) and GP/FP

Table 5. Likelihood of different OA treatment methods: National Ambulatory Medical Care Survey, 1995–98.

Independent Variable	No. of NAMCS Records	Model 1: NSAID Use Adjusted* Odds Ratio (95%CI)	Model 2: Acetaminophen Use Adjusted* Odds Ratio (95% CI)	Model 3: Any Treatment Adjusted* Odds Ratio (95% CI)
Age				
45–59	403	1.83 (1.19–2.82)	0.88 (0.46–1.70)	1.76 (1.17–2.66)
60–74	732	1.43 (1.05–1.93)	0.83 (0.52–1.32)	1.26 (0.94–1.68)
75+	593	1.00 (reference)	1.00 (reference)	1.00 (reference)
Gender				
Female	1123	0.97 (0.74–1.28)	0.88 (0.58–1.34)	0.91 (0.69–1.18)
Male	605	1.00 (reference)	1.00 (reference)	1.00 (reference)
Race				
Non-white	295	1.14 (0.82–1.58)	1.13 (0.68–1.88)	1.15 (0.84–1.59)
White	1433	1.00 (reference)	1.00 (reference)	1.00 (reference)
Physician specialty				
GP/FP	344	1.11 (0.81–1.52)	0.84 (0.51–1.39)	1.05 (0.78–1.43)
Orthopedic surgery	618	0.40 (0.27–0.59)	0.67 (0.37–1.21)	0.40 (0.28–0.58)
Rheumatology	118	2.04 (1.24–3.36)	2.15 (1.12–4.13)	2.68 (1.60–4.50)
Other	210	0.92 (0.58–1.47)	0.78 (0.36–1.69)	0.89 (0.57–1.39)
Internal medicine	438	1.00 (reference)	1.00 (reference)	1.00 (reference)
Payment source				
Medicare	969	1.02 (0.71–1.46)	0.82 (0.48–1.40)	1.03 (0.73–1.45)
Other	255	0.89 (0.56–1.31)	0.56 (0.27–1.15)	0.79 (0.53–1.20)
Private/HMO	504	1.00 (reference)	1.00 (reference)	1.00 (reference)

*Adjusted for all other variables in the table.

(37.1%) had intermediate NSAID prescribing rates (p = 0.001 for comparison across all specialties). Logistic regression analysis (Model 1) confirmed these differences in NSAID use between rheumatologists, orthopedic surgeons, and internists. Only small specialty differences were found in acetaminophen usage (Table 4).

The use of medications to protect against possible NSAID induced GI bleeds was uncommon in 1995-98. Histamine-2 receptor blockers (5.3% of OA visits where NSAID were reported) were used most frequently, followed by proton pump inhibitors (2.8%) and misoprostol (1.6%).

DISCUSSION

NSAID remained the predominant pharmacological agent for the treatment of OA during the time period analyzed. In 1995-98, NSAID were at least 3 times more likely to be used than acetaminophen. Among the NSAID reported most often were ibuprofen and aspirin, both of which are inexpensive and have relatively good safety profiles compared to other nonselective NSAID[33]. Also among the most frequently reported NSAID were naproxen, diclofenac, nabumetone, and etodolac. Most of these medications are substantially more expensive, but they have been shown to be effective and potentially safer than other NSAID[33,34,45-47]. In contrast, the rapid decline in piroxicam usage may be due to the report of its high toxicity index[33].

Since 1989-91, however, there was a substantial decrease in NSAID usage from 46% to 33% of OA visits. This decrease in NSAID use was most pronounced among older patients. We found that NSAID therapy was used less frequently for this patient population and that the likelihood of older patients receiving NSAID decreased steadily over time. These trends suggest that physicians had begun to respond to the 1995 ACR guidelines and to other studies highlighting safety concerns about the use of NSAID in OA[18-20,23,24].

Further, we believe that this cautious attitude surrounding the use of existing NSAID for OA has helped engender an environment suitable for the rapid influx of COX-2 inhibitors. Unfortunately, the time period covered by our data did not allow assessment of COX-2 inhibitor use. Nonetheless, other available data show that COX-2 inhibitors, with their improved safety profile, are currently used significantly more frequently than any other medications for OA[48]. Indeed, NSAID are now recommended as potential first-line agents for more severe or inflammatory OA[27]. While it is impossible to discount the influence of marketing strategies, this explosion of COX-2 usage suggests, in part, a continued effort to use safer medications in OA therapy.

The decline in NSAID use in our study, however, was not offset by an increase in acetaminophen usage. From 1989-91 to 1995-98, NSAID use decreased 13.6% while acetaminophen increased only 5.4% (4.6% in 1989-91 to 10.0% in 1995-98), resulting in about 9% fewer visits with a report of either medication. Based on our national estimates for the total number of OA visits made between 1995 and 1998, this decrease represents about 4.5 million fewer

visits with pharmacological therapy reported. It is possible that other recommended treatment modalities, including counseling for exercise, diet, or weight reduction[23,24,26], have partially substituted for pharmacotherapy in the treatment of OA. The NAMCS data, however, do not include questions pertaining to all 3 forms of counseling in each year of our analysis.

The low rate of use of histamine-2 blockers (5.3% of visits with a report of NSAID in 1995-98), proton pump inhibitors (2.8%), and misoprostol (only 1.7%) to help prevent NSAID induced side effects was also lower than expected. Misoprostol can induce mild to moderate diarrhea[13], which may account for its infrequent use; recent studies of omeprazole and ranitidine, however, found that both medications are well tolerated and potentially effective[14,15].

In addition, we found some evidence that treatment strategies may not be consistently applied across all patient types. Between 1989-91 and 1992-94, the rate of NSAID use for white patients with OA decreased more than the rate for nonwhite OA patients, resulting in statistically significant differences in NSAID usage between the 2 populations. This finding might suggest that the apparent shift away from NSAID occurred earlier for white patients.

This study has several limitations. Within the NAMCS data, there is a possibility of underreporting of medications. During the time period we assessed, many NSAID became available as over-the-counter (OTC) drugs. It is conceivable that physicians did not include OTC drugs on the NAMCS form, especially if the patient was taking multiple medications for other conditions and/or failed to inform the doctor of OTC drug use. A previous study reported that patients fail to inform their physicians of OTC drug use almost 50% of the time[49]. Additionally, it is difficult to confirm the diagnosis of OA, to confidently identify OA patients at risk for GI bleeding, to evaluate the severity of reported OA, or to determine whether other medications were tried previously. We also recognize that not all patients with OA may be recorded within NAMCS, and those patients reported to have OA may be not be representative of all patients with OA. These restrictions limit our ability to assess the appropriateness of NSAID or acetaminophen use.

Further, our analysis of the effects of physician specialty on OA treatment must be interpreted with caution. These findings may reflect our small sample size for OA rheumatology visits and may be confounded by issues related to disease severity and patient referral patterns. Rheumatologists may see patients with severe OA referred by their primary care physician after initial treatment has failed. Thus, the continued high use of NSAID by rheumatologists for OA therapy may be justified considering the types of patients they treat. In addition, orthopedic surgeons primarily treat patients with refractory OA who have been referred by a patient care physician, rendering interpretation of their prescribing patterns complex.

Despite these limitations, our data suggest that from 1995 to 1998, physicians began to limit their use of NSAID and that they responded to the literature citing important differences in individual NSAID toxicity. However, these changes in pharmacotherapy were not consistent across all patient populations, and acetaminophen, at the time considered a potential first-line pharmacological agent for OA, continued to be used infrequently. While some of our data have been superseded by the advent of COX-2 inhibitors, valid conclusions concerning the use of the literature remain. Our findings suggest that a more rapid and comprehensive response to the literature might have further optimized pharmacotherapy for OA and may have helped prevent possible variations in treatment based on nonclinical factors. Such a response would be of particular importance today, considering the rapidity with which the pharmacological industry continues to expand the arsenal of medications available for OA treatment.

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