Nonsteroidal Antiinflammatory Drug Toxicity Monitoring and Safety Practices

FAUSTO G. PATINO, JASON OLIVIERI, JEROAN J. ALLISON, TED R. MIKULS, LARRY MORELAND, STACEY H. KOVAC, LUCIA JUAREZ, SHARINA PERSON, JEFFREY CURTIS, and KENNETH G. SAAG

ABSTRACT. ***Objective.*** Nonsteroidal antiinflammatory drug (NSAID) related gastrointestinal (GI) and renal adverse events are commonly reported. Although published guidelines recommend periodic laboratory monitoring, NSAID safety practices of physicians have not been investigated at a population level. We examined the associations of physician specialty and patient characteristics with NSAID safety practices.

Methods. Using administrative data and medical record review from a regional managed care organization, we studied a retrospective cohort of 373 frequent NSAID users (≥ 3 consecutive NSAID prescriptions and ≥ 1 month of continuous NSAID use and followup). NSAID safety measures included: complete blood count (CBC) testing, creatinine testing, use of GI cytoprotective agents, and lack of simultaneous prescriptions for different NSAID (NSAID overlap).

Results. The mean duration of cumulative NSAID use was 14.4 ± 7.7 months/patient, patient age was 62.0 ± 11.4 years, and 63% were women. About two-thirds of patients received CBC (238, 63.8%) and creatinine monitoring (263, 70.5%), one-third (120, 32.2%) were prescribed cytoprotective agents, and one-fourth (97, 26%) had at least one NSAID overlap. After multivariable adjustments, concomitant use of disease-modifying antirheumatic drugs (OR 2.5, 95% CI 1.1–5.8), longer NSAID exposure (OR 1.3, 95% CI 1.1–1.4), and a greater number of physician visits/year (OR 1.1, 95% CI 1.0–1.2) were significantly associated with receipt of a CBC. A history of hypertension (OR 2.0, 95% CI 1.2–3.2), longer NSAID exposure (OR 1.3, 95% CI 1.2–1.4), and more physician visits/year (OR 1.1, 95% CI 1.0–1.2) were significantly associated with serum creatinine testing. Rheumatologists, and to a lesser extent internists, trended toward more NSAID toxicity monitoring than family/general practitioners. However, family/general practitioners and internists were more likely to monitor creatinine than rheumatologists among patients with renal risk factors.

Conclusion. While rheumatologists and internists trended toward more CBC and creatinine testing, visit frequency, duration of NSAID use, and comorbidities were the factors most consistently associated with safety monitoring. (J Rheumatol 2003;30:2680–8)

Key Indexing Terms:
NONSTEROIDAL ANTIINFLAMMATORY DRUGS DRUG SAFETY
DRUG TOXICITY MONITORING

Drug related gastrointestinal (GI) and renal toxicity in individuals taking nonsteroidal antiinflammatory drugs (NSAID) has been widely reported[1-9]. These adverse events occur at higher frequency in individuals with predisposing risk factors such as advanced age and in conjunction with particular comorbidities and concomitant drug use.

To improve NSAID safety, physician groups such as the American College of Rheumatology[10], the American College of Gastroenterology[11], the National Kidney Foundation[12], and the Canadian Consensus Conference[13,14] have promulgated quality of care guidelines. In hopes of early detection of NSAID related toxicity, these guidelines include recommendations for baseline and periodic laboratory testing such as serum creatinine and complete blood counts (CBC). Table 1 shows similarities and differences in NSAID toxicity monitoring and safety practices proposed by different professional associations.

Despite these dissemination efforts, studies suggest that these guidelines have done little to influence physician practices[15,16]. However, studies have either not been population based or have not examined determinants of toxicity monitoring practices. Using a retrospective cohort of patients from a large regional managed care organization (MCO), we

From the Division of Clinical Immunology and Rheumatology, Center for Education and Research on Therapeutics of Musculoskeletal Disorders, University of Alabama at Birmingham, Birmingham, Alabama, USA.

Supported in part by NIH grant P60 AR20614-23 and AHRQ grant U18HS10389. Dr. Saag has served as a consultant for Merck & Co. and has received research grants from Merck & Co. and Pfizer & Co.

F.G. Patino, MD, DrPH; J. Olivieri, MPH; J.J. Allison, MD, MSc; L. Moreland, MD; S.H. Kovac, PhD; L. Juarez, MA; S. Person, PhD; J. Curtis, MD, MPH; K.G. Saag, MD, MSc, Divisions of Clinical Immunology and Rheumatology and General Internal Medicine, and the Center for Education and Research on Therapeutics of Musculoskeletal Disorders, Department of Internal Medicine, University of Alabama at Birmingham; T.R. Mikuls, MD, MSPH, Section of Rheumatology and Immunology, University of Nebraska Medical Center and Omaha Veterans Affairs Medical Center, Omaha, Nebraska.

Address reprints requests to Dr. K.G. Saag, Center for Education and Research on Therapeutics of Musculoskeletal Disorders, University of Alabama at Birmingham, Birmingham, AL 35294-3408.
E-mail: ksaag@uab.edu

Submitted November 26, 2002; revision accepted April 22, 2003.

Table 1. Statements on NSAID and analgesic safety and monitoring recommendation.

Consensus Groups	Informing Patients About Risk	Alternative Approaches in NSAID Treated Patients at High GI Risk	Side Effect Monitoring Practices
American College of Rheumatology[60-62]	Cautious use of acetaminophen in patients with existing liver disease and avoidance in patients with history of chronic alcohol abuse	Low dose prednisone, Nonacetylated salicylate, COX-2 selective NSAID, Nonselective NSAID with misoprostol or PPI	GI: CBC at baseline and yearly Renal: creatinine at baseline; serial measurement of creatinine may be required (weekly for at least 3 weeks in patients receiving concomitant ACE inhibitors or diuretics)
The Canadian Consensus Conferences[13, 14]	Discuss safety with patients requiring NSAID (including COX-2)	COX-2 selective NSAID, Non-selective NSAID with misoprostol or PPI	Renal: baseline creatinine clearance and electrolyte concentrations
National Kidney Foundation[12]	Over-the-counter label warning of renal risks	—	Renal: monitor renal function in patients with preexisting volume disease or volume depletion
North of England Evidence Based Guideline Developement Project[63]	Discuss risk and side effects of NSAID with patients before treatment	Paracetamol, Low dose ibuprofen, Co-codamol, Lower NSAID dose*	—
US Preventive Services Task Force[64]	Discuss GI risk of aspirin in those taking for coronary heart prophylaxis	—	—
International COX-2 Study Group[65]	—	COX-2 selective or nonselective NSAID with misoprostol or PPI in users on low dose aspirin	Renal: at-risk patients (preexisting cardiac, renal, or hepatic disease) should be monitored (including COX-2)
American College of Gastroenterology[11]	—	Nonselective NSAID with misoprostol or PPI	—

NSAID: Nonsteroidal antiinflammatory drug, GI: gastrointestinal, PPI: proton-pump inhibitor, COX-2: Cyclooxygenase (COX-2) selective inhibitor, ACE: angiotensin-converting enzyme. * No evidence of cost-effectiveness of NSAID plus GI prophylaxis in OA patients.

analyzed patient and provider characteristics associated with safe NSAID practices to better understand the daily decisions made by physicians. Since variations in practice patterns for musculoskeletal disorders are well documented[17,18], we hypothesized that risk factors for NSAID toxicity would be positively associated with NSAID monitoring and safety practices, and that rheumatologists would be more likely to perform routine NSAID toxicity monitoring and safety practices than internists and family or general practitioners.

MATERIALS AND METHODS

Data sources and data collection. With approval from the University of Alabama at Birmingham Institutional Review Board, we identified NSAID users with pharmacy benefits from a large regional MCO that is currently Alabama's largest MCO, with over 240,000 clients. This MCO currently contracts with more than 80 hospitals in Alabama, with more than 4000 participating providers consisting of both primary care physicians (28%) and specialists (72%). National drug codes were used to identify all NSAID prescriptions from pharmacy claims. Study patients were restricted to chronic NSAID users, defined as those receiving at least 3 consecutive non-aspirin NSAID prescriptions from June 1998 to December 1999. To assess provider factors, NSAID users were stratified by the specialty of their prescribing physician. We focused on providers who were more likely to care for chronic NSAID users (family or general practitioners, internists, and rheumatologists) and we deliberately oversampled rheumatologists (all of those in the MCO with the minimum number of eligible patients) to address our hypothesis about different quality of care among providers. Out of 2334 eligible patients using NSAID, 680 (29%) patients and their corresponding 136 providers (5 patients per provider) were randomly selected. To prevent the effect of patient disenrollment on the likelihood of toxicity monitoring and other NSAID safety measures, only patients with at least one month of NSAID use and followup by their physicians were included in the final analysis.

Sociodemographic factors such as age, sex, and type of insurance coverage, as well as provider information on physician specialty and number of covered patients using NSAID in the sampling population, were collected from administrative claims and provider databases. Pharmacy claims data were only used to identify subjects. All analyses were based on data from medical record review. Over-the-counter medication, such as nonprescription NSAID and acetaminophen, were not considered in this study.

Medical record abstraction process. Medical record review included all chart documentation between June 1998 and April 2001. Trained nurse abstractors used a customized version of the MedQuest software (developed by Fu and associates under contract from the Health Care Financing Administration, website: http://www.fu.com/PRODUCTS.HTM) for chart abstraction. Medical record abstractors achieved 97% interrater reliability for all primary variables.

Detailed medical record review provided information on NSAID and other medication use. Particular attention was devoted to medications that might adversely interact with NSAID, that served as markers for potential NSAID renal toxicity (diuretics, beta blockers, angiotensin-converting enzyme inhibitors), or that were indicative of a predilection to NSAID GI

toxicity (corticosteroids, coumadin, GI cytoprotective drugs, H_2 blockers, and proton-pump antagonists). A Charlson Comorbidity Index[19] was also computed for each patient. Hypertension, an important risk factor for NSAID toxicity, which is not part of the Charlson index, was separately examined in the analysis. Based on the results of prior investigations, GI risk for NSAID toxicity was defined as having any of the following: age ≥ 65 years; concomitant use of oral glucocorticoids or coumadin; or history of GI bleeding, gastritis, or peptic ulcer[2,3,20-25]. Similarly, renal risk for NSAID toxicity was defined as having any of the following: age ≥ 65; concomitant use of angiotensin-converting enzyme inhibitors, diuretics, beta blockers, or other hypertensives; or history of renal disease, hypertension, or diabetes[7,9,26-28].

Intervals of NSAID use and cumulative use of NSAID were computed for each patient. Each interval represented a period of uninterrupted NSAID use during the followup period. One NSAID could have more than one interval if the patient used the drug intermittently. Cumulative NSAID use represented the sum of days in each NSAID interval subtracting the overlap periods (when a patient was taking more than one NSAID).

To analyze NSAID toxicity monitoring we identified safety measures based on published guidelines and recommendations[10,12-14,29] and input solicited from content experts specifically for this study. We focused on 4 potential safety measures that could be consistently identified from the medical records: CBC testing, creatinine testing, concomitant use of GI cytoprotective agents, and lack of NSAID overlap. Receipt of CBC and creatinine were examined as the total number of tests performed and dichotomously as at least one test performed during NSAID use or within 90 days before NSAID initiation.

Statistical analyses. Chi-square and one-way ANOVA or Student t tests were used to describe categorical and continuous variables, respectively. To seek evidence of confounding or effect modification of physician specialty by the frequency of visits or the differential use of disease modifying antirheumatic drugs (DMARD), we analyzed the association of CBC and creatinine monitoring with patient's physician specialty after stratifying the data either by DMARD use (use vs non-use) or by the frequency of visits (low and moderate tertiles vs highest tertile of visits per 12 months of followup).

To determine predictors of NSAID toxicity monitoring, we performed multivariable logistic regression analysis using model-building techniques described by Hosmer and Lemeshow[30]. Generalized estimating equations[31] were used to adjust for artificial inflation of statistical significance resulting from patients being nested within physicians. Due to their clinical relevance, all multivariable analyses were adjusted for age and sex. Other variables required a bivariate p value ≤ 0.25 to enter the models. Multivariable model calibration and discrimination were evaluated using Hosmer-Lemeshow goodness-of-fit statistic and the c-statistic, respectively[32,33]. Data management, reduction, and analyses were conducted in Microsoft Access (Microsoft Corp., Redmond, WA, USA), SAS (SAS Institute, Cary, NC, USA), and SPSS (SPSS Inc., Chicago, IL, USA).

RESULTS

We requested 680 medical records (from 136 providers) and received 452 records (66% response rate) from 103 physicians (43 internists, 44 general and family practitioners, 16 rheumatologists; 76% physician response rate). There were no significant differences in sex and age between patients whose records were reviewed and those whose records were not provided. Of the 452 NSAID users identified, 373 met criteria of at least one month of both NSAID use and physician followup for this analysis. Comparing these 373 patients with the 79 patients that were excluded from the current analysis due to less than one month of NSAID use or followup, we found no differences for age, sex, and comorbidity (GI or renal risks and Charlson Comorbidity Index). Patients seen by family or general practitioners were more likely to have less than one month of NSAID use or followup.

Characteristics of these 373 patients, stratified by physician type, are shown in Table 2. Patients seen by internists and rheumatologists were older and more likely to have GI risk factors compared to those seeing family or general practitioners. Compared to internists and family or general practitioners, rheumatologists were less likely to have patients with hypertension, diabetes, and renal risk factors and had patients with a lower Charlson Comorbidity Index. Patients seen by family or general practitioners and internists took more non-NSAID medications than patients seen by rheumatologists, but as expected, those seen by rheumatologists were considerably more likely to take DMARD. Over an average 21.7 ± 7.3-month observation period, mean cumulative duration of NSAID use per patient was 14.4 ± 7.7 months. Patients seen by rheumatologists had a shorter mean followup period and fewer visits per year than patients seen by family or general practitioners and internists; however, they had longer cumulative NSAID use duration and more intervals of NSAID use.

About two-thirds of patients received CBC (238, 63.8%) and creatinine monitoring (263, 70.5%); one-third (120, 32.2%) were prescribed cytoprotective agents and one-fourth (97, 26%) had at least one NSAID overlap during the followup period. Safety practices stratified by physician specialty are shown in Table 3. Consistent with their greater NSAID use, patients seen by rheumatologists received significantly more CBC and creatinine tests (number of test per year of NSAID use); however, there were no significant differences for CBC and creatinine testing ever. About one-fourth of patients in each physician specialty group received at least one NSAID overlap prescription during the study period. Internists were significantly more likely to prescribe GI cytoprotective agents than rheumatologists and family or general practitioners.

Safety monitoring practices according to patient GI or renal risk is illustrated in Figure 1. Patients were more likely to receive cytoprotective agents or creatinine testing if they had GI or renal risk, respectively. CBC testing showed no difference between patients with or without GI risk.

Referent to patients without renal risk factors, family and general practitioners (OR 3.5, 95% CI 1.6–7.7) and internists (OR 3.2, 95% CI 1.2–8.6) were more likely to selectively test creatinine among patients with renal risk factors (Figure 2A). There were no significant differences within specialty classifications for CBC testing (Figure 2B).

Stratifying patients according to the frequency of their physician visits, the pattern for CBC and creatinine monitoring testing showed that rheumatologists were more likely to order CBC testing than general or family practitioners and internists (OR 1.9, 95% CI 1.0–3.7) as well as creatinine

Table 2. Patient characteristics and patterns of NSAID use by physician type.

Patient Characteristics	General or Family Practitioner, n = 140	Internist, n = 168	Rheumatologist, n = 65
Demographics			
Women, n (%)	87 (62.1)	104 (61.9)	44 (67.7)
Age, yrs, mean (SD)¶	58.3 (12.8)	65.4 (9.4)	61.3 (10.4)
Comorbidities			
GI disease, n (%)*	20 (14.3)	24 (14.3)	7 (10.8)
GI risk, n (%)†¶	62 (44.3)	116 (69.0)	46 (70.8)
Congestive heart failure, n (%)	5 (3.6)	7 (4.2)	0
Hypertension, n (%)¶	82 (58.6)	106 (63.1)	9 (13.8)
Diabetes, n (%)#	22 (15.7)	39 (23.2)	2 (3.1)
Renal risk, n (%)‡¶	106 (75.7)	150 (89.3)	42 (64.6)
Charlson Comorbidity Index, mean (SD)¶	1.5 (1.2)	1.9 (1.5)	1.1 (0.5)
Concomitant drug use			
DMARD use, n (%)¶	3 (2.1)	8 (4.8)	32 (49.2)
Cumulative medication count (excluding NSAID), mean (SD)¶	14.5 (9.2)	16.2 (8.6)	9.0 (4.2)
Health care encounters			
Duration of followup, mo, mean (SD)§	21.08 (7.76)	22.81 (6.71)	20.18 (7.21)
Number of visits per year, mean (SD)¶	6.70 (4.64)	5.61 (2.90)	4.42 (2.02)
NSAID use			
NSAID duration, mo, mean (SD)§	13.30 (7.64)	14.33 (7.81)	16.76 (7.34)
No. of NSAID intervals, mean (SD)	2.57 (1.43)	2.68 (1.44)	2.95 (1.61)

* Gastrointestinal (GI) disease includes: gastritis, GI bleeding, or peptic ulcer. † GI risk includes: age ≥ 65, concomitant use of oral glucocorticoids or coumadin, or history of gastritis, GI bleeding, or peptic ulcer. ‡ Renal risk includes: age ≥ 65, concomitant use of angiotensin-converting enzyme inhibitors, diuretics, beta blockers, or other hypertensives; history of renal disease, hypertension, or diabetes. § $p < 0.05$, # $p < 0.01$, ¶ $p < 0.001$.

Table 3. NSAID safety practices by physician type.

Safety Practice	General or Family Practitioner, n = 140	Internist, n = 168	Rheumatologist, n = 65
		n (%)	
CBC testing ever*	85 (60.7)	105 (62.5)	48 (73.8)
Creatinine testing ever*	89 (63.6)	123 (73.2)	51 (78.5)
Cytoprotective agent use ever†	36 (25.7)	65 (38.7)	19 (29.2)
NSAID overlap ever	38 (27.1)	42 (25.0)	17 (26.2)
		mean (SD)	
No. of CBC tests per year of NSAID use‡	0.65 (1.08)	0.68 (0.93)	2.12 (2.53)
No. of creatinine tests per year of NSAID use‡	0.80 (1.21)	0.83 (1.01)	1.94 (2.10)

CBC: complete blood count. * Having at least one test done during NSAID use or within 90 days before start of NSAID. † $p < 0.05$, ‡ $p < 0.001$ by chi-square trend or ANOVA.

testing (OR 2.1, 95% CI 1.0–4.3) in patients within the low or moderate frequency of visits group (data not shown). However, among patients in the high frequency of visits group, the effect of specialty was not significant. Stratifying by DMARD use, rheumatologists had a nonsignificant trend to monitor more than general or family practitioners and internists among patients who were not taking DMARD (OR 1.3, 95% CI 0.6–2.7).

After multivariable adjustment for potential confounders, use of DMARD, number of physician visits per year, and duration of NSAID use remained significantly and positively associated with CBC monitoring (Table 4). The multivariable model was not improved by the addition of an interaction term containing visit frequency by physician type.

Table 5 shows the multivariable regression analyses exploring patient and provider characteristics associated with creatinine monitoring. History of hypertension, number of physician visits per year, and duration of NSAID use were positively associated with creatinine monitoring. Rheumatologists trended toward higher creatinine testing than internists and family or general practitioners. As with CBC monitoring, the multivariable model was not improved by the addition of an interaction term containing visit frequency by physician type.

Additional multivariable analyses showed significant

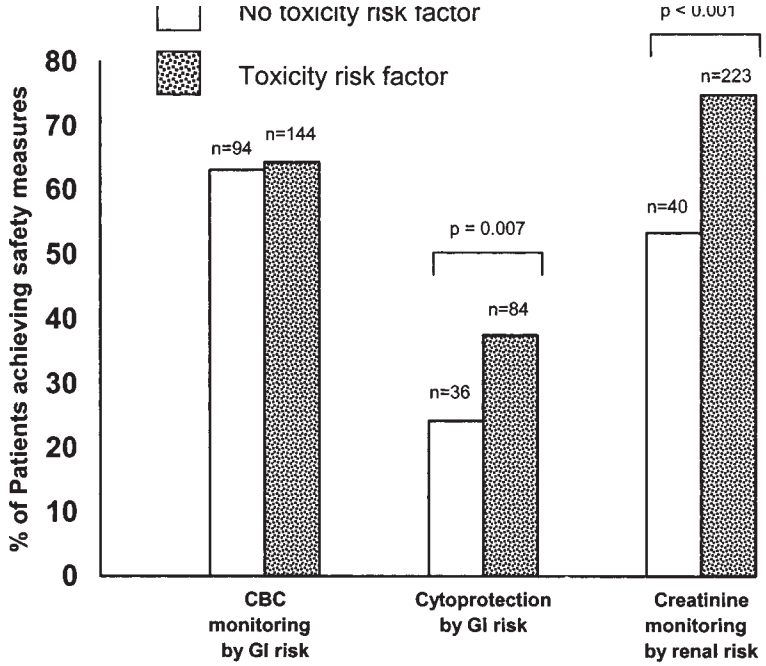

Figure 1. NSAID safety practices by patient gastrointestinal (GI) and renal risk status. GI risk includes: age ≥ 65 years, concomitant use of oral glucocorticoids or coumadin, or history of GI bleeding, gastritis, or peptic ulcer. Renal risk includes: age ≥ 65; concomitant use of angiotensin-converting inhibitors, diuretics, beta-blockers, or other antihypertensive medication; history of renal disease, hypertension, or diabetes. CBC and creatinine monitoring refer to having at least one test done during use of NSAID or within 90 days before starting NSAID. Cytoprotection refers to receipt of cytoprotective medications (histamine-2 blockers, misoprostol, and proton-pump antagonists).

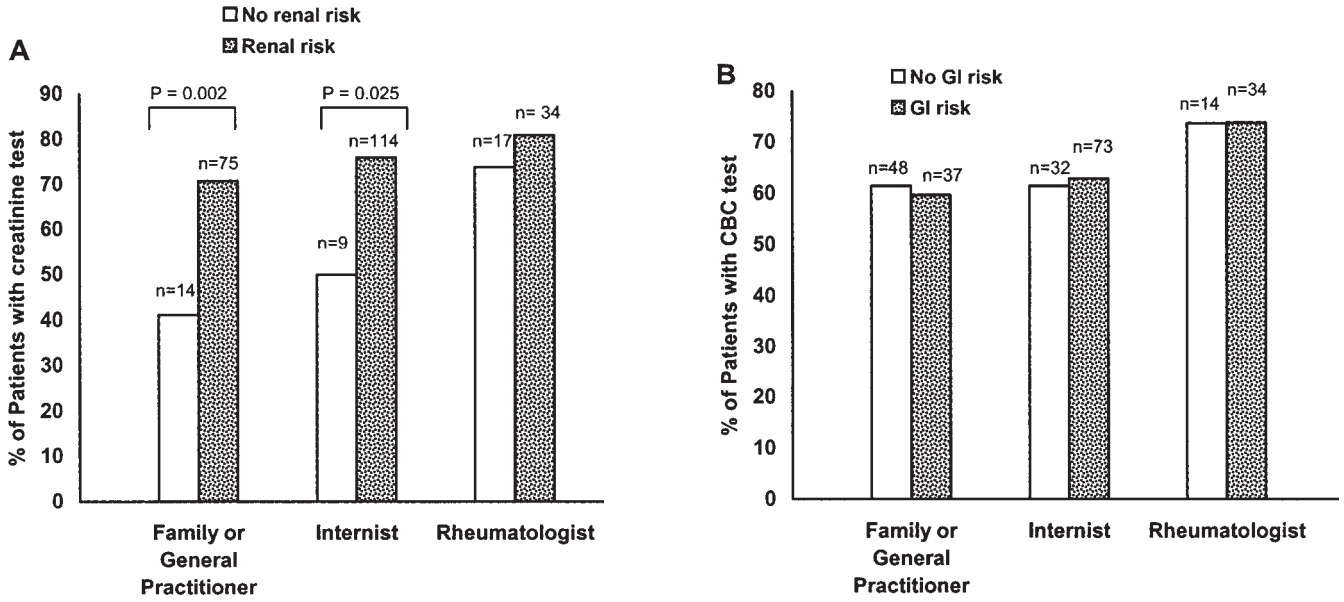

Figure 2. A. Proportion of patients with and without renal risk ever receiving a creatinine test, stratified by physician specialty. B. Proportion of patients with and without gastrointestinal (GI) risk ever receiving a CBC test, stratified by physician specialty. Renal risk includes any of: age ≥ 65 years, concomitant use of angiotensin-converting inhibitors, beta blocker, diuretics, or other antihypertensives, or history of renal disease, hypertension, or diabetes. GI risk includes any of: age ≥ 65 years, concomitant use of oral glucocorticoids or coumadin, or history of GI bleeding, gastritis, or peptic ulcer. CBC and creatinine testing includes at least one test performed during NSAID use or within 90 days before starting NSAID.

Table 4. Patient and provider characteristics associated with complete blood count (CBC) monitoring ever.

Variable	Unadjusted OR	95% CI	Adjusted OR*	95% CI
Age, yrs				
18–49	1.0	Referent	1.0	Referent
50–64	0.7	0.3–1.4	0.6	0.2–1.4
65+	1.1	0.5–2.2	0.8	0.3–2.0
Female sex	1.2	0.8–1.9	1.4	0.8–2.3
Concomitant use of DMARD	2.7	1.2–6.1	2.5	1.1–5.8
No. of physician visits per 12 observation months	1.1	1.0–1.1	1.1	1.0–1.2
Cumulative duration of NSAID exposure (no. of trimesters)	1.2	1.1–1.3	1.3	1.1–1.4
Provider type				
General of family practitioner	1.0	Referent	1.0	Referent
Internist	1.1	0.7–1.7	1.1	0.6–2.2
Rheumatologist	1.8	1.0–3.5	1.3	0.5–3.5

* Includes age, sex, and variables with univariate $p < 0.25$. c statistic = 0.7; Hosmer and Lemeshow goodness-of-fit statistic, $p = 0.1$.

Table 5. Patient and provider characteristics associated with creatinine monitoring ever.

Variable	Unadjusted OR	95% CI	Adjusted OR*	95% CI
Age				
18–49	1.0	Referent	1.0	Referent
50–64	1.7	0.9–3.4	1.1	0.5–2.4
65+	2.6	1.3–5.3	1.4	0.6–3.4
Female sex	1.1	0.7–1.8	1.2	0.7–2.1
Concomitant use of DMARD	2.0	0.9–4.4	1.7	0.7–4.5
No. of other concomitant drugs	1.0	1.0–1.1	1.0	1.0–1.0
Hypertension	2.0	1.3–3.1	2.0	1.2–3.2
Charlson Comorbity Index	1.5	1.2–2.0	1.3	1.0–1.8
No. of physician visits per 12 observation months	1.0	0.9–1.1	1.1	1.0–1.2
Cumulative duration of NSAID exposure (no. of trimesters)	1.3	1.2–1.4	1.3	1.2–1.4
Provider type				
General or family practitioner	1.0	Referent	1.0	Referent
Internist	1.6	1.0–2.5	1.3	0.6–2.8
Rheumatologist	2.1	1.1–4.1	2.1	0.7–6.4

* Includes age, sex, and variables with univariate $p < 0.25$. c statistic = 0.7; Hosmer and Lemeshow goodness-of-fit statistic, $p = 0.7$.

positive associations of cytoprotective medication use with history of GI disease (OR 4.5, 95% CI 2.4–8.72) and greater number of concomitant drugs other than NSAID or cytoprotective agents (OR 1.1, 95% CI 1.0–1.1) (data not shown).

A greater number of physician visits per year (OR 1.1, 95% CI 1.1–1.2) and longer cumulative duration of NSAID use (OR 1.2, 95% CI 1.1–1.4) were also determinants of NSAID overlap (data not shown).

DISCUSSION

Roughly two-thirds of chronic NSAID users in a regional managed care organization received CBC and creatinine monitoring, one-third received cytoprotective agents, and about one-fourth had at least one prescribed period of NSAID overlap. Although high-risk users underwent more safety testing, many chronic NSAID users never underwent a CBC or creatinine test, did not receive cytoprotective therapy, or had periods of NSAID overlap. The lack of uniform agreement and supporting evidence for safety practices among NSAID toxicity precludes exact specification of NSAID quality practices among health providers in our study.

Notwithstanding, a number of expert panels have endorsed baseline and/or periodic testing as well as use of cytoprotective agents among patients who are at risk for NSAID related adverse events. Our findings are noteworthy and consistent with previous research showing limited adherence of physicians to clinical guidelines for NSAID use[15,16] as well as for the management of other chronic diseases[34-40]. Discordance with published guidelines has been attributed to numerous barriers in physicians' knowledge, attitudes, and behaviors regarding those guide-

lines[34,39,41] or difficulties in interpreting or applying the presented evidence in clinically and financially complicated settings[42] that may be different from those reported in the guidelines[43]. More variation in the adherence to guidelines may be expected when there is controversy or unclear indication of use[35,36,41]. It should be noted that adherence to guidelines does not inherently lead to improved health outcomes[35,36,44].

In our study, visit frequency, duration of NSAID use, and hypertension were the factors most consistently associated with safety monitoring (CBC and creatinine testing) among frequent NSAID users. DMARD receipt was also associated with CBC monitoring and likely indicates the use of cotherapies requiring periodic blood counts. Consistent with this finding, patient comorbidity (e.g., hypertension, history of GI bleeding) also appeared to appropriately influence creatinine monitoring practices and the prescription of cytoprotective agents.

Although our results did not fully support the hypothesis that rheumatologists would be more likely to monitor for NSAID toxicity than internists and family or general practitioners, rheumatologists trended toward performing more CBC and creatinine monitoring than the other 2 types of specialists. This trend may be partially explained by the fact that although guidelines have a limited overall effect on physicians' practices, specialists tend to have higher confidence in guidelines issued by their specialty organizations[39].

Physicians who see their patients more frequently may be more likely to prescribe drugs and order laboratory tests than those who see their patients less[45,46]. A higher frequency of physician visits may indicate a patient's higher morbidity, in turn, influencing physician ordering of monitoring tests. In contrast to the potentially beneficial association of more testing with higher visit frequency, visit frequency and duration of NSAID use were deleteriously associated with the overlapping use of NSAID.

Physicians appeared more willing to monitor for NSAID toxicity in patients with longer NSAID utilization. This finding is consistent with the association of increased risks, especially for renal disease, with extended duration of NSAID use[8]. Patients with hypertension and other comorbidities have an enhanced susceptibility to NSAID induced renal complications as well as those receiving combinations of NSAID[7,9]. Physicians in our study were more likely to obtain a creatinine test for these patients. Generalists and internists were more selective in their test ordering among these at-risk patients, and this is consistent with a previous study[47] involving this cohort in which family or general practitioners, but not rheumatologists, were more likely to selectively prescribe the newer coxibs over traditional NSAID among their patients with GI disease history. This is important because over 60% of patients with musculoskeletal disorders are treated primarily by generalists[48] and more than 20% of all encounters with primary care providers are for musculoskeletal complaints[49,50]. This finding suggests that generalists and internists may be more sensitive to medical costs than various other specialists[51], particularly in lower-risk patients.

One limitation of our study is that we measured process of care rather than patient outcomes. For some of these process measures, such as CBC and creatinine testing, it is unknown if identification of patients with abnormal results on these laboratory tests actually leads to fewer adverse outcomes. Moreover, clinical outcomes in chronic musculoskeletal disorders evolve very slowly and may be more dependent on the nature of the condition than on the specific care rendered. Thus, when assessing health care quality in chronic diseases, process indicators are often recommended, particularly when comparing care provided by different specialists[52].

Although frequently used in studies of this type, data from medical records have limitations. Medical record review is potentially constrained by completeness and accuracy of information recorded[53]; therefore, our analysis may partially reflect quality of documentation rather than quality of care. This limitation is of importance when analyzing NSAID overlap, which is very sensitive to medical record documentation of medication start and stop dates; therefore, particular caution is needed when interpreting this finding. It should be noted, however, that results of laboratory tests are usually reported in medical records, enhancing the accuracy of these analyses. In addition, medical records do not provide accurate information on adherence to medical treatment or on the magnitude of use of over-the-counter medications[54-57] as well as other important clinical information (i.e., physical examination, review of systems)[53,55-59]. While the abstraction process itself may be imperfect, the high rate of interrater reliability among our medical record abstractors suggests that this was not a major source of bias. Finally, medical record review precludes addressing important physician factors, such as attitudes toward guidelines.

Another limitation in this study is that the managed care organization did not routinely collect racial or ethnic information, and only about one-half of the medical records documented this data. The patient selection requirement of a minimum one-month period of NSAID use and followup may have imposed a possible bias that overestimates physician adherence to the measured practices, since physicians not intending to test may be less likely to request that their patients return for followup. Given the manner in which our sample was constructed and its restriction to one geographical area, our results may not be generalizable to other groups of chronic NSAID users.

Despite these potential limitations, the data for this study came from a large regional managed care organization, which involved linked data from charts, pharmacy claims, and administrative files. The random selection of patients and high quality of medical record abstraction were also

strengths of this study. Medical record review also allowed extensive consideration of detailed patient factors.

Safety monitoring among chronic NSAID users was more common among high-risk patients and varied across a number of process of care measurements. Although rheumatologists trended toward more monitoring, visit frequency, more so than provider or patient factors, prominently influenced NSAID safety practices. This study suggests a need to see chronic NSAID users at least intermittently as a means to trigger discussion and possible testing for potential adverse effects. Assessing these patterns and predictors of health care quality is the necessary first step in improving quality of care for users of these extremely commonly prescribed medications.

REFERENCES

1. Bollini P, Garcia Rodriguez LA, Perez Gutthann S, Walker AM. The impact of research quality and study design on epidemiologic estimates of the effect of nonsteroidal anti-inflammatory drugs on upper gastrointestinal tract disease. Arch Intern Med 1992;152:1289-95.
2. 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.
3. Hernandez-Diaz S, Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Arch Intern Med 2000;160:2093-9.
4. Ofman JJ, MacLean CH, Straus WL, et al. A metaanalysis of severe upper gastrointestinal complications of nonsteroidal antiinflammatory drugs. J Rheumatol 2002;29:804-12.
5. Ailabouni W, Eknoyan G. Nonsteroidal anti-inflammatory drugs and acute renal failure in the elderly. A risk-benefit assessment. Drugs Aging 1996;9:341-51.
6. Evans JM, McGregor E, McMahon AD, et al. Non-steroidal anti-inflammatory drugs and hospitalization for acute renal failure. QJM 1995;88:551-7.
7. Griffin MR, Yared A, Ray WA. Nonsteroidal antiinflammatory drugs and acute renal failure in elderly persons. Am J Epidemiol 2000;151:488-96.
8. Perneger TV, Whelton PK, Klag MJ. Risk of kidney failure associated with the use of acetaminophen, aspirin, and nonsteroidal antiinflammatory drugs. N Engl J Med 1994;331:1675-9.
9. Pommer W, Bronder E, Greiser E, et al. Regular analgesic intake and the risk of end-stage renal failure. Am J Nephrol 1989;9:403-12.
10. American College of Rheumatology Ad Hoc Committee on Clinical Guidelines. Guidelines for monitoring drug therapy in rheumatoid arthritis. Arthritis Rheum 1996;39:723-31.
11. Lanza FL. A guideline for the treatment and prevention of NSAID-induced ulcers. Members of the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. Am J Gastroenterol 1998;93:2037-46.
12. Henrich WL, Agodoa LE, Barrett B, et al. Analgesics and the kidney: summary and recommendations to the Scientific Advisory Board of the National Kidney Foundation from an Ad Hoc Committee of the National Kidney Foundation. Am J Kidney Dis 1996;27:162-5.
13. Tannenbaum H, Davis P, Russell AS, et al. An evidence-based approach to prescribing NSAIDs in musculoskeletal disease: a Canadian consensus. Canadian NSAID Consensus Participants. Can Med Assoc J 1996;155:77-88.
14. Tannenbaum H, Peloso PM, Russell AS, Marlow B. An evidence-based approach to prescribing NSAIDs in the treatment of osteoarthritis and rheumatoid arthritis: The Second Canadian Consensus Conference. Can J Clin Pharmacol 2000;7 Suppl A:4A-16A.
15. MacLean CH, Louie R, Leake B, et al. Quality of care for patients with rheumatoid arthritis. JAMA 2000;284:984-92.
16. Rothenberg RJ, Holcomb JP. Guidelines for monitoring of NSAIDs. Who Listened? J Clin Rheumatol 2000;6:258-65.
17. Mazzuca SA, Brandt KD, Katz BP, et al. Comparison of general internists, family physicians, and rheumatologists managing patients with symptoms of osteoarthritis of the knee. Arthritis Care Res 1997;10:289-99.
18. Criswell LA, Redfearn WJ. Variation among rheumatologists in the use of prednisone and second-line agents for the treatment of rheumatoid arthritis. Arthritis Rheum 1994;37:476-80.
19. Charlson M, Szatrowski T, Peterson J, Gold J. Validation of a combined comorbidity index. J Clin Epidemiol 1994;47:1245-51.
20. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995;123:241-9.
21. Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF. Gastrointestinal tract complications of nonsteroidal anti-inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. Arch Intern Med 1996;156:1530-6.
22. Shorr RI, Ray WA, Daugherty JR, Griffin MR. 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.
23. Garcia Rodriguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994;343:769-72.
24. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991;114:735-40.
25. Hernandez-Diaz S, Rodriguez LA. Steroids and risk of upper gastrointestinal complications. Am J Epidemiol 2001;153:1089-93.
26. Perez Gutthann S, Garcia Rodriguez LA, Raiford DS, Duque Oliart A, Ris Romeu J. Nonsteroidal anti-inflammatory drugs and the risk of hospitalization for acute renal failure. Arch Intern Med 1996;156:2433-9.
27. Whelton A. Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure. A prospective, randomized, crossover comparison. Ann Intern Med 1990;112:568-76.
28. Sandler DP, Burr FR, Weinberg CR. Nonsteroidal anti-inflammatory drugs and the risk for chronic renal disease. Ann Intern Med 1991;115:165-72.
29. Bennett WM, Henrich WL, Stoff JS. The renal effects of nonsteroidal anti-inflammatory drugs: summary and recommendations. Am J Kidney Dis 1996;28 Suppl 1:S56-62.
30. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons; 1989.
31. Diggle PJ, Liang KY, Zeger SL. Analysis of longitudinal data. New York: Oxford University Press; 1994.
32. Lemeshow S, Hosmer JDW. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol 1982;115:92-106.
33. Harrell FEJ, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modeling strategies for improved prognostic prediction. Stat Med 1984;2:143-52.

34. Weingarten S, Stone E, Hayward R, et al. The adoption of preventive care practice guidelines by primary care physicians: do actions match intentions? J Gen Intern Med 1995;10:138-44.
35. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 1993;342:1317-22.
36. Woolf S. Practice guidelines: a new reality in medicine. Impact on patient care. Arch Intern Med 1993;153:2646-55.
37. Lomas J, Anderson G, Dominick-Pierre K, Vayda E, Enkin M, Hannah W. Do practice guidelines guide practice? The effect of a consensus statement on the practice of physicians. N Engl J Med 1989;321:1306-11.
38. Hayward RS, Guyatt GH, Moore KA, McKibbon KA, Carter AO. Canadian physicians' attitudes about and preferences regarding clinical practice guidelines. Can Med Assoc J 1997;156:1715-23.
39. Tunis SR, Hayward RS, Wildon MC, et al. Internists' attitudes about clinical practice guidelines. Ann Intern Med 1994;120:956-63.
40. Davis DA, Taylor-Vaisey A. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. Can Med Assoc J 1997;157:408-16.
41. Cabana M, Rand C, Powe N, et al. Why don't physicians follow clinical practice guidelines?: A framework for improvement. JAMA 1999;282:1458-65.
42. Hayward RS. Clinical practice guidelines on trial. Can Med Assoc J 1997;156:1725-7.
43. Farquhar D. Recipes or roadmaps? Instead of rejecting clinical practice guidelines as "cookbook" solutions, could physicians use them as roadmaps for the journey of patient care? Can Med Assoc J 1997;157:403-4.
44. Worrall G, Chaulk P, Freake D. The effects of clinical practice guidelines on patient outcomes in primary care: a systematic review. Can Med Assoc J 1997;156:1705-12.
45. Hartley RM, Charlton JR, Harris CM, Jarman B. Patterns of physicians' use of medical resources in ambulatory settings. Am J Publ Health 1987;77:565-7.
46. Mehl-Madrona LE. Frequent users of rural primary care: comparisons with randomly selected users. J Am Board Fam Pract 1998;11:105-15.
47. Patino FG, Allison J, Olivieri J, et al. The effects of physician specialty and patient comorbidities on the use and discontinuation of coxibs. Arthritis Rheum 2003;49:293-9.
48. Yelin E, Bernhard G, Pflugrad D. Access to medical care among persons with musculoskeletal conditions. A study using a random sample of households in San Mateo County, California. Arthritis Rheum 1995;38:1128-33.
49. Spitzer WO, Harth M, Goldsmith CH, et al. The arthritic complaint in primary care: prevalence, related disability, and costs. J Rheumatol 1976;3:88-99.
50. Kahl LE. Musculoskeletal problems in the family practice setting: guidelines for curriculum design. J Rheumatol 1987;14:811-4.
51. Donohoe MT. Comparing generalist and specialty care: discrepancies, deficiencies, and excesses. Arch Intern Med 1998;158:1596-608.
52. Solomon DH, Katz JN. Generalist, specialist, or both? J Rheumatol 2002;29:1345-7.
53. Allison JJ, Wall TC, Spettell CM, et al. The art and science of chart review. Jt Comm J Qual Improv 2000;26:115-36.
54. Gilchrist WJ, Lee YC, Tam HC, Macdonald JB, Williams BO. Prospective study of drug reporting by general practitioners for an elderly population referred to a geriatric service. BMJ 1987;294:289-90.
55. Beers MH, Munekata M, Storrie M. The accuracy of medication histories in the hospital medical records of elderly persons. J Am Geriatr Soc 1990;38:1183-7.
56. Jaski ME, Schwartzberg JG, Guttman RA, Noorani M. Medication review and documentation in physician office practice. Eff Clin Pract 2000;3:31-4.
57. Lau HS, Florax C, Porsius AJ, De Boer A. The completeness of medication histories in hospital medical records of patients admitted to general internal medicine wards. Br J Clin Pharmacol 2000;49:597-603.
58. Hannan TJ. Detecting adverse drug reactions to improve patient outcomes. Int J Med Inf 1999;55:61-4.
59. Shenfield GM, Robb T, Duguid M. Recording previous adverse drug reactions — a gap in the system. Br J Clin Pharmacol 2001;51:623-6.
60. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the management of rheumatoid arthritis: 2002 update. Arthritis Rheum 2002;46:328-46.
61. Hochberg MC, Altman RD, Brandt KD, et al. American College of Rheumatology guidelines for the medical management of osteoarthritis. Part I. Osteoarthritis of the hip. Arthritis Rheum 1995;38:1535-40.
62. Hochberg MC, Altman RD, Brandt KD, et al. American College of Rheumatology guidelines for the medical management of osteoarthritis. Part II. Osteoarthritis of the knee. Arthritis Rheum 1995;38:1541-6.
63. Eccles M, Freemantle N, Mason J. North of England evidence based guideline development project: summary guideline for non-steroidal anti-inflammatory drugs versus basic analgesia in treating the pain of degenerative arthritis. The North of England Non-Steroidal Anti-Inflammatory Drug Guideline Development Group. BMJ 1998;317:526-30.
64. US Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. Ann Intern Med 2002;136:157-60.
65. Simon LS, Smolen JS, Abramson SB, et al. Controversies in COX-2 selective inhibition. J Rheumatol 2002;29:1501-10.