

A Group Randomized Trial to Improve Safe Use of Nonsteroidal Anti-inflammatory Drugs

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Objective: To determine whether audit/feedback and educational materials improve adherence to recommendations for laboratory monitoring and cytoprotective agents to detect and prevent adverse events caused by nonsteroidal anti-inflammatory agents (NSAIDs).

Study Design: Controlled, cluster-randomized trial.

Methods: Physicians commonly prescribing NSAIDs were identified within a large managed care organization and randomized to a control or an intervention group (audit/feedback with peer-derived benchmarks and continuing medical education). Medical records were examined 10 months before and after the intervention for clinical data and receipt of complete blood count (CBC), creatinine testing, and cytoprotective agents (process measures). Primary analysis compared intervention versus control physicians among those who initially performed below a peer-derived benchmark. General estimating equations accounted for patient clustering.

Results: Of 101 physicians initially randomized, 85 remained eligible (38 internists, 36 family physicians, 11 rheumatologists) postintervention. Mean percent change in performance between intervention and control physicians for CBC monitoring was 16% versus 10%; for creatinine monitoring, 0% versus 17%; and use of cytoprotective agents, -3% versus -1%. None of these changes were significant. Rheumatology specialty, number of NSAID prescriptions and physician visits, and patient risk factors for NSAID-related toxicity were more strongly associated with improved safety practices than the intervention.

Conclusions: Audit/feedback and educational materials had no observed effect on improving NSAID-related safety practices. Potentially contributing factors include high baseline performance (ceiling effect), dilution of the intervention effect by case mix and provider factors, nonreceipt of intervention materials, and diverse indications for lab tests.

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inappropriately to older Americans, based on the presence of comorbid diseases known to increase the risk for NSAID toxicity.⁶

In light of widespread NSAID use and the potential for related toxicity, several physician groups have promulgated guidelines recommending NSAID safety-monitoring practices.⁷⁻¹⁰ These include identifying users at high risk for common NSAID-related complications, monitoring with complete blood count (CBC) and creatinine testing to screen for early GI and renal toxicity, and using cyclooxygenase-2 (COX-2) selective NSAIDs or coprescription of cytoprotective agents in high-risk patients. However, physician adherence to these recommendations is low.¹¹⁻¹³ For example, 1 study of 1355 rheumatoid arthritis patients found that physician adherence to recommended NSAID toxicity monitoring was only approximately 50%.¹¹ Historically, various strategies designed to alter physician behavior, including guideline formulation and written educational materials, have met with poor results. One strategy that has shown promise in effecting change in provider practice patterns is audit and feedback.^{14,15} With the goal of improving the quality of care provided to chronic NSAID users, we conducted a group randomized trial of a multimodal intervention designed to improve safety practices related to NSAID prescribing. We hypothesized that intervention physicians would show greater improvement in 3 safe NSAID-prescribing process measures between the baseline and follow-up periods compared with improvement shown by the control physicians.

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used medications worldwide.^{1,2} Adverse events associated with chronic NSAID use are common and often result in substantial morbidity and mortality.³ Among arthritis patients who use NSAIDs regularly, approximately 0.5% are hospitalized each year for a serious gastrointestinal (GI) event.^{4,5} Other adverse events associated with NSAID use include hypertension, worsened congestive heart failure, and several forms of renal injury. NSAIDs are among the most common medications prescribed

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METHODS**Baseline Cohort**

After approval by the University of Alabama at Birmingham institutional review board, we identified all adult patients with pharmacy benefits enrolled in a large regional managed care organization (MCO) receiving 1 or more NSAID prescriptions during a 7-month period from August 1999 to February 2000. National Drug Codes were used to identify NSAID prescriptions from pharmacy claims. No information regarding use of over-the-counter NSAIDs was available. We focused on patients of providers who were more likely to prescribe and continue to follow long-term NSAID users (family or general practitioners, internists, and rheumatologists) and deliberately oversampled rheumatologists. These patients and their associated prescribing physicians comprised the baseline cohort. Patient and provider information was obtained using the MCO administrative claims and provider databases.

From a total of 2334 eligible patients using NSAIDs, 680 (29%) patients and their corresponding 136 providers (5 patients per provider) were randomly selected, with preference given to patients with 3 or more NSAID prescriptions. We requested and received a total of 452 records (66% record response rate) from 103 physicians (43 internists, 44 general and family practitioners, 16 rheumatologists) (76% physician response rate).

Baseline Medical Record Abstraction

Medical record review included all chart documentation and laboratory data between August 1999 and June 2000. This 10-month interval ensured a minimum of 90 days of follow-up past the last NSAID prescription identified via pharmacy claims. Trained abstractors used a customized version of the MedQuest software for chart abstraction (Fu Associates, Ltd, under contract from the Health Care Financing Administration; <http://www.fu.com/products.htm>). Process measures characterizing safe NSAID prescribing were developed using the published literature.^{8,16} Medical record abstractors achieved 97% interrater reliability for all main variables.

Multimodal Intervention to Improve NSAID Safety

Participating physicians were stratified by specialty (ie, rheumatologist vs other physician type) and randomized to either the intervention or the control arm. Two University of Alabama at Birmingham physicians involved in the study design were excluded from randomization. After dissemination of intervention

materials, we were notified that 1 physician in the intervention group had died.

Physicians randomized to the intervention arm were exposed to a multimodal intervention. Under the general theme of "Safer Use of NSAIDs," the mailed intervention packet contained (1) a brochure consisting of provider-specific audit and feedback on indicators of safe NSAID practices for the physician's NSAID-treated patients, along with comparison with the performance of the top 10% of cohort physicians (the Achievable Benchmark of Care¹⁷); (2) key NSAID-related literature citations, with the opportunity for continuing medical education (CME) credits; and (3) a hyperlink to a case-based, educational Web site focused on safe NSAID-prescribing.

The intervention packet was disseminated twice. The first was mailed via the US Postal Service in February 2002, and a second delivery of the material occurred via overnight courier 1 month later. Several weeks after the initial mailing, a faxed questionnaire was distributed to assess receipt of materials and to obtain physician feedback on the intervention. The fax was broadcast weekly for 5 consecutive deliveries in April and May of 2002.

NSAID Safety Quality Indicators

Using data from the 10-month observation period, performance feedback was given to each physician for the following 3 process-of-care measures: (1) the proportion of the physician's patients with an increased risk for NSAID GI toxicity who had at least 1 CBC test performed (increased risk was defined as age ≥ 65 years, concomitant glucocorticoid or warfarin use, and/or history of GI bleeding including peptic ulcer disease); (2) the proportion of the physician's patients with an increased risk for NSAID renal toxicity who had at least 1 creatinine test performed (increased renal risk was defined as age ≥ 65 years; concomitant use of an angiotensin-converting enzyme inhibitor, diuretic, or other antihypertensive agent; and/or documented hypertension or diabetes); and (3) the proportion of users of traditional NSAIDs with NSAID-related GI risk (defined above) receiving a cytoprotective agent (misoprostol or a proton pump inhibitor).

Follow-up Cohort

Approximately 6 months after the intervention was distributed, we again identified all NSAID prescriptions written by both intervention and control physicians. Patients were eligible to be included in the follow-up cohort if they received 1 or more NSAID prescriptions in the 7 months from February 2002 to August 2002. Of the 101 physicians in the baseline cohort, 5 did not

have any eligible patients for the follow-up cohort (2 intervention and 3 control physicians). From a total of 2426 eligible patients using NSAIDs, 563 (23%) patients and their corresponding 96 providers (5.9 ± 0.70 patients per provider) were randomly selected with the intent to obtain 5 patients per provider. Preference in the random selection of patients was again given to individuals receiving ≥ 3 NSAID prescriptions written by the same physician. Medical records were reviewed by 5 trained abstractors over a similar 10-month period for the same 3 primary processes of care of interest using the methods and tools described above. The abstractors were blind to physicians' study arm assignment.

Statistical Analyses

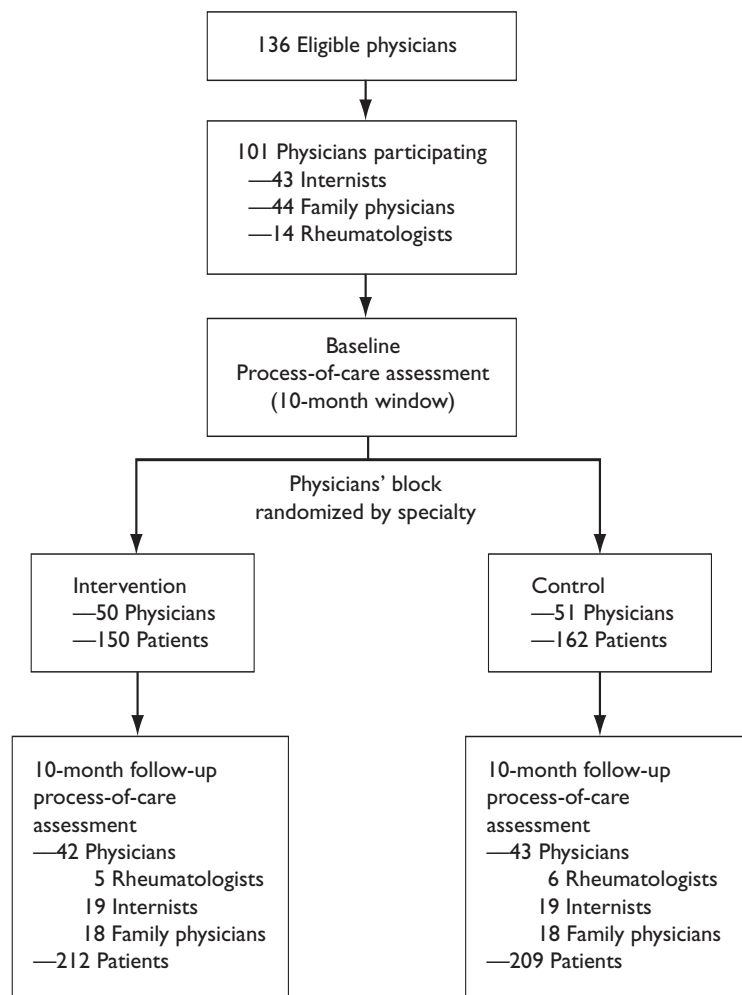
The primary analysis was to compare the absolute performance for each of the 3 processes of care (CBC testing, creatinine testing, and coprescription of cytoprotective agents) for the intervention and control physicians who performed below the Achievable Benchmark of Care in the baseline period. In secondary analyses, we examined change in performance among only high-risk patients (CBC testing and cytoprotective use among high-GI-risk patients, and creatinine testing among high-renal-risk patients). We also allowed satisfaction of the cytoprotective-use process measure to include substitution of COX-2 NSAIDs (eg, celecoxib, rofecoxib) for traditional, nonselective NSAIDs. Finally, we examined factors specific to patients, providers, and receipt of the intervention that were associated with improvement between the 2 time periods. Improvement was defined as postintervention physician performance that exceeded preintervention physician performance.

Main analyses were performed using postintervention patient-level variables aggregated at the provider level. For the primary analysis, the performance of the physicians was analyzed by their assignment to either the intervention or the control group. In secondary/exploratory analyses that were likely underpowered, intervention physicians also were categorized as either having (1) never responded or (2) returned the mailed postcard or fax indicating receipt of the intervention packet, or logged onto the NSAID CME Web site. In multivariable models that examined improvement in performance,

adjustment was made for each physician's baseline performance.

Student *t* tests or analysis of variance and chi-square tests were used to compare continuous and categorical variables, respectively. Generalized estimating equations were used to control for differences in case mix, account for cluster randomization, and adjust for the physician's baseline performance rates.¹⁸ Univariate associations were required to be significant at $P < .25$ for inclusion in further model building. The study was initially designed to have 80% power to detect a 10% difference between intervention and control groups for each of the 3 primary end points, which led to the determination of the number of physicians to recruit and patient records to review. Data collection and management were performed using Microsoft Access (Microsoft Corporation, Redmond, Wash), and statistical tests were performed using SAS software (SAS Institute, Cary, NC).

Figure 1. Overview of Trial Study Design



RESULTS

Patient Selection and Chart Requests

After our selection process and subsequent request for medical records, we received 66% of the requested medical charts (n = 312). There were no significant differences in sex and age between patients whose records were reviewed and those whose records were not sent to us for review. A total of 101 physicians were randomized into the intervention or the control arms of the study. An overview of the trial design is presented in **Figure 1**.

Six months after our intervention, we received 83% of the requested medical records from 85 of the 96 physicians (n = 421). Characteristics of the interven-

tion and control physicians and their associated NSAID-treated patients are described in **Table 1**. Only minimal differences were observed between the demographics and patient case mix of intervention physicians compared with control physicians. Fewer than 5% of the patients in the baseline cohort were represented in the follow-up cohort.

Response to Intervention Targeted at Improving NSAID Safety

After the mailed intervention, 20 of the 50 intervention physicians responded (40%) via the Web site (n = 1), postcard (n = 14), or fax (n = 11) (numbers include multiple responses from individual physicians). CME was awarded to 15 physicians.

Table 1. Demographics and Case Mix of Physicians Prescribing NSAIDs

Characteristic	Preintervention No. (%) or Mean \pm SD		Postintervention No. (%) or Mean \pm SD	
	Intervention	Control	Intervention	Control
Physicians				
No.	42*	43*	42*	43*
Age, y	50 \pm 8	50 \pm 7	50 \pm 8	48 \pm 6
No. (%) male	37 (88)	37 (86)	37 (88)	37 (86)
Specialty				
Internal medicine	19 (45)	19 (44)	19 (45)	19 (44)
Family practice	18 (43)	18 (42)	18 (43)	18 (42)
Rheumatology	5 (12)	6 (14)	5 (12)	6 (14)
Patients				
No.	150	162	212	209
Age, y	62 \pm 11	62 \pm 12	54 \pm 13	55 \pm 12
No. (%) male	95 (63)	105 (65)	93 (44)	96 (46)
Patients with GI risk [†]	87 (58)	102 (63)	78 (37)	73 (35)
Patients with renal risk [‡]	127 (85)	127 (78)	138 (65)	127 (61)
No. of NSAID prescriptions [§]	4.0 \pm 2	3.4 \pm 2	4.4 \pm 2	4.5 \pm 2
Patients receiving 3 or more NSAID prescriptions [§]	109 (73)	106 (65)	182 (86)	174 (83)
No. of non-NSAID prescriptions [¶]	15 \pm 9	13 \pm 8	7 \pm 5	8 \pm 6
Modified Charlson comorbidity index score [¶]	0.9 \pm 1	0.9 \pm 1	0.6 \pm 1	0.7 \pm 1
Patients receiving DMARDs [¶]	13 (9)	11 (7)	17 (8)	19 (9)
Office visits to any physician [¶]	10.4 \pm 8	8.9 \pm 6	3.5 \pm 2 [‡]	4.1 \pm 3 [‡]

DMARD indicates disease-modifying antirheumatic drug; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

*Includes only physicians with eligible patients in both periods.

[†]Age \geq 65 years; history of GI bleeding, gastritis, or peptic ulcer disease; or concomitant glucocorticoid or warfarin use.

[‡]Age \geq 65 years; history of hypertension, diabetes, or renal disease; or antihypertensive prescription.

[§]During 10 months of observation.

^{||} $P < .01$.

[¶]During 20 months of observation in the baseline cohort and 10 months of observation in the follow-up cohort.

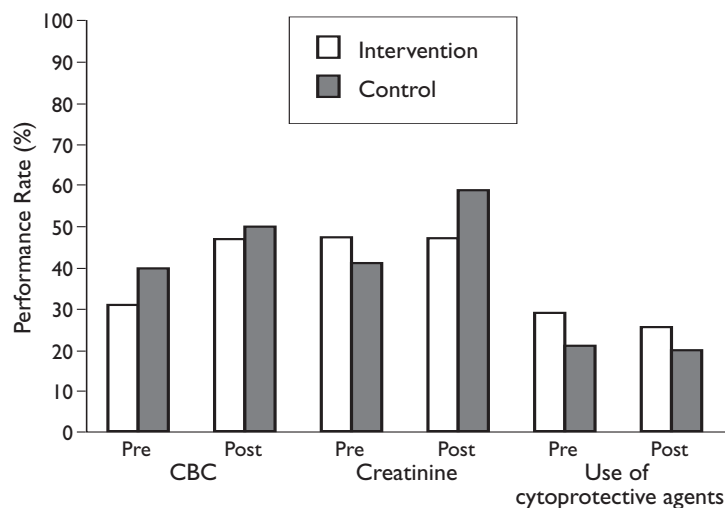
[‡] $P < .05$.

Primary and Secondary Analyses

Performance rates for the 3 main process measures including CBC testing, creatinine testing, and cytoprotective use for the preintervention and postintervention time periods were similar at baseline between the intervention and control group physicians (Figure 2). For CBC testing, the performance of intervention physicians increased from 31% in the baseline time period to 47% in the follow-up period. The performance of control physicians similarly increased from 40% at baseline to 50% in follow-up. For creatinine testing, the performance of intervention physicians was 47% and did not change, in contrast to the performance of control physicians, which increased from 41% at baseline to 58% in follow-up. Only small, nonsignificant changes were observed in the use of cytoprotective agents between the baseline and follow-up time periods for both arms of the intervention. There were no significant differences in performance between intervention and control physicians at either time point for any of the 3 process-of-care measures. In secondary analyses, no differences in performance between the intervention and control groups were observed when all cohort physicians were included, when the analysis was restricted to high-risk patients only, or when the cytoprotective process measure included COX-2-selective NSAID use (data not shown).

Multivariable analysis examining factors associated with improvement in NSAID safety practices is presented in Table 2. Because performance in the baseline period was expected to impact improvement measured in the follow-up period, we included baseline performance as a covariate in our model examining improvement. A greater number of patient office visits, more NSAID prescriptions, and higher risk patients were associated with an increased likelihood of adherence to NSAID safety-monitoring guidelines. Rheumatologists also were more likely than family practice physicians to increase their rate of toxicity monitoring. The performance of intervention physicians was analyzed both in aggregate (data not shown) and separately in subgroups based on their confirmation of receipt of intervention materials and/or participation in CME activities. Neither analysis showed significant differences in the likelihood for improvement in performance compared with control physicians. However, when absolute performance was examined, the performance of physicians who confirmed receipt of the intervention materials

Figure 2. Change in Performance After NSAID Safety Intervention for Physicians Initially Performing Beneath the Benchmark



"Pre" and "Post" refer to before and after the NSAID safety intervention. CBC indicates complete blood count; NSAID, nonsteroidal anti-inflammatory drug. Benchmarks for CBC, creatinine, and use of cytoprotective agents were 100%, 100%, and 96%, respectively. The number of intervention and control physicians for each of the 3 process measures were 38 and 41, respectively, for CBC testing; 32 and 34, respectively, for creatinine testing; and 41 and 42, respectively, for use of cytoprotective agents. $P = NS$ for all pairwise comparisons.

and/or engaged in the optional CME activities showed a higher but nonsignificant trend compared with both the remaining intervention physicians and also the control physicians (data not shown).

DISCUSSION

With the goal of improving NSAID safety practices, we conducted a group randomized trial of a multimodal intervention utilizing audit and feedback, and comparison with the performance of the top 10% of cohort physicians. We recruited physicians that prescribe NSAIDs in both primary care and specialty settings within a diverse managed care environment. Despite our use of a multimodal methodology previously shown to be effective for changing practice in other chronic diseases,¹⁷ we failed to detect significant differences in NSAID safety-monitoring practices. Provider and patient factors and health services utilization instead were more strongly associated with both absolute and relative improvement in adherence to NSAID safety-monitoring guidelines.

Several methodologies, including some of those used in this study, have achieved varying degrees of success in changing physician practice and improving adherence to evidence-based clinical practice guidelines.

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Table 2. Factors Predicting Improvement in NSAID Safety Practices in Postintervention Cohort of Physicians*

Factor	CBC Testing (n = 48)		Creatinine Testing (n = 34)		Use of Cytoprotective Agents (Ever) [†] (n = 34)	
	OR	95% CI	OR	95% CI	OR	95% CI
Specialty (general/family practice referent)						
Internal medicine	1.0	0.6, 1.7	1.4	0.7, 2.7	—	—
Rheumatology	9.0	1.9, 41.7	7.7	2.0, 28.9	—	—
No. of NSAID prescriptions (10-month observation period)	1.31	1.13, 1.51	—	—	—	—
No. of physician visits (10-month observation period)	1.27	1.11, 1.45	1.25	1.06, 1.48	1.29	1.15, 1.45
High renal risk [‡]	—	—	2.38	1.17, 4.83	—	—
Baseline performance	1.02	1.01, 1.04	1.02	1.01, 1.04	1.04	1.02, 1.06
Intervention arm (control group referent)						
Intervention physicians who did not confirm receipt of materials	1.44	0.80, 2.61	0.68	0.37, 1.26	1.79	1.07, 2.98
Intervention physicians who did confirm receipt of materials and/or participate in additional CME activities	1.02	0.58, 1.79	0.71	0.36, 1.40	1.05	0.67, 1.66

CBC indicates complete blood count; CI, confidence interval; CME, continuing medical education; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

*Improvement was defined as postintervention performance that was better than preintervention performance.

[†]Defined for each patient as 1 or more prescriptions for a proton pump inhibitor or misoprostol in a 10-month observation period.

[‡]Age ≥65 years; history of hypertension, diabetes, or renal disease; or antihypertensive prescription.

Those demonstrating only limited benefit include traditional CME activities and passively consumed written educational materials.^{19,20} Others showing more promise include electronic reminder systems,²¹ local opinion leaders,²² and academic detailing.²³ We used audit and feedback, which previously have been demonstrated by us and others to be efficacious in a variety of chronic diseases.^{17,24,25} At best, small to moderate effect sizes have been observed with most of these interventions, and no single intervention or set of interventions has been proven effective to alter physician practice patterns in all settings.²¹

Although the results of our trial were negative, we incorporated previously recognized important elements of successful uses of audit and feedback. We offered audit and feedback that was specific to each physician's practice. We included comparison with both the physician's peer group and with the top performers via the Achievable Benchmark of Care.¹⁷ We attempted to enhance the validity of our intervention by referencing evidence-based guidelines advocating identification of patients at high risk for NSAID-relat-

ed complications and appropriate monitoring. We coupled our audit and feedback with CME activities offered in both written and electronic format. Processes of care were assessed in a blinded fashion by multiple abstractors who achieved high rates of interobserver agreement.

Despite these strengths, several limitations may have contributed to our negative results. Because we focused on laboratory tests as a process measure of toxicity monitoring and because these tests are ordered for a variety of indications, we likely had a lower than optimal "signal-to-noise" ratio in our laboratory-monitoring outcomes. Similar issues are relevant for prescription of cytoprotective medications. Additionally, we had greater-than-expected attrition among study physicians and more variability in our process-of-care measures than we expected. Post-hoc power calculations based on our actual data suggested that we were powered at 80% to detect a 17% difference between intervention and control groups, a larger difference than observed for changes in CBC testing, for example.

Physicians who had 100% adherence to the NSAID safety practice guidelines in the preintervention period reduced the number of individuals for whom measurable improvement could be demonstrated (a ceiling effect). High ceiling effects are known to reduce the measurable effectiveness of audit and feedback.²⁵ Difficulties in capturing the attention of busy physicians also likely contributed to our negative results. Indeed, fewer than half of the doctors randomized to the intervention responded that they received the intervention packet despite repeated mailings. However, our results suggested a trend towards higher performance among physicians who reported receipt of the intervention materials and participated in the CME activities.

Our negative results stand in contrast to our previous success with using audit and feedback with the peer-derived Achievable Benchmark of Care to improve care for diabetic patients.¹⁷ In contrast to nationally recognized diabetes quality measures,²⁶ quality measures for NSAID monitoring may be less widely known or less accepted by physicians. Although $\geq 83\%$ of patients received at least 3 NSAID prescriptions in 7 months, the remainder received only 1 or 2, and their physicians may not have believed that these patients were appropriate candidates for the measured processes of care because they were not chronic users. Moreover, some of the NSAID users we identified were lower risk based on younger age or lack of medical comorbidities.²⁷ The peer-derived Achievable Benchmark of Care benchmark for all 3 process measures was at near or equal to 100%, perhaps reducing its face validity. Although recent safety data for NSAIDs suggest the need for revision of NSAID prescription and monitoring guidelines, our study predated most of these safety concerns and should not have been temporally affected by these newer data.

Our results highlight the challenges of interventions designed to improve adherence of NSAID safety-monitoring guidelines. Difficulties in engaging physicians despite repeated mailings, a ceiling effect in baseline performance rates, and nonspecific indications for the processes of care of interest were significant factors that likely contributed to the negative effect of our multimodal intervention for increasing NSAID toxicity monitoring and use of cytoprotective therapy. In contrast to our intervention, disease severity and frequency of care were more important in identifying those most likely to get toxicity monitoring. The clinical and methodologic insights gained from this work will lead future studies to greater success in improving physician adherence to evidence-based practice guidelines.

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