A Cohort Study of NSAID Use and the Management of Related Gastrointestinal Symptoms by Primary Care Patients

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ABSTRACT

Objectives and Study Design. Because little is known about the adherence of primary care patients to prescribed regimens of nonsteroidal anti-inflammatory drugs (NSAIDs) and their management of NSAID-related gastrointestinal (GI) symptoms, a prospective cohort study was performed, with baseline and follow-up surveys conducted at two and six weeks.

Population. The patients (n = 440) were aged 50 years and older. They were in a family practice research network and had received a prescription (new or renewal) for an NSAID for any indication with an expected duration of treatment of 14 or more days. Patients were classified as new NSAID users, changed NSAID users, or renewal NSAID users, according to their previous exposure to NSAID therapy.

Outcomes. Measured outcomes included (1) self-reported NSAID continuation rates at two and six weeks; (2) any reasons for discontinuation; (3) GI symptoms, classified as dyspeptic or other; and (4) any actions taken by patients in response to their symptoms.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) constitute one of the most widely used classes of agents in primary care; more than 70 million prescriptions for NSAIDs are filled in the U.S. each year. Some investigators have estimated that 5% to 10% of the adults in the U.S. (approximately 15 to 25 million people) use NSAIDs regularly. More than 30 billion over-the-counter (OTC) NSAID tablets are sold annually in the U.S.1,2

The widespread use of these products is often accompanied by significant adverse events, primarily of the gastrointestinal (GI) tract. In general, 10% to 20% of patients reportedly have dyspepsia while taking NSAIDs, although the true prevalence may be as high as 50%.3,4 More serious GI complications requiring hospitalization for upper GI bleeding are estimated at about 1% to 4% per year for patients taking NSAIDs over the long term.5

In primary care, NSAIDs are prescribed for a variety of chronic and acute conditions. To understand more about patient adherence to their NSAID regimens and their management of NSAID-induced GI symptoms, we undertook a prospective observational study of NSAID users with two objectives:

1. to characterize NSAID use and discontinuation in a cohort of primary care patients taking prescription NSAIDs
2. to characterize patterns of self-reported GI symptoms in patients taking prescribed NSAIDs and the patients’ management of these GI symptoms

METHODS

Patients were selected from participating practices of the Tri-State Primary Care Research Network.6 This network includes more than 25 practices and 200 physicians in the greater metropolitan Philadelphia area. Ten practices with a total of 76 physicians participated. Two of the practices were family practice residency programs with attending and resident physicians. In these practices, second-year and third-year resident physicians as well as attending physicians participated in the study. The other eight practices consisted of solo practitioners or small groups with two to four physicians each. All of the practices provide comprehensive primary care to diverse patient populations.
Self-Management of NSAID-Related Symptoms

Eligible patients were 50 years of age or older and had received a prescription (new or renewal) for an NSAID for any indication with an expected duration of treatment of 14 or more days. Potential subjects were identified by their primary care physicians and referred to one of two research assistants to determine their eligibility. Patients who could not understand or complete the baseline interview or who did not anticipate being available for the two scheduled follow-up visits were excluded from enrollment.

After reviewing and signing a consent form, participants completed an interviewer-administered baseline survey that lasted 20 to 30 minutes. Two and six weeks after the baseline survey, a research assistant contacted the participants by telephone. Each telephone interview took five to 10 minutes. Patients were paid for their participation.

The investigators developed and pilot-tested the survey instruments in conjunction with an independent organization specializing in test construction. The baseline survey asked patients about demographics and their general health in addition to their knowledge, attitudes, and practices regarding previous NSAID therapy. The follow-up surveys assessed patterns of NSAID use and any reasons for discontinuing therapy.

Patients were also asked about any GI symptoms they experienced while taking prescription NSAIDs, and how they managed these symptoms, and about their use of prescription or OTC gastroprotective medications. To facilitate the patients’ recognition of prescription and nonprescription products, the research assistant gave them professionally produced cards with pictures of available gastroprotective medicines. The institutional review boards that were responsible for the practice sites approved all of the procedures.

Because we anticipated that the patients’ perceived effectiveness and drug tolerability would be related to their previous exposure to NSAIDs, we categorized patients according to their self-reported earlier experience with these agents as follows:

- **New** NSAID users received a prescription for an NSAID at the baseline visit and reported that they had not taken NSAIDs for more than one day during the previous two weeks.
- **Changed** NSAID users reported using an OTC or prescription NSAID in the previous two weeks but then receiving a different NSAID prescription from their physician.
- **Renewal** NSAID users received a continuing prescription for NSAIDs.

The study was designed to follow patients’ experiences with NSAIDs under normal practice conditions, with no attempt made to influence the physicians’ patterns of NSAID-prescribing behaviors or their instructions to their patients. Patients received no instructions about their medication use. Drug adherence was not protocol-driven, and all survey data were collected separately from the physician–patient interactions. The SAS® PC program, version 8.0 (Windows™ statistical package, SAS Institute, Cary, North Carolina) was used to analyze the data.

### Table 1

<table>
<thead>
<tr>
<th>Demographics of Patients Taking Nonsteroidal Anti-inflammatory Drugs</th>
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<tbody>
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<td>------------------</td>
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<tr>
<td><strong>Gender (% female)</strong></td>
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<tr>
<td><strong>Age, Years: Mean (SD)</strong></td>
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<tr>
<td><strong>Ethnicity (%)</strong></td>
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<tr>
<td>African-American</td>
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<tr>
<td>White</td>
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<tr>
<td>Other</td>
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<tr>
<td><strong>Current smoker? (% Yes)</strong></td>
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<tr>
<td><strong>Insurance pay for medications? (%)</strong></td>
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<tr>
<td>Full</td>
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<tr>
<td>Part</td>
</tr>
<tr>
<td>Nothing</td>
</tr>
<tr>
<td><strong>Education (%)</strong></td>
</tr>
<tr>
<td>Less than high school</td>
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<tr>
<td>High school graduate or some college</td>
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<tr>
<td>College or postgraduate study</td>
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Rx = prescription; SD = standard deviation.

### RESULTS

Of the 467 patients identified by their physicians as meeting the study’s inclusion criteria, 447 (96%) agreed to participate. The most frequent reason given for not participating was “not enough time.” Of the patients who completed a baseline survey, 440 (98%) completed the two follow-up surveys according to the timeline in the study protocol. All analyses include only these 440 subjects.

#### Demographics

The patients ranged in age from 50 to 99 years (mean = 65.3 years, median = 63 years), and 78% were women (Table 1). The racial breakdown (55% African-American, 38% white) reflected the practices from which the patients were recruited. Most subjects (52%) described themselves either as high school graduates or as having attended some college; 19% had completed college or postgraduate work.

According to the study definitions, 83 patients were categorized as new NSAID users, 29 as changed NSAID users, and 328 as renewal NSAID users upon enrollment. Demographic profiles in the three user groups were similar.

#### Indications for NSAIDs

The most common reasons reported for needing an NSAID prescription were arthritis of any type (256, or 58% of all subjects) and musculoskeletal pain, including back pain (254, or 58% of all patients). Some patients chose more than one reason. Less commonly chosen indications were headache (4%), postsurgical pain (2%), and miscellaneous causes (1%).
Self-Management of NSAID-Related Symptoms

Choice of NSAID
Two NSAIDs—ibuprofen (e.g., Motrin®, McNeil Consumer) and naproxen sodium (e.g., Naprosyn®, Roche)—accounted for more than half (56%) of all the NSAIDs prescribed at the baseline evaluation. Two other unique classes of NSAIDs—the cyclooxygenase–selective (COX-2) formulations (rofecoxib [Vioxx®, Merck] and celecoxib [Celebrex®, Pfizer; Pharmacia & Upjohn]) (16%) and an NSAID combined with a gastroprotective agent, diclofenac/misoprostol (Anthrotec®, Searle) (4%)—were the next most commonly prescribed. COX-2 NSAIDs comprised 13% of the NSAIDs prescribed for renewal NSAID users, 19% of those for new NSAID users, and 38% of those for changed NSAID users.

Reduction in Pain
On a scale from 0 (“no pain”) to 10 (“the worst pain you can imagine”), the total study population described their pain as 4.2 ± 3.0 (standard deviation) at baseline (Figure 1). All three groups reported an improvement in pain at the two-week and six-week follow-up visits.

NSAID Discontinuation
Most of the patients in all three groups reported still taking NSAIDs at the two-week and six-week follow-up visits (Table 2). Patients who were no longer taking NSAIDs were asked to explain why they had discontinued the prescribed drug. At the two-week visit, only four patients reported that they had stopped the medication because of side effects. At the six-week visit, only eight patients cited side effects as the reason for discontinuing NSAIDs.

Gastrointestinal Symptoms and NSAID Use
Patients who continued taking NSAIDs were asked whether they had experienced GI symptoms and to consult a checklist. Symptoms were categorized as dyspeptic (heartburn, nausea, vomiting, abdominal pain) or non-dyspeptic (bloating, gassiness, constipation, diarrhea). The “changed” NSAID users reported the highest rates of GI symptoms (Figure 2). Overall, nearly two-thirds of all GI symptoms were dyspeptic in nature.

Management of Gastrointestinal Symptoms
Patients who experienced GI symptoms were asked to explain, after selecting from a list of options, which actions they took in response to these symptoms (Table 3). Overall, 54 (12%) patients reported dyspeptic symptoms (a total of 60 symptoms) at two weeks, and 44 patients (10%) reported dyspeptic symptoms (a total of 47 symptoms) at six weeks. These actions were then categorized as follows:

- Patients managed without involving a physician (e.g., “did nothing,” “took with food,” “reduced dose on own,” and “took OTC meds”).
- Patients managed by taking prescription gastroprotective medications.
- Patients managed by involving a physician (e.g., “called doctor,” “visited doctor,” and “went to hospital or emergency room”).

Fewer patients (7% at two weeks and 3% at six weeks) reported lower GI symptoms (all diarrhea or constipation) while taking prescription NSAIDs. Nearly all (93%) of these symptoms were managed without physician involvement.

DISCUSSION
NSAIDs represent one of the most widely prescribed classes of drugs in the U.S. Although data on NSAIDs abound in randomized, controlled trials, they are limited in terms of patients’ experiences in actual practice. Ours is one of the first studies to examine patient-reported, NSAID-related experiences and behaviors in a primary care setting. We limited our study population to patients 50 years of age and older because of their increased risk of NSAID-related gastropathy.7,8

Regardless of their previous experience with NSAIDs, most patients continued taking these agents two and six weeks after receiving their index prescriptions. All patient groups experienced a reduction in pain at the two-week visit, even those who received a renewal prescription for a presumably chronic condition.

GI symptoms, two-thirds of which were dyspeptic in quality, were common in these NSAID users. Among patients receiving chronic NSAID therapy (the renewal NSAID group), 20% reported dyspeptic symptoms at the baseline visit, a number consistent with the 10% to 20% rate reported in earlier stud-
Interestingly, the proportion of patients reporting dyspeptic symptoms decreased at the two-week and six-week visits; this finding could not be explained by the small number of patients who discontinued NSAIDs because of side effects.

The incidence of dyspepsia in patients who had changed their prescription NSAID at the index visit was higher than that in patients who either were given a renewal prescription or who had not recently been taking NSAIDs. These “changed” NSAID patients were also more likely to have been prescribed a COX-2 inhibitor (39%) than were “new” NSAID users (19%) or “renewal” NSAID users (13%). It is possible that patients prone to NSAID-related dyspepsia would be overrepresented in the changed NSAID group because their prescription adjustments might have been prompted by dyspeptic symptoms associated with previous NSAID use.

Only limited data have previously addressed NSAID-associated GI symptoms in primary care patients. In an observational study from England, Jones and Tait found no difference in the prevalence of dyspepsia over 12 months between NSAID users and controls (46% vs. 43%). In contrast, Talley et al. used the Elderly Bowel Symptom Questionnaire to determine how much upper abdominal pain and heartburn in older patients could be explained by NSAID use; they found an odds ratio of 1.9 for dyspepsia among NSAID users compared with non-NSAID users.

Perhaps our most surprising finding is that patients reported managing their dyspeptic symptoms without involving or even informing their doctors. For the most part, patients reported adjusting their own doses or schedules, taking their medication with food, or starting nonprescription or already available prescription gastroprotective medicines in order to continue their NSAID use. This might be attributed to the perceived beneficial effects of the NSAIDs on pain and quality of life.

Previous research in patients with rheumatoid arthritis has demonstrated a clear hierarchy in desired treatment outcomes. Patients with this chronic illness consistently value relief of disability and discomfort above freedom from iatrogenic effects. In short, from the study by Gabriel et al., patients desire, first, to function normally; second, to be free from pain and other physical, psychological, or social symptoms; third, to be free of iatrogenic problems from the treatment regimen; fourth, to remain in financial health after medical expenses; and fifth, to be alive as long as possible.

According to this model, then, patients would accept symptoms of dyspepsia (without consulting a doctor) as a trade-off for relief of pain and disability.

In other studies, patients also tolerated upper GI symptoms during NSAID treatment. Gabriel et al. interviewed patients with rheumatoid arthritis and asked them to rank 18 mutually exclusive health states. Respondents ranked the following states as least desirable (in order of increasing desirability): surgery, hospitalization, prophylaxis-induced diarrhea, and outpatient ulcer treatment. Scenarios that included ulcer symptoms (dyspepsia) and the inconvenience...
of an additional medication taken four times daily (miso-prostol) did not significantly affect the patients’ preferences. The patients placed a much higher value on avoiding lower-bowel symptoms, such as diarrhea, than on any upper GI symptoms.

Jones and Tait also found that NSAID users were more likely to stop taking these agents because of constipation than because of dyspepsia. In our six-week observational study, the low incidence of constipation and diarrhea might also help explain our low reported dropout rate. A longer period of follow-up might have increased the number of patients who discontinued NSAIDs.

Our study did not address physician management of NSAID-associated dyspepsia. Algorithms in the literature for physician management of dyspepsia with no “alarm symptoms” (i.e., bleeding, anemia, or weight loss) include:

- discontinuing the NSAID, if possible.
- decreasing the dose.
- switching to another class of NSAIDs.

Although experts suggest adding antisecretory agents when symptoms persist, the restricted formularies of many managed care health plans have limited the use of proton pump inhibitors (PPIs) to radiographically or endoscopically proven ulcer disease. Even though 94% of the patients in this study had at least partial prescription coverage, most would have had to pay out of pocket for PPIs if these medications had been prescribed prophylactically. Physicians in this study may have discussed other options for managing side effects at the time.

### Table 3  Management of Dyspeptic Symptoms by Patients Taking Nonsteroidal Anti-inflammatory Drugs

<table>
<thead>
<tr>
<th>User Group (No. of Patients*/Total) with Dyspeptic Symptoms</th>
<th>No. Managing without Involving Physicians</th>
<th>No. Taking Gastroprotective Medications</th>
<th>No. Involving Physicians in Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At Two Weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renewal Rx (33/328, 10%)</td>
<td>31/36</td>
<td>4/36</td>
<td>1/36</td>
</tr>
<tr>
<td>Changed Rx (n = 7) (7/29, 21%)</td>
<td>6/7</td>
<td>1/7</td>
<td>0</td>
</tr>
<tr>
<td>New Rx (n = 14) (14/83, 17%)</td>
<td>16/17</td>
<td>1/17</td>
<td>0</td>
</tr>
<tr>
<td><strong>At Six Weeks</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renewal Rx (29/328, 9%)</td>
<td>22/31</td>
<td>6/31</td>
<td>3/31</td>
</tr>
<tr>
<td>Changed Rx (4/29, 14%)</td>
<td>3/4</td>
<td>1/4</td>
<td>0</td>
</tr>
<tr>
<td>New Rx (1/83, 13%)</td>
<td>11/12</td>
<td>1/12</td>
<td>0</td>
</tr>
</tbody>
</table>

* In each column, the numerator represents the number of symptoms managed as described; the denominator is the total number of dyspeptic symptoms reported by patients in the user group. Some patients chose more than one reason for discontinuing their NSAID medications.
they prescribed the NSAID. In any event, the patients indicated that they did not consult their physicians when symptoms of dyspepsia developed. Instead, they used their own remedies to manage their dyspeptic symptoms by stopping the medicine, lowering the dose, taking NSAIDs with food, or adding nonprescription histamine H2-blockers or antacids.

Our study was observational in design, with no control group, and we did not account for baseline GI diagnoses such as gastroesophageal reflux disease (GERD) or peptic ulcer disease, which would influence symptoms and medication usage. For these reasons, we cannot definitively attribute the GI symptoms of our patients to the use of NSAIDs.

Regardless of the cause of the symptoms, we found that most patients tolerated and managed their upper GI symptoms without calling their physicians and continued taking NSAIDs as long as they provided pain relief. We did not assess patients’ perceptions of how accessible their physician was for follow-up visits or for telephone consultations regarding the management of side effects. Many factors (e.g., type of insurance coverage, office scheduling, and telephone systems) might have affected patients’ perceptions of the physicians’ availability. In addition, the racial mix and the predominance of women in our sample, although not reflective of the U.S. population as a whole, were representative of the urban Philadelphia practices from which subjects were recruited. Our study results might not be generalizable to the wider population of older patients.

Although we made attempts not to influence the behavior of either physicians or patients, the enrollment of patients by research assistants at the index visit and the administration of either physicians or patients, the enrollment of patients by research assistants at the index visit and the administration of three surveys may have affected patients’ medication-taking routines and their reporting of symptoms. Consistent with this, we found that nearly all patients reported less pain and general improvement at their follow-up visits, perhaps because of the involvement of the research assistants.

Physicians who treat patients with chronic NSAID therapy are likely to be most concerned about the 1% to 4% rate of serious adverse GI events (perforations, symptomatic ulcers, and bleeding). These events can occur without warning; in fact, 81% of patients with serious adverse GI complications reported no prior dyspepsia. Patients, however, do have other concerns. The American Gastroenterological Association, in a survey of 807 patients who had taken NSAIDs, found that 75% of regular NSAID users did not know about—or were unconcerned about—NSAID-related GI complications.

Our study suggests that physicians should be proactive when informing patients about possible side effects associated with NSAID use. Older patients are more likely to have chronic medical problems for which NSAIDs are commonly prescribed. Because older patients usually continue to take NSAIDs despite symptoms as long as the medications are providing relief, physicians should help patients to recognize warning signals and should review strategies for avoiding or managing side effects at follow-up visits.

Acknowledgments. The authors would like to thank Catherine Mills for preparing the manuscript.

REFERENCES


Disclosure

Dr. Straus and Ms. Weeks are employees of Merck & Co., Inc., which sponsored the study.