

# National Adherence to Evidence-Based Guidelines for the Prescription of Nonsteroidal Anti-Inflammatory Drugs

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**Background & Aims:** Our objective was to assess adherence to evidence-based guidelines by providers of the Department of Veterans Affairs nationwide. **Methods:** This was a cross-sectional study among veterans prescribed a nonsteroidal anti-inflammatory drug (NSAID) from January 1, 2002, to December 31, 2002. Prescription data were linked to inpatient and outpatient medical records and death files. The population was characterized as high risk based on the following: age 65 years or older, concurrent corticosteroid or anticoagulant use, history of peptic ulcer, and high average daily dose of NSAIDs. Adherence was defined as the prescription of a traditional NSAID with gastroprotection or a coxib in high-risk NSAID users. Univariate and multivariate analyses assessed the potential predictors of adherence. **Results:** Three hundred three thousand seven hundred eighty-seven met our definition of high risk. Most (97.3%) were male; 55.6% were white, 9.6% black, and 34.8% of other/unknown race. Age 65 years or older was the largest high-risk subset (87.1%). Overall, only 27.2% of high-risk veterans (n = 82,766) were prescribed an adherent strategy. Among veterans with at least 2 risk factors, adherence was 39.7%; among those with 3 risk factors, adherence was 41.8%. Predictors of adherence included history of upper gastrointestinal events, anticoagulant use, rheumatologic disease, high Deyo comorbidity index score, use of low-dose salicylates, and concurrent corticosteroid use. Predictors of nonadherence included prescriptions  $\geq 90$  days and high average daily dose of NSAIDs. **Conclusions:** Adherence to evidence-based guidelines for safe prescription of NSAIDs in the Department of Veterans Affairs is low (27.2%). The likelihood of adherence is further decreased if veterans are prescribed NSAIDs for  $\geq 90$  days.

therapy,<sup>2-4</sup> a 4-fold increase over that of nonusers.<sup>5,6</sup> Among the elderly, upper gastrointestinal events from NSAID therapy contribute to 10–20 hospitalizations per 1000 person-years<sup>7-10</sup> and 30% of ulcer-related hospitalizations are attributable to NSAIDs,<sup>7,11,12</sup> with a 4-fold increased risk of death.<sup>11</sup> Strategies to minimize NSAID-related upper gastrointestinal events are outlined in evidence-based guidelines<sup>13-15</sup> and include the use of cyclooxygenase-2-selective drugs (coxibs) or the combination of an NSAID with a gastroprotective agent.

The guidelines are consistent in identifying certain characteristics of high-risk NSAID users based on data from observational studies. Elderly age, prior upper gastrointestinal events, and concurrent use of warfarin are identified as markers of risk in each of these guidelines based on consistent findings from epidemiologic studies.<sup>16</sup> Some observational studies have identified concurrent corticosteroid use and high-dose corticosteroid use as risk factors.<sup>16,17</sup> Thus, these additional risk factors are included in most of the guidelines.<sup>13,14,18</sup>

Each of the guidelines provides several options for preventing NSAID-related upper gastrointestinal events. There is direct evidence from randomized controlled trials that coxibs have an improved gastrointestinal safety profile.<sup>2,4</sup> There is also evidence from a large randomized controlled trial of the efficacy of misoprostol in preventing upper gastrointestinal events.<sup>3</sup> The evidence that proton pump inhibitors (PPIs) are protective in users of traditional NSAIDs is based on studies that use an intermediate clinical end point, that of ulcers detected on scheduled surveillance endoscopy.<sup>19,20</sup> There are no studies quantifying the effectiveness of guideline adherence in preventing adverse gastrointestinal events; however,

Twenty million Americans regularly use nonsteroidal anti-inflammatory drugs (NSAIDs), filling more than 111 million prescriptions per year.<sup>1</sup> The incidence of clinically significant upper gastrointestinal events from NSAID therapy is 1–2 per 100 person-years of

*Abbreviations used in this paper:* CI, confidence interval; OR, odds ratio; PPI, proton pump inhibitor; VA, Department of Veterans Affairs.

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several groups have incorporated safer NSAID use as an indicator of quality of prescribing.<sup>21–23</sup>

Despite the existence of evidence-based guidelines, the frequency of use of safer NSAID strategies among high-risk individuals is estimated to be <30% in some populations.<sup>24,25</sup> However, these studies were limited to low-income or elderly persons enrolled in a state Medicaid benefits program<sup>24</sup> or performed before the availability of the coxibs.<sup>25</sup> The goal of this study was to ascertain adherence to evidence-based guidelines for the safe prescription of NSAIDs among veterans who receive their care at 176 Department of Veterans Affairs (VA) health care facilities, through a national equal-access health care system.

## Patients and Methods

### Study Design

We performed a cross-sectional study of veterans aged 18–99 years who were prescribed a coxib or a traditional NSAID at one of 176 VA facilities in the United States from January 1, 2002, to December 31, 2002. The institutional review board of Baylor College of Medicine and the VA Research and Development Committee of the Michael E. DeBakey VA Medical Center approved the research protocol. In accordance with 46 CFR 46.110c, this protocol qualified for waiver of consent under Health Insurance Portability and Accountability Act guidelines.

### Databases

The records of patients prescribed an NSAID or a coxib were obtained from the PBM Strategic Healthcare Group (Hines, IL). This VA database provides prescription dispensing elements (fiscal year 1999 to present), including dates of fill and refill, prescription identifiers (prescription number, name, drug class name, and formulary indicator), dosing instructions, days' supply, and total quantity of the drug dispensed. Patient records were linked using standard algorithms to 3 other national VA administrative databases: the Patient Treatment File from 1999 to 2002, the Outpatient Clinic File from 1999 to 2002, and the Beneficiary Identification and Records Locator Subsystem Death File from 2000 to 2002.

The Patient Treatment File contains inpatient demographic data, primary admission and discharge data, endoscopic/surgical procedures, one primary discharge diagnosis, and up to 9 secondary discharge codes (ICD-9).<sup>26,27</sup> Previous validation was conducted for demographic, admission, and discharge data.<sup>26,27</sup> The Outpatient Clinic File contains the date of outpatient visit, a record of patient attendance at up to 15 different clinics per day, first-listed medical or surgical diagnosis, and up to 9 additional diagnoses for each medical encounter. Although there are no published validity studies on data elements, data are generated and collected in the same manner as the Patient Treatment File data, so similar accuracy would be expected. The Beneficiary Identification and Records

Locator Subsystem Death File contains the date of all deaths as reported to the Veterans Benefits Administration. Between 90% and 95% of deaths among veterans are captured by the Beneficiary Identification and Records Locator Subsystem Death File as compared with the National Death Index.<sup>27–29</sup> By merging these 3 databases, a longitudinal record of the patient's VA health care history was created.

### Study Population

Veterans aged 18–99 years of age who were prescribed an NSAID, salicylates >325 mg/day, or a coxib between January 1, 2002, and December 31, 2002, were eligible for study entry. Inclusion criteria included prior inpatient or outpatient VA encounters in the 365 days preceding index prescription (to increase the probability of regular use of VA health care facilities) and evidence of continuing use of VA facilities 60 days after index prescription, as defined by an outpatient or inpatient visit, any other prescription, and no death. All patient identifiers were removed from the analysis data sets in compliance with Health Insurance Portability and Accountability Act regulations.

### Drugs of Interest

**Index prescription.** Index prescription was defined as the first prescription for a traditional NSAID (Table 1), a coxib (celecoxib, rofecoxib, or valdecoxib), or salicylates >325 mg/day<sup>24</sup> during the study period for a minimum duration of 14 days. The average daily dose of each index prescription was calculated by multiplying the dose of the prescribed medication by the number of pills and dividing the total by the days' supply.

**Gastroprotective agents.** The prescription of gastroprotective therapy was defined as prescription of the following medications (at the appropriate average daily dose): cimetidine (1600 mg), ranitidine (600 mg), nizatidine (600 mg), famotidine (80 mg), omeprazole (20 mg), rabeprazole (20 mg), pantoprazole (40 mg), esomeprazole (40 mg), lansoprazole (30 mg), and misoprostol (600 µg) within 60 days of index prescription. Overlap with the index NSAID prescription was required.

### High-Risk NSAID Users

The evidence-based guidelines vary slightly in their definition of high-risk users; however, all identify previous upper gastrointestinal events and concurrent use of anticoagulants as risk factors.<sup>13,14,18</sup> All include age as a risk factor either explicitly (as a cutoff point)<sup>13,14,18</sup> or by using advancing age as part of a "risk scoring system."<sup>30</sup> One guideline included "high-dose NSAID" as a risk factor,<sup>14</sup> while another mentioned NSAID dose as an important consideration in the narrative.<sup>13</sup>

For the primary analyses in this study, we defined high-risk users as those 65 years or older, or with a history of upper gastrointestinal events, concurrent use of anticoagulants or corticosteroids, or high dose of NSAIDs (that exceeded the manufacturer's maximum recommendation for any indication;

**Table 1.** Frequency of Prescription of Common NSAIDs and the Median Average Daily Dose of Index Prescription

NSAID	Frequency	Median average daily dose (mg/day)	Manufacturer's high average daily dose (mg/day)
Salicylates <sup>a</sup>	10,987	361	3000
Celecoxib	21,924	200	400
Choline magnesium trisalicylate	2366	2000	3000
Diclofenac NA	20,801	150	200
Diclofenac potassium	36	150	200
Diflusal	884	1000	1500
Etodolac	60,301	800	1000
Fenoprofen Ca	14	1200	3200
Flurbiprofen	169	200	300
Ibuprofen	263,514	1800	2400
Indomethacin	32,513	75	150
Ketoprofen	470	200	300
Ketorolac tromethamine	1207	30	40
Meclofenamate NA	94	200	400
Meloxicam	476	7.5	15
Nabumetone	4918	1000	2000
Naproxen	163,122	1000	1500
Naproxen NA	8725	1100	1500
Oxaprozin	4255	1200	1800
Phenylbutazone	2	250	500
Piroxicam	20,867	20	40
Rofecoxib	21,350	25	50
Salsalate	46,105	2000	2400
Sulindac	20,114	400	400
Tolmetin NA	1962	1200	1800
Valdecoxib	148	10	40

<sup>a</sup>At doses >325 mg/day.

see Table 1). Our definition was based on guidelines disseminated by the American College of Rheumatology<sup>13,18</sup> and the American College of Gastroenterology.<sup>14</sup> The American College of Rheumatology guidelines were the most contemporaneous and included the use of coxibs as a gastroprotective strategy. We adapted the American College of Rheumatology guidelines to include the prescription of high-dose NSAIDs, as recommended by the American College of Gastroenterology.

The VA Pharmacy Benefits Management Plan does not have evidence-based guidelines for the safe prescription of NSAIDs. However, they did publish guidelines (2001–2002)<sup>30</sup> for the appropriate use of coxibs among veterans based on a patient self-assessed risk stratification tool developed from the Arthritis, Rheumatism, and Aging Medical Information System database.<sup>31</sup> This stratification score (“GI score”) is based on a Cox proportional hazards model used to quantify the risk of upper gastrointestinal events in patients with osteoarthritis or rheumatoid arthritis. The GI score does not include concomitant use of anticoagulants or high-dose NSAIDs as risk factors for upper gastrointestinal events but does include rheumatoid arthritis, dyspeptic symptoms, advancing age, patient self-assessment of overall health, and concomitant use of corticosteroids. We chose not to use this risk stratification system for

the primary definition of our high-risk population because it has not been shown to be widely generalizable and does not include known risk factors for upper gastrointestinal events such as concomitant anticoagulant use or high-dose NSAIDs.

To assess an individual patient's risk status, we examined the Patient Treatment File and Outpatient Clinic File to identify age at the time of index prescription and assessed history of upper gastrointestinal events in the 365 days before index prescription, defined as the occurrence of any single inpatient hospital encounter (Patient Treatment File) with primary or secondary discharge diagnoses of peptic ulcer disease (ICD-9 codes 531–534), bleed (578.0–578.9), or perforation (531.1, 531.2) or 2 outpatient encounters with ICD-9 codes 531–534, 578.0–578.9, 531.1, or 531.2. The VA Pharmacy Benefits Management Database was evaluated for the concurrent use of oral corticosteroids or anticoagulants within 60 days before or after the index prescription with evidence of overlap with the index prescription.

## Outcome

The primary outcome of interest was adherence to NSAID evidence-based guidelines. Adherence was defined as a dichotomous variable based on the prescription of an NSAID with a gastroprotective agent or a coxib in a patient defined as a high-risk NSAID user. We did approximate the VA risk stratification system to assess provider adherence based on the VA Pharmacy Benefits Management Plan guidelines for the appropriate use of a coxib.<sup>30</sup> The VA guidelines consider the use of salsalate as an additional adherent strategy among high-risk individuals. Among those individuals at moderate risk for gastrointestinal injury, salsalate or etodolac would be considered an appropriate alternative first-choice agent.

## Potential Predictors of Guideline Adherence

**Low-dose salicylates.** Prescription of low-dose salicylates ( $\leq 325$  mg/day) alone was not an inclusion criterion. Evidence-based guidelines do not specify low-dose salicylates as an indication for gastroprotective therapy; however, some have suggested it is a risk factor for upper gastrointestinal events.<sup>4,32,33</sup> Among patients with an index prescription for an NSAID or a coxib, we identified prescription of low-dose salicylates within 60 days of index prescription and controlled for it in the analyses.

**Long-term NSAID prescription.** The current evidence-based guidelines do not define long-term NSAID use as a high-risk factor. However, we wished to identify if duration of index prescription was an independent predictor of guideline adherence. We defined long-term NSAID prescription as an index prescription with a  $\geq 90$ -day supply and controlled for it in the analyses.

**Comorbidity not specific to NSAID-related gastrointestinal toxicity.** For each patient, we calculated a comorbidity score, modified from the previously validated Deyo chronic disease index.<sup>34</sup> In constructing the index, we excluded ICD-9 codes associated with peptic ulcer disease (531.4–531.7, 532.4–532.7, 533.4–533.7, 534.4–534.7) (examined

separately as a risk factor) and rheumatologic disease (710–710.1, 710.4, 714.0–714.2, 714.81, 715, 725). The presence of rheumatologic disease in the 365 days before index prescription was recorded if present in 2 encounters and considered an independent predictor variable.

### Analytic Methods

Patients were categorized as high risk versus low risk according to the presence of at least one risk factor for an NSAID-related upper gastrointestinal event. The high-risk patients were then classified according to index prescription: coxib, NSAID with gastroprotective agent, or NSAID alone. Baseline demographic features were compared between high-risk and low-risk groups. Univariate comparisons between dichotomous variables were made using  $\chi^2$  tests, while unpaired *t* tests were used to compare continuous variables.

The proportion of adherence to evidence-based guidelines was calculated by dividing all high-risk patients on an appropriate strategy (ie, coxib or NSAID with a gastroprotective agent) by the total number of patients at high risk for an NSAID-related upper gastrointestinal event. Univariate analysis of the potential predictors of adherence was conducted. Multiple logistic regression analysis was used to assess predictors of adherence, including the Deyo index of comorbidity, sex, race, rheumatologic disease, long-term NSAID prescription, and low-dose salicylate use. Wald's  $\chi^2$  tests were used to test for the significance of the influence of each independent variable. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. All analyses were performed using SAS version 9.1 (SAS Institute, Inc, Cary, NC).

### Results

From January 1, 2002, to December 31, 2002, 707,244 veterans met our study inclusion criteria and formed the study cohort. This population represents the national population of the VA; 94.3% were male, and the percentages identified as white, black, or other/unknown race were 52.2%, 13.6%, and 34.3%, respectively. Approximately 43.0% (n = 303,787) met our definition for high-risk individuals. When compared with low-risk individuals, those at high risk were more likely to be white, male, have long-term NSAID prescriptions, or have a low-dose salicylate coprescription. Additionally, high-risk individuals were more likely to have a history of rheumatologic disease or a Deyo score  $\geq 2$  (Table 2). High-risk patients were also more likely to be prescribed a coxib agent when compared with low-risk individuals.

The majority (81.0%) of high-risk individuals had limited comorbidity, as measured by the Deyo comorbidity score (values  $< 2$ ). Rheumatologic disease was recorded in 19.0% of high-risk patients. Almost three fourths of high-risk individuals (36.0%) had a history of NSAID prescription for  $\geq 90$  days (ie, long-term use).

**Table 2.** Baseline Characteristics and Risk Factors of Veterans With an Index NSAID Prescription, According to Whether or Not They Were Considered at High Risk for Upper Gastrointestinal Events

Clinical characteristic	High risk (n = 303,787; 43.0%)	Low risk (n = 403,457; 57.0%)
Mean age (SD)	70.8 (9.7)	50.5 (8.8)
Male (%)	295,578 (97.3)	371,021 (92.0)
White (%)	168,937 (55.6)	196,509 (48.7)
Black (%)	29,228 (9.6)	71,072 (17.6)
Other/unknown race (%)	105,622 (34.8)	135,876 (33.7)
With rheumatologic disease (%)	57,830 (19.0)	45,151 (11.2)
Adjusted <sup>a</sup> Deyo score $\geq 2$ (%)	83,212 (27.4)	49,390 (12.2)
On low-dose salicylates (%)	90,197 (29.7)	74,040 (18.4)
Long-term prescription (%)	109,490 (36.0)	121,592 (30.1)
NSAID with long half-life (%)	77,068 (25.4)	123,693 (30.7)
Prescribed coxib (%)	28,587 (9.4)	15,275 (3.8)
Prescribed coxib with gastroprotective agent (%)	5769 (1.9)	3211 (0.80)

NOTE. *P* value for all comparisons between high- and low-risk groups was  $< .001$ .

<sup>a</sup>Deyo score was calculated after excluding ICD-9 codes associated with peptic ulcer and rheumatologic disease.

Low-dose salicylates were coprescribed to 29.7% of high-risk individuals, with the majority (67.3%) on no adherent strategy to reduce the risk of upper gastrointestinal events.

Individuals 65 years or older (87.1%) constituted the largest high-risk subset (n = 264,679) (Table 3). The next most common risk factor was high average daily NSAID dose, occurring in 13.3% (n = 40,530). The concurrent use of an NSAID with anticoagulants or corticosteroids was present in 4.4% and 3.5%, respectively. A history of upper gastrointestinal events was noted in 2.0% (n = 6086).

Of the 303,787 high-risk patients, 27.2% (n = 82,766) had an index NSAID prescription that was adherent to evidence-based guidelines. An NSAID with a gastroprotective agent was prescribed for 17.8% of patients and a coxib for 9.4% of patients. A nonselective NSAID without an appropriate gastroprotective strategy was prescribed to 222,021 high-risk veterans (Table 3).

Among high-risk patients with concurrent prescription of anticoagulants, 35.4% were prescribed a coxib, 14% were prescribed an NSAID with a gastroprotective agent, and 50.6% were prescribed neither. Among those with a history of upper gastrointestinal events, 38.4% of patients were prescribed an NSAID with a gastroprotective agent, 19.2% were prescribed a coxib, and 41.6% were prescribed neither adherent strategy. Those persons on high-dose NSAIDs were prescribed an adherent strategy in only 22.1% of cases (Table 3).

**Table 3.** Adherence to Evidence-Based Guidelines for NSAID Use Among High-Risk Veterans With an Index Prescription for an NSAID

Clinical characteristic	NSAID with gastroprotective agent (n = 54,179; 17.8%)	Coxib (n = 28,587; 9.4%)	NSAID alone (n = 221,021; 72.8%)
<b>Demographic characteristics</b>			
Mean age (SD)	70.1 (9.8)	73.5 (8.0)	70.6 (9.9)
Male (%)	52,612 (17.8)	27,763 (9.4)	215,203 (72.8)
White (%)	34,227 (20.3)	17,483 (10.3)	117,227 (69.4)
Black (%)	4947 (16.9)	2114 (7.2)	22,167 (75.9)
Other/unknown race (%)	15,004 (14.2)	8990 (8.5)	81,627 (77.3)
<b>Risk factors (%)</b>			
Age 65 years or older	45,540 (17.2)	26,396 (10.0)	192,743 (72.8)
Concomitant anticoagulants	1881 (14.0)	4759 (35.4)	6811 (50.6)
Concomitant corticosteroids	2847 (26.6)	1438 (13.4)	6435 (60.0)
History of upper gastrointestinal events	2388 (39.2)	1168 (19.2)	2530 (41.6)
High average daily dose	8730 (21.5)	221 (0.6)	31,579 (77.9)
<b>Other characteristics (%)</b>			
With rheumatologic disease	11,686 (20.2)	9811 (17.0)	36,333 (62.8)
Deyo score $\geq 2$	17,526 (21.1)	9012 (10.8)	56,674 (68.1)
On low-dose salicylates	22,504 (24.9)	7384 (8.2)	60,309 (66.9)
Long-term prescription	20,780 (19.0)	7524 (6.9)	81,186 (74.1)

Each of the 4 extant evidence-based guidelines (American College of Gastroenterology, American College of Rheumatology, VA Pharmacy Benefits Management Plan, and the Assessing Care of Vulnerable Elders project) has a somewhat different definition of high-risk NSAID users. Thus, we calculated both the number of high-risk users and the proportion of overall adherence to evidence-based guidelines according to each of these. We also performed these calculations for an inclusive composite that included all veterans identified as high risk by any of the 4 guidelines (Table 4). The number of high-risk veterans who were NSAID users ranged from 398,907 (56.4%) of all NSAID users (inclusive composite) to 198,667 (28.1%) of NSAID users (the Assessing Care of Vulnerable Elders project). For each of the guidelines, adherence among high-risk individuals was <34%.

When stratified according to number of risk factors per patient, the overall proportion of adherence increased with the presence of average daily additional risk factors (Table 5). Among the patients with at least 2 risk factors, adherence to evidence-based guidelines was 39.7%. However, among those who had at least 3 risk factors, overall adherence to evidence-based guidelines was only 41.8%.

In a multivariable model, the following variables were significant predictors of adherence to guidelines: a history of upper gastrointestinal events (OR, 4.07; 95% CI, 3.84–4.31), anticoagulant use (OR, 2.65; 95% CI, 2.55–2.75), rheumatologic disease (OR, 1.60; 95% CI, 1.57–1.63), Deyo comorbidity index score  $\geq 2$  (OR, 1.22; 95% CI, 1.19–1.24), use of low-dose salicylates (OR, 1.60; 95% CI, 1.57–1.62), use of high-dose NSAIDs (OR, 1.26; 95% CI, 1.22–1.31), and concurrent

**Table 4.** Adherence to Safe Prescribing of NSAIDs Among High-Risk Veterans, According to Specific Evidence-Based Guideline Criteria

Clinical guideline	No. of patients at high risk (%)	Adherence among patients at high risk (%)
Our study definition of high-risk patient <sup>a-e</sup>	303,787 (43)	82,766 (27.2)
American College of Rheumatology <sup>a,b,d,e,f</sup>	330,171 (46.7)	91,666 (27.8)
American College of Gastroenterology <sup>b-e,g</sup>	361,591 (51.1)	95,567 (26.4)
Assessing Care of Vulnerable Elders <sup>b,e,h</sup>	198,667 (28.1)	57,836 (29.1)
VA Pharmacy Benefits Management Plan <sup>a,b,d,f,i,j</sup>	357,496 (50.6)	119,081 (33.3) <sup>k</sup> 142,464 (39.9)
Most inclusive guideline combination <sup>b-g</sup>	398,907 (56.4)	105,942 (26.5)

<sup>a</sup>Age 65 years or older.

<sup>b</sup>History of upper gastrointestinal events.

<sup>c</sup>High average daily dose NSAID.

<sup>d</sup>Concurrent corticosteroid use.

<sup>e</sup>Concurrent anticoagulant use.

<sup>f</sup>Significant comorbidity (Deyo score  $\geq 2$ ).

<sup>g</sup>Age 60 years or older.

<sup>h</sup>Age 75 years or older.

<sup>i</sup>Dyspepsia.

<sup>j</sup>Rheumatoid arthritis.

<sup>k</sup>Where adherent strategies among patients at highest risk for gastrointestinal toxicity include salsalate, a non-cyclooxygenase-selective formulary NSAID with gastroprotective agent (ie, PPI, misoprostol, or famotidine), or a cyclooxygenase-2 inhibitor.

<sup>l</sup>Where adherent strategies among patients at moderate risk for gastrointestinal toxicity include that salsalate or etodolac should be attempted as first-line therapy and then a non-cyclooxygenase-2 selective formulary NSAID with gastroprotective agent (ie, PPI, misoprostol, or famotidine).

**Table 5.** Assessment of At-Risk Population and Proportion of Adherence Based on the Number of Risk Factors for NSAID-Related Upper Gastrointestinal Events

No. of risk factors	No. of patients at risk	Adherent (%)
At least 1	303,787	82,766 (27.2)
At least 2	30,133	11,952 (39.7)
3 or more	1503	629 (41.8)

NOTE. Risk factors include age 65 years or older, concomitant corticosteroid use, concomitant anticoagulant use, history of upper gastrointestinal events, and high average daily dose.

corticosteroid use (OR, 1.87; 95% CI, 1.79–1.95). Patients with an index prescription for  $\geq 90$  days (OR, 0.87; 95% CI, 0.85–0.88) were significantly less likely to be prescribed an adherent strategy, whereas race was not a significant risk factor (OR, 0.99; 95% CI, 0.96–1.03).

## Discussion

This study shows that 43.0% of the veterans prescribed NSAIDs in 2002 are considered to be at high risk for upper gastrointestinal events. Among this group, only 27.2% were prescribed gastrointestinally safer forms of NSAID therapy in adherence with currently published evidence-based guidelines. Among high-risk patients, the overall proportion of adherence increases with the presence of more than one risk factor per patient; even the presence of 3 risk factors was associated with 41.8% adherence. When the VA Pharmacy Benefits Management Plan guideline<sup>30</sup> was used to assess adherence among the highest-risk patients, adherence increased to 33.3%. Among patients at moderate risk for gastrointestinal injury, provider adherence to guidelines was 39.9%.

Among the highest-risk patients, those with a history of peptic ulcer disease or gastrointestinal bleeding treated in the outpatient or inpatient setting, provider adherence to guidelines improved to 58%. This finding is comparable to a previous VA study of hospitalized veterans with peptic ulcer disease or gastrointestinal bleeding showing that 20% were prescribed NSAIDs in the first 6 months after discharge.<sup>35</sup> Of these, 75% were coprescribed PPIs, H<sub>2</sub>-receptor antagonists, or misoprostol.

NSAID prescribing patterns are less than optimal in other settings. In a previous study of Tennessee Medicaid (TennCare) enrollees, adherence to NSAID prescribing guidelines occurred 12% of the time among those older than 75 years and only 32% of the time when there was a history of ulcer disease.<sup>24</sup> In a study of community-dwelling elderly persons<sup>36</sup> that assessed the quality of pharmacologic care as benchmarked by the Assessing Care of Vulnerable Elders project guidelines,<sup>23</sup> only 11%

(95% CI, 4%–15%) were prescribed appropriate gastrointestinal prophylaxis. These patients were all enrolled in a pharmaceutical benefit program covering branded and generic prescriptions with a co-payment of \$10 or less. A study of elderly Medicare beneficiaries from Pennsylvania enrolled in a pharmacy benefits plan showed that only 7% of NSAID users with at least one risk factor for gastrointestinal bleeding received a PPI or misoprostol.<sup>37</sup> Similar findings have been shown in The Netherlands, where use of gastroprotective therapy with traditional NSAIDs occurred in only 20% of persons with a prior ulcer.<sup>38</sup>

There are several strengths to the present study. It represents the largest examination of adherence to NSAID prescribing guidelines and uses objective measurements of drug prescribing and dispensing. The use of the national VA databases allowed the identification of a large cohort of patients prescribed NSAIDs and assessment of individual patient factors that are important in the determination of adherence. Another strength of the study is that the study population consisted of patients throughout the United States whose medical care is provided by a large, equal-access health care system.

Limitations of our results include their generalizability to women and nonveterans. It is also possible that persons who receive NSAIDs at the VA may take either out-of-(VA)-system or over-the-counter PPIs and H<sub>2</sub>-receptor antagonists. In most cases, however, the cost of these gastroprotective agents is greater than the small co-payment (\$2.00 before February 2002 and \$7.00 after February 2002) required at the VA. It is more likely that the VA pharmacy data underestimate the veterans at risk for adverse gastrointestinal events because out-of-system or over-the-counter NSAID and aspirin use is inexpensive and likely to occur commonly.<sup>39</sup>

There is likely to be a variable degree of misclassification in identifying those with risk factors. This is less likely for concurrent use of anticoagulants and more likely for a history of peptic ulcer disease or upper gastrointestinal bleeding event based on hospital or outpatient encounter data. Therefore, we were likely to underestimate the prevalence of this risk factor, thus making the findings of low adherence even more relevant.

Despite the widespread dissemination of evidence-based guidelines by national societies,<sup>13,14,18</sup> managed care organizations,<sup>30</sup> and well-publicized multicenter studies,<sup>23</sup> it is clear from this and other studies<sup>24,36</sup> that high-risk NSAID use is frequently not accompanied by appropriate use of safer drugs. A lack of dissemination is unlikely to explain this phenomenon entirely, given that these guidelines were published in high-visibility journals<sup>13,14,18,23,24</sup> and the presence of a major marketing

effort from the pharmaceutical makers of newer coxib agents that highlight the risk of traditional NSAIDs.

Alternative explanations for the observed lack of adherence must be entertained. Clinicians aware of the guidelines may consider the guidelines of marginal validity or underestimate the absolute risk of unsafe NSAID prescriptions. Additionally, the lack of a single, definitive algorithm for safer NSAID use may influence providers to choose none of the recommended alternatives. Furthermore, although the validity of the evidence-based guidelines is supported by data from randomized trials, the clinical consequences of nonadherence to these guidelines in routine clinical practice have not been documented.

Because coxibs and PPIs are expensive and because they can be prescribed on the basis of clinical considerations other than individual patient risk,<sup>37</sup> systematic barriers such as prior authorization or restricted use are often used in both VA and non-VA settings. In a study among a Medicaid population, the requirements for prior authorization in some states were associated with decreased use of coxibs.<sup>40</sup> During our study period, the VA Pharmacy Benefits Management Plan did publish guidelines and criteria for the appropriate use of these drugs. However, specific policies regarding the prescription of coxibs and PPIs varied in the VA at both the local (facility) and the regional (VISN) level. Thus, an examination of the effects of prior authorization or the restricted use of these drugs (limited to subspecialty experts) on overall provider adherence was not performed.

There is reasonable evidence to support the gastrointestinal benefits of cytoprotective agents as recommended by evidence-based guidelines. Misoprostol (with an NSAID) and coxibs are associated with a 50% decrease in risk of upper gastrointestinal events.<sup>2-4</sup> However, misoprostol is associated with a high degree of patient intolerance,<sup>3</sup> and questions regarding the cardiovascular safety of the coxibs still remain.<sup>41</sup> The combination of traditional NSAIDs with PPIs has been shown to reduce endoscopic ulcers<sup>19,20,42,43</sup> but has not been tested for the reduction of "clinically important" upper gastrointestinal events. The data for the effectiveness of H<sub>2</sub>-receptor antagonists in preventing NSAID-associated adverse events are less convincing.<sup>32</sup>

In summary, adherence to evidence-based guidelines for safe prescription of NSAIDs among high-risk individuals is low, even in the presence of multiple risk factors. The likelihood of adherence is further decreased among patients who are prescribed NSAIDs on a long-term basis. Given the withdrawal of several coxib drugs from the market, the existing guidelines will likely be revised to reflect the competing risks of cardiovascular

and gastrointestinal toxicity. Nonetheless, future studies are required to identify the consequences of nonadherence to NSAID evidence-based guidelines and to identify interventions successful in improving provider adherence.

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