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### **Authors**

Marcum, Zachary A Hanlon, Joseph T Strotmeyer, Elsa S <u>et al.</u>

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## Gastroprotective Agent Underuse in High-Risk Older Daily Non-Steroidal Anti-Inflammatory Drug Users Over Time

Zachary A. Marcum, PharmD, MS<sup>1</sup>, Joseph T. Hanlon, PharmD, MS<sup>1,2,3,4</sup>, Elsa S. Strotmeyer, PhD<sup>4</sup>, Anne B. Newman, MD, MPH<sup>1,4</sup>, Ronald I. Shorr, MD, MS<sup>5</sup>, Eleanor M. Simonsick, PhD<sup>6</sup>, Douglas C. Bauer, MD<sup>7</sup>, Robert Boudreau, PhD<sup>4</sup>, Julie M. Donohue, PhD<sup>8</sup>, Subashan Perera, PhD<sup>1,9</sup>, and for the Health ABC Study

<sup>1</sup>Division of Geriatric Medicine, School of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

<sup>2</sup>Department of Pharmacy and Therapeutics, School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

<sup>3</sup>Center for Health Equity Research and Geriatric Research Education and Clinical Center (GRECC), Veterans Affairs (VA) Pittsburgh Healthcare System, Pittsburgh, Pennsylvania, USA

<sup>4</sup>Department of Epidemiology, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

<sup>5</sup>VA GRECC, VA Medical Center, Gainesville, Florida, USA

<sup>6</sup>Intramural Research Program, National Institute on Aging, Baltimore, Maryland, USA

<sup>7</sup>Department of Medicine (General Internal Medicine), School of Medicine, University of California, San Francisco, San Francisco, California, USA

<sup>8</sup>Department of Health Policy and Management, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

*Critical revision of the manuscript for important intellectual content*: Marcum, Hanlon, Strotmeyer, Newman, Shorr, Simonsick, Bauer, Boudreau, Donohue, Perera.

**Corresponding Author:** Zachary A. Marcum, PharmD, MS; 3471 Fifth Avenue, Suite 500, Pittsburgh, Pennsylvania, USA; Phone 412-894-2894; Fax 412-692-2370; zam12@pitt.edu. **Alternate Corresponding Author:** Joseph T. Hanlon, PharmD, MS; 3471 Fifth Avenue, Suite 500, Pittsburgh, Pennsylvania, USA; Phone 412-864-2507; Fax 412-692-2370; jth14@pitt.edu.

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Author Contributions

Drs. Marcum and Hanlon had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Marcum, Hanlon, Strotmeyer, Newman, Shorr, Simonsick, Bauer, Boudreau, Donohue, Perera. Acquisition of data: Marcum, Hanlon.

Analysis and interpretation of data: Marcum, Hanlon, Strotmeyer, Newman, Shorr, Simonsick, Bauer, Boudreau, Donohue, Perera. Drafting of the manuscript: Marcum, Hanlon, Strotmeyer, Newman, Shorr, Simonsick, Bauer, Boudreau, Donohue, Perera.

Statistical analysis: Marcum, Perera.

Obtained funding: Hanlon, Newman.

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Study supervision: Marcum, Hanlon.

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<sup>9</sup>Department of Biostatistics, School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

#### Abstract

**Background/ Objectives**—Non-steroidal anti-inflammatory drug (NSAID) use is a major risk factor for peptic ulcer disease (PUD) in older adults; thus, a gastroprotective agent is recommended in high-risk patients. This study of older daily NSAID users examined whether gastroprotective agent underuse decreased over time.

Design—Before-after study.

Setting—Health, Aging and Body Composition study.

**Participants**—Daily users of an NSAID (prescription and over-the-counter [OTC]) at the 2002–03 (pre-period; n=404) and 2006–07 (post-period; n=172) visits. The sample had a mean (standard deviation [±SD]) age of 78.2 [±2.7] years and 81.9 [±2.7] years at the visits, respectively. The majority were white, women and with 12 years of education.

**Measurements**—Underusers were defined as: (1) persons taking non-selective NSAIDs at risk of PUD (due to current warfarin or glucocorticoid use, or history of PUD) and not using a proton pump inhibitor, or (2) COX-2 selective NSAID users taking aspirin at risk of PUD (i.e., having at least one risk factor) and not using a proton pump inhibitor.

**Results**—Daily NSAID use decreased from 17.6% to 11.3% (p<0.001), and gastroprotective agent underuse decreased from 23.5% and 15.1% (p=0.008) over time. Controlling for important covariates, having prescription insurance was somewhat protective from underuse in the preperiod (adjusted odds ratio [AOR] 0.78, 95% confidence interval [CI] 0.46–1.34; p=0.37), but more so and significantly in the post-period (AOR 0.41, 95% CI 0.18–0.93; p=0.03). Over time, having prescription insurance was more protective in the post versus pre-period (i.e., less gastroprotective agent underuse; adjusted ratio of OR 0.53, 95% CI 0.22–1.29; p=0.16), but this increased protection was not statistically significant.

**Conclusion**—Among high-risk older daily NSAID users, having prescription insurance and adequate gastroprotective use was more common in the post than in the pre-period.

#### Keywords

NSAID; older adults; gastroprotection

#### INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are a common class of analgesics used for persistent pain due to osteoarthritis and other musculoskeletal disorders in older adults.<sup>1</sup> An estimated 40% of people aged 65 years fill at least one prescription for an NSAID annually.<sup>1,2</sup> Considering that NSAIDs are also available over-the-counter (OTC) in the US, even larger numbers of older adults are exposed.

Although these agents can be effective in treating inflammation and pain, older adults are at increased risk for adverse drug events (ADEs).<sup>3</sup> As a result, NSAID use causes an estimated

41,000 hospitalizations and 3,300 deaths annually among older adults.<sup>1</sup> The most common ADEs from NSAID use in older adults are gastrointestinal (GI) in nature, ranging from dyspepsia to life-threatening gastric bleeding.<sup>2,4</sup> Thus, a gastroprotective agent (i.e., proton pump inhibitor [PPI]) is recommended in high-risk patients.<sup>5</sup> In the US, PPIs are available by prescription and over-the-counter (omeprazole [Priolsec<sup>®</sup>] since 2003).

While much has been written recently about the risk of overuse of PPIs and their association with adverse effects (e.g., *Clostridium dificile*-associated diarrhea, osteoporosis), underuse in high-risk daily NSAID users is important as well. Previous non-US literature has shown that gastroprotection is underused in high-risk older adults taking NSAIDs.<sup>6, 7</sup> For example, a time-trend analysis (1996 to 2006) of gastroprotection with NSAIDs among adults age 50 years and older in Netherlands found that underuse was reported in 60% of NSAID users at high-risk of complications.<sup>6</sup> Because in the US OTC medication data are not available in administrative pharmacy claims, there is limited prior literature taking this type of medication exposure into account.

One barrier to using gastroprotective agents in high-risk NSAID users is out-of-pocket medication costs. Medicare Part D, implemented in 2006, cut in half the number of older adults lacking drug coverage.<sup>8,9</sup> Studies indicate that Part D has been associated with a reduction in out-of-pocket costs, and increases in prescription medication use across a range of chronic and acute conditions.<sup>8,9</sup> However, little is known about its impact on medication in categories where there are OTC and prescription alternatives available. In addition, there have been substantial changes to the NSAID pipeline over the past decade, with two COX-2 inhibitors being withdrawn from the market due to cardiovascular safety concerns. Given these changes, in this study we examine in the US whether the extent of gastroprotective agent underuse decreased over time among older high-risk community-dwelling daily NSAID users using data from a cohort study capturing both OTC and prescription medication use.

#### METHODS

#### **Data Source and Sample**

This before-after study used data from the Health, Aging and Body Composition (Health ABC) study, a population-based, prospective, observational study of community-dwelling older adults. Informed consent was obtained from each participant prior to data collection. The baseline sample included 3,075 Black and White men and women aged 70–79 years who reported no difficulty walking ¼ mile, climbing 10 steps, and who lived in specified zip codes surrounding Pittsburgh, PA and Memphis, TN.<sup>10</sup> For purposes of analysis in the current study, the sample included 404 daily (i.e., not as needed) prescription and OTC NSAID users in 2002–03 (i.e., pre-time period) and 172 daily NSAID users in 2006–07 (i.e., post-time period).

#### **Data Collection**

Trained research assistants saw patients annually in clinic or during in-home visits to collect demographic, health, access to care and physiological measures. At year 6 (2002/03) and

year 10 (2006/07), interviewers queried participants as to whether they had additional insurance that helped them pay for their prescription medications. No specific information was collected at both interviews regarding the specific prescription coverage (e.g., employer or Part D after January 1, 2006).

At years 6 and 10, participants were asked to show the trained research assistants all prescription and non-prescription medicines used in the previous two weeks; the interviewer then recorded the information from the vial/package. The interviewer recorded the drug name, strength, dosage form, prescription or non-prescription status, and the number of dosage forms the respondent reported using the previous day, week or month. In addition, the interviewer recorded whether the medicine was prescribed to be taken regularly or asneeded.<sup>11</sup> A similar approach was used via telephone for those who could not be seen at home or in clinic. Medication information was entered into a computer and matched to a dictionary of prescription and non-prescription drugs using the Iowa Drug Information System. Of note, NSAIDs were classified as either non-selective (e.g., ibuprofen, naproxen, aspirin >325 mg per day) or COX-2 selective (i.e., celecoxib, rofecoxib, valdecoxib).

#### Primary Outcome

The primary outcome was a dichotomous variable of any underuse of gastroprotection in older high-risk daily NSAID users. To determine if these daily NSAID users were high-risk and, thus, requiring gastroprotection, both the Assessing Care of Vulnerable Elders (ACOVE) criteria and recent guidelines from the American College of Gastroenterology (ACG) were applied.<sup>5,12</sup> According to the ACOVE criteria, "If a vulnerable elder is older than 75 years of age, is treated with warfarin, or has a history of peptic ulcer disease of GI bleeding, and is being treated with a COX non-selective NSAID, then he/she should be offered concomitant treatment with either misoprostol or a PPI." According to the ACG guidelines, "GI risk is arbitrarily stratified into low (no risk factors), moderate (presence of one or two risk factors), and high risk group (multiple risk factors, a history of ulcer complications, or concomitant use of steroids and anticoagulants)." The risk factors specified include: age >65 years, high dose NSAID therapy, a previous history of uncomplicated ulcer, and concurrent use of aspirin, corticosteroids, or anticoagulants. Therefore, to operationalize our definition for gastroprotection indication, we used a combination of both guidelines based on the data available in this cohort.

Of note, COX-2 selective NSAID users also using low-dose aspirin were considered equal to non-selective NSAID users for gastrointestinal risk. For purposes of analysis, underusers were defined as: (1) persons taking non-selective NSAIDs at risk of PUD (due to current warfarin or glucocorticoid use, or history of PUD) and not using a proton pump inhibitor, or (2) COX-2 selective NSAID users taking aspirin (i.e., equal gastrointestinal risk to non-selective NSAID users) at risk of PUD (due to current warfarin or glucocorticoid use, or history of PUD) and not using a proton pump inhibitor. No one at either time point reported the use of misoprostol.

#### **Primary Independent Variables and Covariates**

The primary independent variables were time (pre, 2002–2003 vs. post, 2006–2007), prescription medication insurance, and their interaction. Covariates were also accounted for that may influence the association between time, prescription insurance and gastroprotection underuse in high-risk NSAID users.<sup>13</sup> Demographic factors included age, sex, race, site, education and marital status. Health status factors included current smoking status and self-rated health (poor/fair vs. good/very good/excellent). Access to healthcare factors included family income, non-Medicare health insurance, having an established physician, and having a recent hospitalization (past 6 months).

#### **Statistical Methods**

Generalized estimating equations (GEE) models were used with gastroprotective underuse as the dichotomous response variable; a binomial distribution for the outcome variable; a logit link function; time (pre/post), prescription medication insurance (yes/no) and their interaction as the main factors of interest; and an exchangeable working correlation structure to account for the presence of some of the same participants across time. Odds ratios (OR), 95% confidence intervals and their statistical significance were calculated to quantify the association between underuse of appropriate gastroprotection and having prescription insurance. We calculated the ratio of ORs (ROR) to determine if there was a reduction in prescription insurance-related disparities (i.e., a change in the differences between prescription insurance groups) from the pre- to post-periods. Covariates were selected using a backward selection approach. All analyses were conducted using SAS<sup>®</sup> software (version 9.3; SAS Institute, Cary, NC) with GENMOD procedure to obtain main results. This study was approved by the University of Pittsburgh and University of Tennessee Memphis Institutional Review Boards.

#### RESULTS

Table 1 presents demographic, health status, and access to care factors for those participants with daily NSAID use at the year 6 (n = 404) and 10 (n=172) visits. The sample had a mean (standard deviation [ $\pm$ SD]) age of 78.2 [ $\pm$ 2.7] years and 81.9 [ $\pm$ 2.7] years at the visits, respectively. The majority were white, women and with 12 years of education. A total of 95 participants were present at both visits.

Daily NSAID use decreased from 17.6% to 11.3% (p<0.001) (Table 2). Among all daily NSAID users, the proportion accounted for by OTC NSAID use was noted to increase from 16.3% to 26.7% over the study time period (data not shown). Of note, the use of COX-2-selective NSAIDs dramatically decreased over the study time period, from 55.2%% to 23.8%% (p<0.001) (Table 2). There were no significant differences in prevalence of risk factors (current regular warfarin use, current regular glucocorticoid use, and history of PUD) between the visits (Table 2). Of note, aspirin use remained consistent with no significant differences across the two visits (40.1% at both years; data not shown). Overall, underuse of gastroprotective agent use decreased from 23.5% to 15.1% (p=0.008) (Figure 1). Only one person at each time period reported the use of OTC omeprazole. However, there was a differential trend in gastroprotective underuse in the two NSAID sub-classes – the rate of

Marcum et al.

underuse decreased for COX-non-selective users (18% vs. 9.2%), whereas it increased for COX-2-selective users (27.8% vs. 34.2%).

Controlling for the covariates, having prescription insurance was weakly protective of underuse during the pre-period (OR=0.78 [0.46-1.34]; p=0.37); and significantly protective during the post-period (OR=0.41 [0.18-0.93]; p=0.03). The said protective effect appears to have increased in magnitude during the post-period compared to the pre-period, but the increase was not statistically significant (ROR=0.53 [0.22-1.29]; p=0.16).

#### DISCUSSION

To our knowledge, this is the first US study to evaluate whether gastroprotective agent underuse decreased over time in older daily NSAID users. Although our results suggest an improvement in gastroprotection over time, it is important to recognize that 15% of older daily NSAID users still had underuse. Considering that the current study included only those older adults using daily NSAIDs (i.e., excluded those using NSAIDs as-needed), the rate of gastroprotection underuse is likely higher since older adults prescribed NSAIDs on an asneeded basis may actually use them regularly; in addition, even sporadic NSAID use poses a risk.

Surprisingly, OTC use of a PPI was negligible. Moreover, we found a differential trend between the COX-non-selective and COX-2-selective NSAID users, with the latter group showing increased underuse. It is important for clinicians to recognize that COX-2-selective NSAIDs are not without GI risk in those with a history of PUD or taking other drugs that can increase the risk of GI bleeding (e.g., aspirin).<sup>14,15</sup> It is interesting to note that COX-2 NSAID use decreased over the two time periods. This may have been due to publications suggesting cardiovascular risk as well as the removal from the market of two COX-2-selective NSAIDs available in the pre-era (i.e., rofecoxib and valdecoxib) for these problems.<sup>16</sup> Moreover, gastroprotection underuse persisted in this study, particularly among COX-2 inhibitor users, which may be due to regional practice patterns. In addition, previous research has shown that expansions in drug coverage need to be accompanied by other interventions to improve the quality of medication use in older adults.<sup>17</sup>

There are potential important limitations to this study. Because this was an observational study, unmeasured factors may have confounded the results. The analysis plan, however, did control for numerous important potential confounders. Second, we had only two time points for analysis, thus we may not fully understand the trajectories of gastroprotection underuse over time. Third, we had low statistical power for the tests for interactions (i.e. adjusted ROR) due to small sample sizes of daily NSAID users. Fourth, we did not include use of low-dose aspirin as a risk factor for gastroprotection indication since it is not explicitly stated as such in both the ACOVE criteria and ACG guidelines. However, low-dose aspirin use among regular NSAID users does carry important gastrointestinal risk.<sup>18,19</sup> Moreover, secondary analysis revealed that the rate of aspirin use at both time points was the same (40.1%; year 6: 162/404; year 10: 69/172). Thus, although we may have underestimated the rate of gastroprotective underuse among regular NSAID users, there would not have been a differential effect across the time periods evaluated. Fifth, the timeframe of this study is a

limitation since the post-period data come from a time period prior to the guidelines cited. Finally, the Health ABC participants were from two regions of the US, and thus these findings may not generalize to all other community-dwelling older adults.

#### CONCLUSION

In conclusion, among high-risk older daily NSAID users, having prescription insurance improved gastroprotective use over time. Additional initiatives besides changes in health policy (e.g., Medicare Part D) may be necessary to further reduce this public health problem.

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Marcum et al.

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Marcum et al.

Page 9

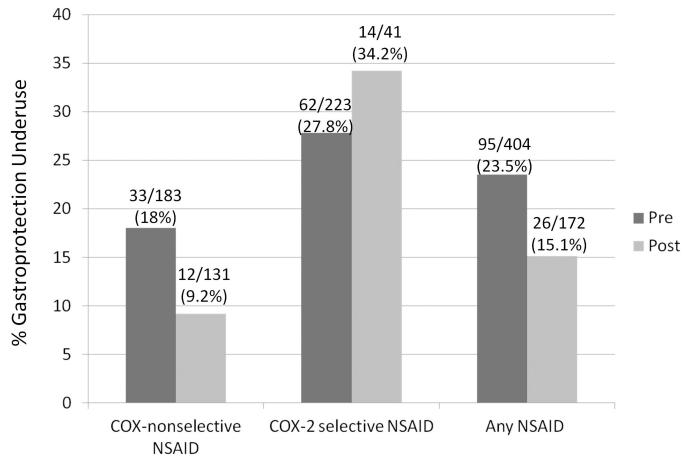


Figure 1.

Underuse of Gastroprotection among Older Daily

#### Table 1

Pre- vs. Post- Comparison of Characteristics of Older Daily NSAID Users

	Pre <sup>*</sup> (Y6;2002–2003) n=404	Post <sup>*</sup> (Y10;2006–2007) n=172	P valu
Characteristic			
Demographics			
Age, mean (SD)	78.2 (2.7)	81.9 (2.7)	< 0.001
Female, n (%)	256 (63.4)	115 (66.9)	0.53
Black race, n (%)	159 (39.4)	58 (33.7)	0.15
Education, n (%)			
< 12 years	100 (24.8)	35 (20.3)	0.14
12 years	303 (75.0)	137 (79.7)	
Missing	1 (0.2)	0 (0)	
Site, n (%)			
Pittsburgh	245 (60.6)	108 (62.8)	0.01
Memphis	159 (39.4)	64 (37.2)	
Marital status, n (%)			
Never/previously married	199 (49.3)	94 (54.7)	0.01
Married	205 (50.7)	78 (45.3)	
Health status			
Self-rated health, n (%)			
E/VG/G	296 (73.3)	116 (67.4)	0.06
F/P	102 (25.2)	52 (30.3)	
Missing	6 (1.5)	4 (2.3)	
Current smoker, n (%)	20 (5.0)	9 (5.2)	0.95
Missing	44 (10.9)	4 (2.3)	
Access to care			
Family Income, n (%)			
\$25,000	163 (40.4)	73 (42.4)	0.32
> \$25,000	173 (42.8)	91 (52.9)	
Missing	68 (16.8)	8 (4.7)	
Health Insurance, n (%)	335 (82.9)	166 (96.5)	0.39
Missing	61 (15.1)	4 (0.6)	
Prescription medication insurance, n (%)	257 (63.6)	144 (83.7)	< 0.001

	Pre <sup>*</sup> (Y6;2002–2003) n=404	Post <sup>*</sup> (Y10;2006–2007) n=172	P value
Established physician, n (%)			
Private doctor	309 (76.5)	157 (91.3)	0.68
Other	37 (9.2)	15 (8.7)	
Missing	58 (14.3)	0 (0)	
Hospitalization in previous 6 months, n (%)			0.43
Yes	35 (8.7)	11 (6.4)	
Missing	0 (0)	4 (2.3)	

\*95 participants were present in both years.

#### Table 2

Pre- vs. Post- Comparison of Daily NSAID Use and, Risk Factors for Gastroprotective Use, Gastroprotective Use

Variables	Pre (2002–2003) Year 6 n=404*	Post (2006–2007) Year 10 n=172	P value		
NSAID Use					
Any NSAID use	404/2300 (17.6)	172/1526 (11.3)	< 0.001		
COX-nonselective NSAID use	183 (45.3)	131 (76.2)	< 0.001		
COX-2 selective NSAID use	223 (55.2)	41 (23.8)	< 0.001		
Risk Factors for Gastroprotective Use					
Current warfarin use, regular	22 (5.5)	10 (5.8)	0.19		
Current glucocorticoid use, regular	18 (4.5)	6 (3.5)	0.99		
History of Peptic Ulcer Disease	69 (17.1)	23 (13.4)	0.77		

\* 2 participants used both a COX-nonselective and COX-2 selective NSAID in year 6