Age and Rising Rates of Cyclooxygenase-2 Inhibitor Use

Results from a National Survey

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BACKGROUND: Cyclooxygenase-2 (COX-2) inhibitors were widely prescribed in the years following their introduction, but little is known about the frequency and context of their use across different age groups.

OBJECTIVE: To determine patterns and context of COX-2 inhibitor use in younger and older adults.

DESIGN: Cross-sectional surveys conducted each year from 1998 to 2002.

PARTICIPANTS: National Ambulatory Medical Care survey, a nationally representative sample of patient visits to community-based outpatient practices.

MEASUREMENTS: New or preexisting medication use recorded at the patient visit.

RESULTS: Cyclooxygenase-2 inhibitor use rose rapidly in all age groups, particularly in elders. By 2002, COX-2 inhibitors accounted for 67% of recorded nonsteroidal anti-inflammatory drug (NSAID) uses in visits by patients age 65 and older, compared with 33% of NSAID uses in adults age 18 to 44 and 54% in adults age 45 to 64 ($P < .001$). Coadministration of proton pump inhibitors or misoprostol with NSAIDs was low throughout the study period in all age groups, ranging from 6.7% of all NSAID users in 1998 (the year before COX-2 inhibitors were introduced) to 8.2% in 2002 ($P = .68$). For both older and younger adults, use of these gastroprotective agents occurred at similar rates among persons taking COX-2 inhibitors compared with those taking nonselective NSAIDs. Among elderly NSAID users in 2001 to 2002, elders with cardiovascular disease were more likely to receive COX-2 inhibitors than those without cardiovascular disease (86% vs 66%, $P < .001$).

CONCLUSIONS: Cyclooxygenase-2 inhibitors were rapidly adopted among all age groups, but particularly among the elderly, where use in patients with cardiovascular disease was especially high. Use of these agents largely supplemented, rather than replaced, older forms of gastroprotective therapy. The rapid and widespread use of COX-2 inhibitors in spite of their higher cost and potential for complications provides important lessons for physicians' approach to new and highly promoted drugs.

KEY WORDS: cyclooxygenase inhibitors; anti-inflammatory agents, nonsteroidal; drug utilization; physician's practice patterns; aged.

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Since their introduction in the late 1990s, cyclooxygenase-2 (COX-2) inhibitors have enjoyed widespread adoption. Patients at substantial risk of gastrointestinal bleeding from

nonsteroidal anti-inflammatory drugs (NSAIDs) have generally been considered to be good candidates for these drugs, including many elders.¹⁻⁴ However, there has been longstanding concern that COX-2 inhibitors have been overused in patients with a low probability of NSAID-induced gastrointestinal bleeding.^{5,6} Use of COX-2 inhibitors in such patients has been discouraged given their high cost in comparison with other NSAIDs and a growing appreciation of their potential cardiovascular risks.⁷⁻¹⁰

These issues are particularly relevant to elders in light of substantial controversy over the appropriateness of routine use of COX-2 inhibitors in older adults.^{4,11} While advanced age is an important risk factor for NSAID-associated gastrointestinal bleeding, it is also a risk factor for ischemic heart disease, thus conferring the potential for excess cardiovascular risk in the same population that stands to gain most from reduced gastrointestinal risk.⁷ However, the role of age has been obscured in recent studies of potentially inappropriate COX-2 inhibitor use, which have focused mainly on strata of gastrointestinal risk. Thus, on a national level relatively little is known about the use of COX-2 inhibitors in different age groups, the degree to which these newer agents have supplanted older forms of gastroprotective therapy in younger and older adults, and patterns of use in elders at varying levels of cardiovascular risk.

To address these issues, we used data from a nationally representative sample of outpatient visits to evaluate patterns of COX-2 inhibitor use from 1998 through 2002. In particular, we focused on age differences in use of COX-2 inhibitors and gastroprotective therapy, and on use in elders with and without cardiovascular disease. Our goal is to understand the context in which COX-2 inhibitors were adopted in the period before safety concerns were widely recognized, so as to better understand recent events, and more generally to understand how new drugs are adopted where risk and benefit vary across the age spectrum.

METHODS

Sample and Study Design

We used data from the National Ambulatory Medical Care Survey (NAMCS), an annual survey of visits to community-based outpatient practices. Each year, physicians are recruited to record information on a sample of patient visits to their outpatient practices, completing a 1-page form at the conclusion of each included visit. Sampling is conducted using a complex design using multiple levels of clustering and stratification, and patient weights are assigned to allow extrapolation of survey results to national estimates.¹²

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Our study included data from 1998 to 2002, with 1998 serving as a historical control (the first COX-2 inhibitor was approved by the Food and Drug Administration in late December of that year).¹³ During each of these years, 1,087 to 1,474 physicians recorded information on 20,760 to 28,738 patient visits. Data collected included patient demographic characteristics, up to 3 diagnoses associated with the visit, and up to 6 medications, either newly prescribed or already used at the time of the visit. Response rates for data fields central to this study exceeded 95%, and discrepancy rates among items requiring medical coding ranged from 0.0% to 1.6% on internal studies of quality control.^{12,14–17}

We identified visits by adults age 18 and older that involved new or ongoing use of an NSAID by searching for the presence of systemically administered NSAIDs in the recorded medication list (not counting aspirin or salicylates as NSAIDs). We then categorized each patient as taking a COX-2-selective NSAID (COX-2 inhibitor) or a nonselective NSAID.

We classified rofecoxib, celecoxib, and valdecoxib as COX-2 inhibitors. All other agents were considered nonselective. Patients whose medication list recorded both an NSAID and a proton pump inhibitor or misoprostol were considered to be taking concurrent gastroprotective therapy (although we cannot confirm that gastroprotection was the reason for which these drugs were prescribed). For the few cases in which both a COX-2 inhibitor and a nonselective NSAID were recorded for the same visit, we classified that visit into the COX-2 inhibitor category.

To evaluate for the presence of cardiovascular disease, we searched the diagnosis list associated with each visit for ischemic heart disease (International Classification of Diseases—ninth edition [ICD-9] code 410-414) or nonhemorrhagic cerebrovascular disease (ICD-9 code 433-438). Because this diagnosis list is insensitive to the presence of comorbid conditions, we did not attempt to detect the presence or absence of clinical conditions that might be risk factors for gastrointestinal bleeding.

We conducted several sensitivity analyses. Because NSAID and gastroprotective agent use may have been underreported in patients taking more than 6 medications (i.e., by exceeding the number of available fields in which medication information could be recorded), we repeated key analyses among patients with 5 or fewer recorded medications. Aside from lower rates of gastroprotective agent use (4.7% overall, compared with 7.6% in the main analysis), other results were not substantially changed. Because some physicians may have prescribed H₂-blockers to protect against NSAID-induced gastrointestinal complications (despite their lesser efficacy for this indication),^{1,18} we conducted additional analyses in which these drugs were also considered gastroprotective agents. Finally, 2 NSAIDs traditionally thought of as nonselective (etodolac and meloxicam) have partial selectivity for the COX-2 enzyme,¹⁹ and 1 (nabumetone) is thought to have reduced gastrointestinal toxicity because of several unique properties.²⁰ Therefore, we conducted sensitivity analyses in which we evaluated these agents as a separate category.

Analyses

All analyses were conducted at the level of the patient visit, using ultimate cluster models recommended by the National

Center for Health Statistics to adjust for the multiple levels of clustering and stratification in NAMCS.²¹ Bivariate analyses were calculated using the design-based *F* statistic (equivalent to a χ^2 test adjusted for clustering) and multivariable analyses using cluster-adjusted logistic regression. For certain analyses, a small number of survey stratum identifiers were reassigned where only 1 survey stratum was present for a given primary sampling unit.²²

All longitudinal analyses evaluated for differences between each of the 5 study years. Because the use of combined therapy with gastroprotective agents was relatively rare in certain age groups, some age-specific estimates of use are derived from less than 30 observations. In these cases, there is convincing evidence of infrequent use, but point estimates of that use should be interpreted cautiously.

All analyses were conducted using Stata 8.0 (College Station, TX). This research was approved by the Research and Development Committee of the San Francisco VA Medical Center, and by the Committee on Human Research of the University of California, San Francisco.

RESULTS

NSAID Use and Sample Characteristics

Between 1998 and 2002, NSAID use was documented in 7.9% of adult outpatient visits, ranging from a low of 6.6% of visits in 1998 to a high of 8.6% visits in 2000 ($P=.03$ for difference across all study years). Nonsteroidal anti-inflammatory drug use was most common in middle-aged adults, being recorded in 7.0% of visits by adults age 18 to 44, 8.9% of visits by adults age 45 to 64, and 8.0% of visits by adults age 65 and older ($P<.001$).

The characteristics of patient visits at which NSAID use was recorded are listed in Table 1. One third of visits were by patients age 65 and older, and two thirds were to physicians in primary care specialties. Consistent with the focus of the survey, the majority of visits were to freestanding private practices.

COX-2 Inhibitor Use in Younger and Older Adults

Between 1998 and 2002, COX-2 inhibitors rose from 0% to 52% of all recorded NSAID uses, accounting for 30 million of 58 million NSAID-associated visits in the final study year. Adoption of these agents was particularly rapid among elders, in whom COX-2 inhibitors accounted for 51% of recorded NSAID uses within 2 years of their introduction (Fig. 1). By 2002, COX-2 inhibitors accounted for 67% of recorded NSAID uses in adults age 65 and older, compared with 33% of uses in adults age 18 to 44 and 54% of uses in adults age 45 to 64 ($P<.001$; Fig. 1). Over the entire study period, persons over 65 years of age accounted for 42% of COX-2 inhibitor uses.

We conducted cross-sectional analyses using data from 2001 and 2002 to evaluate the independent association between age and COX-2 inhibitor use. After controlling for patient gender, race, ethnicity, number of medications, insurance status, physician specialty, clinic type, region, and urban versus rural locale, age remained strongly associated with use of COX-2 inhibitors as a percentage of total NSAID use (adjusted odds ratio [OR] 2.0 for age 45 to 64, 95% confidence interval [95% CI] 1.4 to 2.8; OR 3.1 for age 65 and older, 95% CI 1.9 to 5.2; compared with age 18 to 44).

Table 1. Characteristics of Patient Visits with Recorded NSAID Use, 1998 to 2002

Age	18-44	45-64	≥ 65	P Value
Proportion of total visits (%)	32	37	31	–
Patient characteristics (%)				
Sex				
Female	57	61	66	<.001
Race				
White	84	85	83	.62
Ethnicity				
Non-Hispanic	88	88	89	.86
Expected source of visit payment				
Private	68	70	16	<.001
Medicare	1	7	74	
Other	31	22	10	
Number of drugs recorded				
1 to 2	70	52	36	<.001
3 to 5	27	33	37	
≥ 6	4	14	27	
Provider/clinic characteristics (%)				
Region				
West	23	23	23	.80
Northeast	19	19	22	
Midwest	23	23	21	
South	34	34	34	
Locale				
Urban	85	82	78	.007
Physician specialty				
GP/FP/Internal medicine	65	63	67	.004
General surgery/Orthopedics	14	14	9	
Other	21	23	24	
Type of clinic				
Freestanding private practice	86	88	90	.12
(solo or group)				
HMO	2	2	2	
Other	12	10	9	

GP, general practice; FP, family practice; HMO, health maintenance organization; NSAID, nonsteroidal anti-inflammatory drug.

Among the COX-2 inhibitors available during this period, celecoxib and rofecoxib predominated. Together, these drugs accounted for 83% to 89% of COX-2 inhibitor uses across all age groups in 2002. Among the COX-2 inhibitors, celecoxib was used in greater proportion among elders than in non-

elderly patients (accounting for 52% of COX-2 inhibitor uses in elders in 2002, compared with 35% in adults age 18 to 44 and 43% in adults age 45 to 64, $P=.03$).

Concurrent Use of Gastroprotective Agents

Use of gastroprotective agents was stable and relatively low throughout the study period but varied between age groups. Gastroprotective agents accompanied 6.7% of adult NSAID uses in 1998 (the year prior to introduction of the COX-2 inhibitors) and remained stable over the remainder of the study period (from 6.7% in 1998 to 8.2% in 2002, $P=.68$). Rates of gastroprotective cotherapy were highest among elders, documented in 11.7% of NSAID-using elders across the study period, compared with 2.7% of NSAID-users age 18 to 44 and 8.2% age 45 to 64 ($P<.001$). Among all age groups, gastroprotective therapy was coadministered at similar rates in users of COX-2 inhibitors and of nonselective NSAIDs. Among adults age 18 to 44, gastroprotective drugs were coadministered in 2.1% of COX-2 inhibitor users versus 2.9% of nonselective NSAID users, in 10.0% versus 7.1% of adults age 45 to 64, and in 12.8% versus 10.7% of adults age 65 and older ($P>.10$ for each comparison).

Similar patterns emerged in sensitivity analyses in which H_2 -blockers were also counted as gastroprotective agents. Use of H_2 -blockers, proton pump inhibitors, and misoprostol remained stable over the study period (from 10.4% of NSAID-users in 1998 to 10.8% in 2002, $P=.90$) and were more commonly used in older than in younger adults (being coadministered in 16.3% of elderly NSAID-users, vs 4.1% of NSAID-users age 18 to 44, and 10.4% age 45 to 64, $P<.001$). As in the primary analyses, these gastroprotective agents were coadministered at similar rates with COX-2 inhibitors and with nonselective NSAIDs ($P>.10$ for each age group).

We separately evaluated changes in the use of 3 NSAIDs (etodolac, meloxicam, and nabumetone) that may have less gastrointestinal toxicity than other NSAIDs. During the study period, use of these agents fell from 14.9% of recorded NSAID uses in 1998 to 5.7% in 2002 ($P<.001$). Rates of use were similar in each age group, accounting for 9.8% of recorded NSAID uses in adults age 18 to 44 across the study period,

FIGURE 1. Type of nonsteroidal anti-inflammatory drug use by age category, 1998 to 2002. Gastroprotective drug = proton pump inhibitor or misoprostol.

versus 10.1% in adults age 45 to 64, and 9.7% in adults age 65 and older ($P=.91$).

COX-2 Inhibitor Use in Elders with Cardiovascular Disease

A diagnosis of cardiovascular disease was recorded in 8.1% of visits by NSAID-using patients age 65 years and older in 2001 to 2002. Among these patients, COX-2 inhibitors accounted for 86% of all recorded NSAID uses, compared with 66% among elders without documented cardiovascular disease ($P<.001$). These differences were somewhat attenuated when the analysis was restricted to rofecoxib and valdecoxib (the 2 COX-2 inhibitors that have raised the greatest concern over cardiovascular toxicity). These 2 drugs accounted for 43% of recorded NSAID use in elders with cardiovascular disease versus 29% without ($P=.13$).

DISCUSSION

In this nationwide study, COX-2 inhibitor use in community-based outpatient settings was common in all age groups, but particularly prevalent in elders. Within 2 years of their introduction, COX-2 inhibitors accounted for one half of recorded NSAID uses in elders, rising to 67% by 2002. COX-2 inhibitors largely supplemented, rather than replaced, older means of protecting against NSAID-associated gastrointestinal toxicity that were infrequently used both before and after the introduction of COX-2 inhibitors. Cyclooxygenase-2 inhibitor use was particularly high in elders with cardiovascular disease, in whom these drugs accounted for 6 of 7 recorded NSAID uses.

Use of COX-2 inhibitors has important implications for all age groups, but especially for elders, who use these drugs most frequently and are most susceptible to their potential benefits and harms. Rates of NSAID-associated gastrointestinal bleeding increase with age. However, serious or life-threatening bleeding is uncommon among elders, occurring at a rate equal to or less than the risk of cardiovascular complications from certain COX-2 inhibitors.^{10,19,23} Thus, current data suggest that for most elders it is unlikely that the lowered bleeding risk outweighs the cardiovascular risk of these products. Furthermore, the dramatically higher retail cost of COX-2 inhibitors may be of significant concern to many elders who lack prescription drug coverage. High out-of-pocket drug costs may force elders to cut back on the use of essential medications and reduce their economic resources for other life activities.^{24,25}

While our results are consistent with risk stratification across different age groups, the observed prescribing patterns appear to belie a logical approach to gastrointestinal bleeding risk. Cyclooxygenase-2 inhibitors were frequently prescribed to young adults with a generally low bleeding risk, and alternate forms of gastroprotection were used infrequently among all age groups before (and after) COX-2 inhibitors entered the market, suggesting that this has not historically been a high priority for physicians. Physician concerns over NSAID-associated dyspepsia may explain the rapid adoption of the COX-2 inhibitors. However, although COX-2 inhibitors may cause slightly less dyspepsia and related symptoms than nonselective NSAIDs, the risk difference is low and in most cases does not justify initiation of selective agents.²⁶⁻³⁰

Our findings thus confirm and expand on a recent report using national data that showed different but consistently

high rates of COX-2 inhibitor use in patients with low and high risk scores for gastrointestinal bleeding.⁶ In addition, our results are consistent with other (although not all) research in the United States and other countries, which have found frequent use of COX-2 inhibitors in a variety of health care settings,^{5,31,32} relatively low use of gastroprotective agents relative to COX-2 inhibitors,³¹⁻³³ and equal or higher risk of COX-2 inhibitor use in patients with cardiovascular disease or risk factors.^{31,34-36}

Since late 2004, market withdrawals of rofecoxib and valdecoxib and widespread media reports of safety issues have changed the frequency and nature of COX-2 inhibitor prescribing.^{37,38} However, the history of these agents provides an important lesson about the dissemination and use of new and popular drugs. The rapid adoption of COX-2 inhibitors was particularly striking in light of existing and well-known therapies used to achieve the same goal of gastrointestinal risk reduction (i.e., misoprostol and the proton pump inhibitors, although efficacy data for the latter were limited during most of the study period).

It is important to acknowledge that the cardiovascular risks of COX-2 inhibitors were not widely appreciated during the study period, nor was the extent of their benefit completely defined. Nonetheless, hindsight affords a clear view of the warning signs. The CLASS and VIGOR trials, both published in 2000, were seminal events in establishing the reduced gastrointestinal toxicity of celecoxib and rofecoxib.^{27,28} However, data from the VIGOR trial suggested cardiovascular risk, and cautionary reviews appeared in prominent medical journals shortly thereafter.^{10,28} Thus, the delay in appreciating the harms of COX-2 inhibitors has been increasingly understood to reflect not only scientific uncertainty but also a combination of inattention by the medical profession, an imperfect regulatory process, and marketing efforts to downplay risk.^{9,37,39}

In this context, the rapid uptake of COX-2 inhibitors likely occurred in response to an extensive and highly effective marketing campaign targeted at both patients and physicians.^{6,39,40} One potential effect of this was to convince patients and physicians that COX-2 inhibitors provided better pain control and less gastrointestinal upset than nonselective NSAIDs, despite little evidence of clinically meaningful differences for either of these outcomes.³⁷ Data on gastrointestinal bleeding risk were also presented in a way that would favor COX-2 inhibitors, exemplified by publication of the CLASS trial, in which the prespecified end point and outcome were discarded in favor of an earlier end point and different outcome measure that reflected more favorably on the drug.⁴¹ Safety data were also manipulated to downplay potential cardiovascular risks, despite mounting evidence.³⁹

Our study has several limitations. Data from NAMCS are based on patient visits, and cannot be used to determine the point prevalence of NSAID use in the U.S. population or any age group therein. Medication use was ascertained from data recorded on a research form upon the completion each visit, and likely underreported use of over-the-counter products such as ibuprofen and naproxen, thus probably underestimating the total volume and proportion of nonselective NSAID use. Similarly, prescription medications may not be completely recorded. However, there is little reason to suspect major differences in the frequency of recording of over-the-counter or prescription medications from year to year, and sensitivity analyses suggest that potential age-related differences in un-

derreporting medication use (because of limited space for recording medication use on the research form) had little effect on the results. Together, these suggest internal validity of our findings for comparisons across years and age groups.

In summary, this nationally representative survey of visits to community-based office practices documented rapid and extensive uptake of COX-2 inhibitors in all age groups, particularly among elders. While frequent use of COX-2 inhibitors in elders may have resulted in less gastrointestinal bleeding, higher rates of cardiovascular disease in this same population exposed many elders to cardiovascular risk who may otherwise have had their NSAID-associated bleeding risk managed with the use of proton pump inhibitors or other gastroprotective agents.^{18,19} Although negative media attention and market withdrawals have resulted in decreased use since the end of our study period,³⁸ the history of the COX-2 inhibitors illustrates important lessons about how new, widely promoted drugs may quickly be adopted by physicians and used in potentially inappropriate ways.³⁵ Future drugs that enter the market with a similar degree of excitement and marketing may benefit from dispassionate and aggressive physician education early in their life cycle, and from stricter application of drug utilization criteria to minimize improper use.

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