

National Trends in Cyclooxygenase-2 Inhibitor Use Since Market Release

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Nonselective Diffusion of a Selectively Cost-effective Innovation

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Background: The withdrawal of rofecoxib has highlighted concerns regarding the safety of cyclooxygenase-2 (COX-2) inhibitors. In some patients COX-2 inhibitors may be safer than nonselective nonsteroidal anti-inflammatory drugs (NSAIDs); however, the public health benefit of COX-2 inhibitors depends on their use in patients at higher than normal risk from NSAIDs. We examined trends in COX-2 inhibitor use based on risk for adverse events from NSAIDs.

Methods: We analyzed data from the National Ambulatory Medical Care Survey (1999-2002) and National Hospital Ambulatory Medical Care Survey (1999-2001), nationally representative surveys of community and hospital-based outpatient practices. The main outcome measure was the proportion of patient visits in which COX-2 inhibitors were prescribed, stratified by risk of adverse gastrointestinal (GI) events from NSAIDs.

Results: Of the visits in which either a COX-2 inhibitor or NSAID was prescribed, the frequency of COX-2 inhibitor use increased from 35% (1999) to 55% (2000) to 61% (2001 and 2002). Among patients with the lowest risk for adverse events from NSAIDs, the proportion receiving a COX-2 inhibitor increased from 12% in 1999 to 35% in 2002. Overall, increases in COX-2 inhibitor use among patients in whom NSAIDs could be used accounted for more than 63% of the growth in COX-2 inhibitor use during the period examined.

Conclusions: Marked increases in COX-2 inhibitor use have occurred since their release, primarily among patients at low risk for adverse events from NSAIDs. These findings demonstrate the challenge of limiting innovative therapies to the settings in which they are initially targeted and maximally beneficial.

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THE CLINICIANS' CHOICE BETWEEN cyclooxygenase-2 (COX-2) inhibitors and traditional nonsteroidal anti-inflammatory drugs (NSAIDs) has always been complex. Clinical trials among select populations have demonstrated that COX-2 inhibitors have the same efficacy as NSAIDs but have less gastrointestinal (GI) adverse effects.¹⁻³ However, the shorter experience with COX-2 inhibitors has led to uncertainty regarding their possible adverse effects,³ which was highlighted by the recent withdrawal of rofecoxib from the market in

Because most of the benefit of COX-2 inhibitors accrues to those at highest risk of NSAID-associated GI toxic effects,⁵ many guidelines have limited the use of COX-2 inhibitors to those at highest risk from NSAIDs.^{6,7}

Regardless of the ultimate fate of this innovative pharmaceutical class, lessons regarding the evidence-based use of COX-2 inhibitors are particularly important given concerns regarding rising prescription costs. About 40% of these costs are attributable to the use of new drugs rather than changing patient demographics and an increase in the number of drugs per patient.⁸ Such costs are increasingly paid for out of pocket, pose a growing burden on millions of Americans, and challenge patients, clinicians, and policy makers alike. For individual patients and clinicians, the choice between a COX-2 inhibitor and an NSAID has represented a paradigmatic case of a cost/quality trade-off that may be an important yet neglected topic of discussion in clinical practice.⁹ At a policy level,

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September 2004. Furthermore, the choice of a COX-2 inhibitor in any patient has always come at considerable expense, since the wholesale price of COX-2 inhibitors is markedly greater than that of NSAIDs.⁴

trends in the use of innovative but costly pharmaceuticals have important implications for the long-term viability of initiatives such as the Medicare prescription drug benefit as well as efforts to control escalating prescription drug costs.

New technologies are not adopted homogeneously among a population,¹⁰ and limiting new technologies to settings of maximally proven benefit are seldom successful.¹¹ For example, one recently described study examined the “treatment-risk” paradox of statin use, whereby patients at highest risk of adverse cardiac events were least likely to be treated with these cholesterol-lowering agents.¹² Such nonselective diffusion of technologies may undermine their cost-effectiveness depending on the degree of nonselective uptake and the marginal benefit among different populations of users.¹³

We sought to examine longitudinal trends in the use of COX-2 inhibitors with a focus on the selectivity of use in populations at highest risk for GI adverse events from NSAIDs. In addition to examining patient characteristics, we also explored nonclinical characteristics associated with COX-2 inhibitor use. Although several studies have examined how these characteristics influence the choice to use a COX-2 inhibitor,¹⁴⁻¹⁸ these studies have generally been conducted among homogeneously insured populations and included little detail about physician and visit characteristics that have been demonstrated to be associated with prescribing patterns in other settings.¹⁹⁻²¹

METHODS

DATA

We used data from the National Ambulatory Medical Care Survey²² (NAMCS, 1999-2002) and the National Hospital Ambulatory Medical Care Survey²³ (NHAMCS, 1999-2001). Designed and conducted by the National Center for Health Statistics, Hyattsville, Md, NAMCS is a national probability sample of office-based physicians that provides data on patient office visits. It uses a 3-stage probability sampling procedure that has been previously described.²² The survey uses a 1-page data form completed by the physician or office staff that includes information about patient, physician, and visit characteristics. For each office visit, physicians are asked to record up to 6 prescription or over-the-counter medications for which therapy is either being continued or prescribed. The counterpart of NAMCS, NHAMCS, is a similar national probability sample that uses a 4-stage design to sample visits to outpatient departments of noninstitutional general and short-stay hospitals.²³ Patient visit weights in both surveys are adjusted to account for nonresponse and nonparticipation.

GI RISK ASSESSMENT TOOL

Similar to the method of Doshi et al,²⁴ we used a modified version of the GI score risk assessment tool²⁵ to quantify each patient's risks for NSAID-induced GI adverse events. The GI risk assessment tool is an instrument that weighs 6 items (subject's age, self-reported health, history of rheumatoid arthritis, corticosteroid use, GI bleeding or ulcers, and GI symptoms with NSAID use) to stratify patients into 4 levels of risk from traditional NSAIDs.²⁶ Based on the method of Doshi et al,²⁴ we included the use of anticoagulants and antiplatelets as addi-

tional risk factors. According to this method of risk stratification, subjects with “very low risk” or “low risk” are recommended to receive NSAIDs, subjects with “moderate risk” are recommended to receive different medicines based on the length of expected treatment, and subjects with “high risk” are recommended to receive COX-2 inhibitors. Because we did not have information on self-reported health or length of corticosteroid use in our cross-sectional data, we assumed that subjects were in “fair” health (2 on a 0-4 scale) and that any corticosteroid use was for a moderate duration (3 on 0-5 scale). In our analyses of trends in COX-2 inhibitor use based on the risk of adverse events from NSAIDs, we conducted several sensitivity analyses varying the self-reported health of the population, the duration of corticosteroid use, and the inclusion of antiplatelets and anticoagulants in the GI risk score. We also examined the effect of dichotomizing all patients based on the presence of at least 1 main risk factor for adverse events from NSAIDs (eg, age >65 years) as well as limiting our analyses to patients younger than 65 years who were not receiving anticoagulants.

STATISTICAL ANALYSIS

Because the first COX-2 inhibitors (celecoxib) were released in January 1999, we used descriptive statistics, applying patient sampling weights, to examine trends in the use of COX-2 inhibitors (rofecoxib, celecoxib, and valdecoxib) and NSAIDs (ibuprofen, indomethacin, naproxen, diclofenac, etodolac, flurbiprofen, ketoprofen, ketorolac, meclizolam, meloxicam, nabumetone, oxaprozin, piroxicam, sulindac, tolmetin) from 1999 through 2002. To examine predictors of COX-2 inhibitor use, we defined our outcome variable as the choice between a COX-2 inhibitor and an NSAID, conditional on having received 1 of these 2 medication classes. We excluded the 0.4% of patients with prescriptions for both an NSAID and a COX-2 inhibitor. We used χ^2 analyses to evaluate the bivariate association between hypothesized characteristics of patients (age, sex, race, comorbid conditions, and GI risk score), physicians (specialty and employment status), and visits (source of payment, region of country, new vs established patient, year, type of office, owner of practice, and solo vs group practice) and the outcome of interest. We performed weighted logistic regression for complex survey data to examine the multivariate association between the predictor variables and our outcome variable.²⁷ Initial models included basic demographic characteristics of patient visits, variables significant on bivariate analysis ($P < .25$), and an interaction term between year and GI risk score to assess whether the association between GI risk and the likelihood of COX-2 inhibitor receipt was independently modified by the year of observation. We also examined several other interaction terms that we hypothesized a priori might be important explanatory variables (eg, race interacted with source of payment, physician specialty interacted with time spent with physician, and physician specialty interacted with patient GI risk), but they did not add considerably to the model's goodness of fit. Because most comorbid conditions were present in fewer than 5% of all patient visits, we aggregated these comorbid conditions into 2 categories—those that might be an indication for COX-2 inhibitors rather than NSAIDs (GI bleeding, peptic ulcer disease, rheumatoid arthritis, corticosteroid use, coagulation defects, history of heartburn, stomach pain, nausea, or vomiting) and those that might be a relative contraindication for either COX-2 inhibitors or NSAIDs (congestive heart failure, liver dysfunction, or renal dysfunction). We refined our multivariate model using the Hosmer-Lemeshow goodness-of-fit test and the Pregibon Linktest for Nonlinearity. Our final models were robust, maximized goodness of fit, and included basic sociodemographic variables (eg, race) and variables that

were statistically significant in the earlier models ($P < .05$). We examined the impact of omitting alternative analgesics (opioids, opioid analogues, and acetaminophen) from our analyses. There were no statistically significant trends in the use of these medicines from 1999 through 2002, nor was the use of these analgesics associated with GI risk score. Thus, we reasoned these alternatives were not important substitutes for COX-2 inhibitors or NSAIDs in our analyses. We also conducted sensitivity analyses that examined multivariate models limited to the elements of the GI risk score and that dichotomized patients based on the presence of any of the main risk factors for adverse events from NSAIDs (eg, age >65 years). All analyses were conducted using Stata statistical software (Stata Corporation, College Station, Tex).

RESULTS

PATIENT VISITS WITH COX-2 INHIBITOR OR NSAID USE

There were 4893 visits from 1999 through 2002 in which therapy with a COX-2 inhibitor or an NSAID was either continued or prescribed, corresponding to a national estimate of 221.8 million visits (95% confidence interval [CI], 208.8-238.1 million visits). **Table 1** describes the characteristics of these visits. For example, the mean age of patients among all visits was 52 years, 63% of visits were made by women, 83% of visits were made by white patients, and 70% of visits took place in general medicine or family medicine practices. Among all visits, the risk for adverse events from NSAIDs varied, with 31% classified as "very low risk," 42% as "low risk," 25% as "moderate risk," and 2% as "high risk."

TRENDS IN THE USE OF COX-2 INHIBITORS

Table 2 describes changes in the use of COX-2 inhibitors and NSAIDs over the period examined. Overall, the use of these medicines increased from 42.4 million (95% CI, 35.8-50.1 million visits) of 841.4 million visits (5.0%) in 1999 to 56.9 million (95% CI, 50.6-63.9 million visits) of 890.0 million visits (6.4%) in 2002. Of the visits in which 1 of these 2 drug classes was used, the proportion in which a COX-2 inhibitor was used increased from 35% (1999) to 55% (2000) to 61% (2001 and 2002). This corresponds with a mean increased rate of use of 23% per year, taking into account the 0% change between the years 2001 and 2002.

The **Figure** depicts changes in the types of patient visits in which COX-2 inhibitors were prescribed stratified by risk of adverse GI events. Among patient visits with the lowest risk of GI toxic effects, in 1999, 12% had a COX-2 inhibitor prescription, and this proportion increased to 40% in 2000 and to 37% in 2001. By comparison, the proportion of patient visits with the highest risk of GI toxic effects and a COX-2 inhibitor prescription ranged from 54% to 98% over the same period.

COX-2 INHIBITOR USE STRATIFIED BY GI RISK

Table 3 depicts changes in the frequency of COX-2 inhibitor use stratified by risk of GI adverse events. For example, among patient visits with a very low risk, the num-

Table 1. Characteristics of Patient Visits With COX-2 Inhibitor or NSAID Use (1999-2002)*

Characteristic	Value†
Patient age, y	52 ± 17.7
Female	139.7 (63)
Race	
White	184.1 (83)
Black	31.0 (14)
Asian	6.7 (3)
Hispanic	26.6 (12)
GI risk score	
0-10, Very low risk	69.6 (31)
11-15, Low risk	92.9 (42)
16-20, Moderate risk	55.2 (25)
≥21, High risk	4.1 (2)
COX-2 inhibitor receipt	121.6 (55)
Year	
1999	39.7 (18)
2000	52.2 (24)
2001	66.1 (30)
2002	63.8 (29)
Physician specialty‡	
General medicine or family medicine	154.0 (70)
Surgical specialties	38.4 (17)
Other	29.4 (13)

Abbreviations: COX-2, cyclooxygenase-2; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

*Population-weighted percentages from visits in which therapy with a COX-2 inhibitor or an NSAID was continued or prescribed. National estimate was 221.8 million visits. Data are from the National Ambulatory Medical Care Survey²² (1999-2002) and the National Hospital Ambulatory Medical Care Survey²³ (1999-2001).

†Data are given as number in millions (percentage) of patients or mean ± SD value.

‡Data limited to the National Ambulatory Medical Care Survey.

ber in which a COX-2 inhibitor was used increased from 1.7 million (95% CI, 1.0-2.7 million) in 1999 to 6.1 million (95% CI, 4.6-7.8 million) in 2002. This increase accounts for 22.4% of the growth in COX-2 inhibitor use over this period:

$$(6.1 \text{ Million} - 1.7 \text{ Million}) / (34.6 \text{ Million} - 15.0 \text{ Million}).$$

Our findings from the sensitivity analyses yielded similar patterns of diffusion of COX-2 inhibitors over the period examined. For example, increases in use of COX-2 inhibitors among patient visits over the years examined stratified by very low, low, moderate, and high GI risk ranged from 22.4% to 46.9% (among visits with very low GI risk), 20.9% to 40.8% (among low-risk visits), 16.8% to 46.4% (among moderate-risk visits), and 0.0% to 12.2% (among high-risk visits). Thus, all models indicated that over time growth in COX-2 inhibitor use occurred primarily among visits with lower GI risk, although the magnitude of this shift depended on the specific assumptions of the model. We also examined the potential for underuse of COX-2 inhibitors among patient visits based on risk of adverse GI events from NSAIDs. Rates of NSAID use among visits with moderate or high risk from this drug class using the GI risk tool ranged from 9% to 16% (among visits with moderate risk) and 0% to 2% (among visits with high risk).

Table 2. National Visit Estimates With COX-2 Inhibitor or NSAID Use (1999-2002)*

Prescription	1999	2000	2001	2002
COX-2 inhibitor	15.0 (35)	31.5 (55)	39.4 (61)	34.7 (61)
NSAID	27.4 (65)	26.0 (45)	25.6 (39)	22.2 (39)
Total	42.4 (100)	57.5 (100)	65.0 (100)	56.9 (100)

Abbreviations: COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.

*Data are given as number of visits in millions (percentage). Data are from the National Ambulatory Medical Care Survey²² (1999-2002) and the National Hospital Ambulatory Medical Care Survey²³ (1999-2001); χ^2 test for linear trend ($P < .001$).

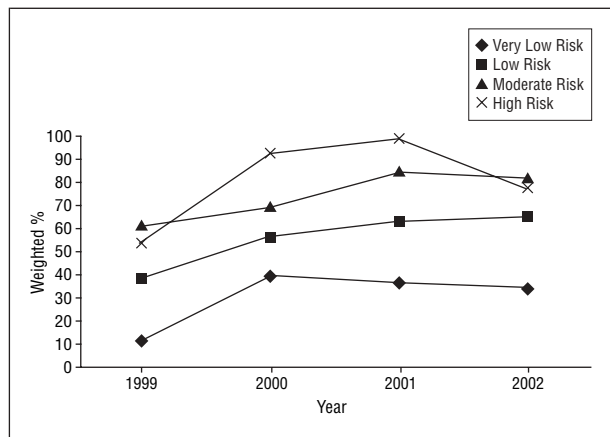


Figure. Cyclooxygenase-2 inhibitor use stratified by risk of adverse events from nonsteroidal anti-inflammatory drugs (1999-2002).

Table 4 depicts trends in COX-2 inhibitor use among patient visits in which a relative contraindication to both COX-2 inhibitors and NSAIDs was reported (eg, congestive heart failure). Among these visits, in 1999, approximately 2.9 million visits were associated with COX-2 inhibitor use and 3.7 million visits with NSAID use. By 2002, the number of patient visits associated with COX-2 inhibitor use increased more than 5-fold by 2002 (16.6 million) whereas the number of visits associated with NSAID use decreased somewhat (2.2 million).

CHARACTERISTICS ASSOCIATED WITH RECEIPT OF A COX-2 INHIBITOR

On multivariate analysis, only a few characteristics were independently associated with COX-2 inhibitor use (**Table 5**). For example, female visits were more likely to include receipt of a COX-2 inhibitor than were male visits (odds ratio [OR], 1.44; 95% CI, 1.19-1.74), patient visits to surgical specialists were more likely to be associated with COX-2 inhibitor use than those to general internists (OR, 1.39; 95% CI, 1.02-1.94), and patient visits that took place in a physician-owned practice were more likely to receive a COX-2 inhibitor than those in a health maintenance organization or hospital-owned setting (OR, 2.32; 95% CI, 1.63-3.30). In our models, GI risk score was associated with COX-2 inhibitor use, and this effect was modified by the year examined, as indicated by the statistically significant interaction term between GI risk score and year.

Although we found higher rates of COX-2 inhibitor use among some physicians, the selectivity of use based on GI risk did not differ markedly based on physician specialty or practice type. For example, analyses limited to patient visits in physician-owned practices showed that from 1999 through 2002, 11% to 24% of COX-2 inhibitors were prescribed in visits with very low risk of adverse events from NSAIDs, while 42% to 45% of COX-2 inhibitors were prescribed in visits with low risk of these events.

Sensitivity analyses limited to the elements of the GI risk score continued to show statistically significant ($P < .05$) increases in the use of COX-2 inhibitors over time (ORs, 1.40-1.44 per additional year) and greater COX-2 inhibitor use among patient visits in physician-owned practices (ORs, 2.38-2.39), although associations between greater COX-2 inhibitor use and visits involving surgical subspecialists varied slightly based on the assumptions of the model (OR, 1.35 [95% CI, 0.98-1.86] for models with patient visits dichotomized into groups based on the presence of any risk factor; OR, 1.39 [95% CI, 1.00-1.93] for models limited to elements of the GI risk score).

COMMENT

To our knowledge, this is the first study to examine the longitudinal pattern of diffusion of COX-2 inhibitors after market release with a focus on the characteristics of those receiving the drug. This examination took place among a broad sample of patient visits in which detailed patient, physician, and visit characteristics were available. We found considerable increases in COX-2 inhibitor use occurring among patients at the lowest risk for GI toxic effects from NSAIDs. We also found that several nonclinical factors were as important as established patient risk factors for NSAID-related GI toxic effects in determining COX-2 inhibitor use.

There are several possible reasons for these trends. Diffusion of new technologies is seldom smooth or uniformly achieved selectively among the population that stands to gain the most from the technology.¹⁰ Our results demonstrate how the phenomenon of "therapeutic creep," which has been described in relation to the adoption of unproven surgical techniques such as carotid endarterectomy²⁸ and cholecystectomy,²⁹ is applicable to the diffusion of pharmaceuticals. This may be in part because of the tendency to equate "newer" with "better" medicines³⁰ and because of the powerful impact that brand loyalty can have on prescribing behavior.³¹ In addition, the impact of marketing and promotional efforts must also be considered. COX-2 inhibitors have been heavily

Table 3. Use of COX-2 Inhibitors Stratified by Risk of Adverse GI Events From NSAIDs (1999-2002)*

Risk of Adverse GI Events From NSAIDs	1999		2000		2001		2002		Increase in No. of Visits, 1999-2002	
	No. of Visits in Millions (95% CI)	%	No. of Visits in Millions (95% CI)	%	No. of Visits in Millions (95% CI)	%	No. of Visits in Millions (95% CI)	%	No. in Millions	%
Very low risk	1.7 (1.0-2.7)	11	7.2 (5.7-9.0)	23	7.6 (5.7-9.8)	19	6.1 (4.6-7.8)	18	4.4	22
Low risk	6.8 (5.7-8.0)	46	13.8 (11.7-15.9)	44	17.6 (15.5-19.8)	45	14.8 (12.1-17.7)	43	8.0	41
Moderate risk	6.0 (4.7-7.3)	40	9.5 (7.7-11.4)	30	13.2 (10.9-15.8)	33	12.9 (10.1-16.1)	37	6.9	35
High risk	0.5 (0.2-1.4)	3	1.0 (0.5-2.1)	3	1.0 (0.5-1.9)	3	0.8 (0.3-2.1)	2	0.3	2
Total	15.0	100	31.5	100	39.4	100	34.6	100	19.6	100

Abbreviations: CI, confidence interval; COX-2, cyclooxygenase-2; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs.

*Data are from the National Ambulatory Medical Care Survey²² (1999-2002) and the National Hospital Ambulatory Medical Care Survey²³ (1999-2001); χ^2 test for linear trend for "very low risk," "low risk," and "moderate risk," $P < .001$; whereas for "high risk," $P = .14$.

Table 4. National Visit Estimates With COX-2 Inhibitor or NSAID Use Among Patients With Congestive Heart Failure, Liver Dysfunction, or Renal Dysfunction (1999-2002)*

Prescription	1999	2000	2001	2002
COX-2 inhibitor	2.9 (44)	3.5 (48)	19.2 (77)	16.6 (88)
NSAID	3.7 (56)	3.8 (52)	5.8 (23)	2.2 (12)
Total	6.6 (100)	7.3 (100)	25.0 (100)	18.8 (100)

Abbreviations: COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.

*Data are number (percentage) of visits in millions. Data are from National Ambulatory Medical Care Survey²² (1999-2002) and the National Hospital Ambulatory Medical Care Survey²³ (1999-2001); χ^2 test for linear trend ($P < .001$).

promoted, both through direct-to-consumer advertising as well as to physicians. For example, in 2000, Vioxx (rofecoxib; Merck and Co Inc, Whitehouse Station, NJ) was the most heavily advertised direct-to-consumer drug with expenditures of \$161 million.³² Given that perceptions of innovations are strong predictors of rates of spread,¹⁰ aggressive marketing techniques to patients and physicians may help to explain the observed growth in COX-2 inhibitor use. Our findings that the growth in COX-2 inhibitor use has exceeded the decrease in the use of NSAIDs suggest that COX-2 inhibitors have not only eroded NSAID market share but have also increased total market demand. This finding is consistent with studies suggesting that direct-to-consumer advertising may increase market share for classes of drugs.³³ Also, independent of advertising effects, increased product variety may facilitate better matches between heterogeneous patient preferences and treatments and thereby increase market size.³⁴

For patients and physicians, our findings raise the concern that the marginal benefit of COX-2 inhibitor use may be increasingly small, considering the growing tendency for their nonselective use in populations that are not at high risk for adverse events from NSAIDs. The market withdrawal of rofecoxib has highlighted the importance of physicians and patients carefully considering the relative risks and benefits of COX-2 inhibitors compared with alternative analgesics. Such considerations should include the new knowledge regarding the risk of cardiovascular events from rofecoxib, as well as the findings that concomitant use of aspirin with COX-2 inhibi-

tors may diminish the selective safety advantage of COX-2 inhibitors among high-risk patients.¹ Our results support the findings of a cross-sectional study that identified suboptimal cost-effective use of COX-2 inhibitors.³⁵ Although the actual out-of-pocket costs of COX-2 inhibitors varies, their mean cost is considerably greater than that of NSAIDs⁴ and may further burden patients already struggling to afford escalating prescription costs.⁹ These and other findings³⁶ indicate that patients should be encouraged to discuss their prescription costs with their physician and increasingly participate in the numerous cost-quality trade-offs often inherent in prescription choice. Such enhanced communication about costs may help to potentiate the cost-effectiveness of tiered formularies, reference-based pricing, and other innovative methods of pharmaceutical regulation.

For policy makers, these results demonstrate that the increasing nonselective use of COX-2 inhibitors among visits with patients who are not at high risk from NSAID-related adverse events threatens their overall cost-effectiveness in actual practice. There is no doubt that, based on currently available evidence, some fraction of patients will benefit from COX-2 inhibitors on the basis of relative contraindications to nonselective NSAIDs. While it may be difficult to estimate this fraction, it is likely to be far lower than the 61% of patient visits with receipt of a COX-2 inhibitor rather than NSAID in 2001 and 2002. Similar to the treatment-risk paradox,¹² the tendency toward increasing nonselective use of a marginally much more costly treatment dramatically reduces the aggregate benefit of the technology.¹³ Cost-effective analy-

Table 5. Association Between Patient, Physician, and Visit Characteristics and COX-2 Inhibitor Use (1999-2002)*

Characteristic	Odds Ratio (95% CI)	P Value
Patient characteristics		
Sex		
Male	1.00 (Referent)	
Female	1.44 (1.19-1.74)	<.001
Race		
White	1.00 (Referent)	
Black	0.88 (0.59-1.31)	.52
Asian	1.00 (0.58-1.71)	.99
GI risk score	1.13 (1.06-1.21)	<.001
Relative contraindication to NSAIDs	1.48 (0.85-2.58)	.16
Presence of CHF, liver dysfunction, or renal dysfunction	0.99 (0.47-2.09)	.99
GI risk score × year†		
GI risk score	1.13 (1.06-1.21)	
Physician characteristics		
Physician specialty		
General medicine or family medicine	1.00 (Referent)	
Surgical specialties	1.39 (1.02-1.94)	.048
Other	0.78 (0.59-1.04)	.09
Visit characteristics		
Region		
Northeast	1.00 (Referent)	
Midwest	0.87 (0.56-1.33)	.51
South	1.58 (1.04-2.40)	.03
West	0.83 (0.53-1.30)	.41
Year	1.23 (0.95-1.59)	.12
Owner of practice		
Hospital/HMO	1.00 (Referent)	
Physician	2.32 (1.63-3.30)	<.001

Abbreviations: CHF, congestive heart failure; CI, confidence interval; COX-2, cyclooxygenase-2; GI, gastrointestinal; HMO, health maintenance organization; NSAIDs, nonsteroidal anti-inflammatory drugs.

*Hosmer and Lemeshow goodness of fit ($P = .30$); Pregibon Linktest ($P = .20$); pseudo $R^2 = 0.14$; data are from the National Ambulatory Medical Care Survey²² (1999-2002).

†Interaction term statistically significant ($P = .047$).

ses of COX-2 inhibitor use have been sensitive to the risk for adverse GI events among the target population.^{37,38} Our results reinforce the importance, when evaluating prospective analyses of innovative therapies, of considering the degree of nonselective uptake that is likely to take place and how this may change over time.^{39,40}

Such policy considerations are especially important in the aftermath of the removal of rofecoxib from the market. The nonselective use of COX-2 inhibitors that we identify led to an unnecessarily large population of patients being exposed to a hitherto not well-characterized cardiovascular risk. As illustrated by the examples of fenfluramine-phentermine (fen-phen) and troglitazone, overall harm from a new pharmaceutical may be increased when rapid expansion of prescribing occurs prior to the development of definitive data on safety. With new drugs whose safety profile is not well characterized, greater regulatory efforts to limit the use of the drug to the clinical population in which an unambiguous outcome benefit exists may minimize the potential for overall public harm.

In addition to the nonclinical patient characteristics that we examined, we also found that visits with physi-

cians in surgical subspecialties and physician-owned practices were more likely to include receipt of a COX-2 inhibitor than were visits with physicians in general medicine or hospital/health maintenance practices, respectively. This variation in practice patterns may be in part due to differences in patient case-mix. Patients who have had prior trials of multiple NSAIDs may be more likely to see a specialist and receive a COX-2 inhibitor prescription. In addition, our findings may be due to differences in the dissemination of information about new medical technologies. Specialists, and perhaps physicians in physician-owned practices, have greater exposure to pharmaceutical detailing of newer drugs than do general practitioners and are quicker to adopt new treatments.⁴¹⁻⁴⁴ Despite these associations, we did not find large differences in the selectivity of COX-2 inhibitor use based on physician specialty or practice ownership.

This study has several limitations. First, NAMCS and NHAMCS measure office visits rather than individual patients and therefore oversample frequent users of medical care, do not sample visits outside of office-based settings, and do not provide information on treatment outcomes. Second, this analysis is limited to prescribed or over-the-counter medications recommended by physicians and thus does not include over-the-counter medicines that patients use without their physicians' knowledge. Third, our cross-sectional data do not allow for us to examine the frequency of drug switches (eg, from NSAIDs to COX-2 inhibitors), systematic trends in the undercoding of variables such as comorbid conditions, or the effect of advertising and promotional efforts on prescription choice. Fourth, alternative methods of stratifying patients by GI risk from NSAIDs could yield different conclusions regarding the selectivity of COX-2 inhibitor use. However, the sensitivity analyses we conducted support our findings of large increases in COX-2 inhibitor use among those at lowest risk for adverse events from NSAIDs. Finally, since we do not have 2002 data for NHAMCS, we may have underestimated or overestimated the true rate of change of COX-2 inhibitor use from 2001 to 2002. However, analysis stratified by data source from 1999 through 2001 suggest similar trends in the growth of COX-2 inhibitor use over this period.

CONCLUSIONS

Our study demonstrates a marked change in the types of patient visits in which COX-2 inhibitors are prescribed since their release in 1998. The evidence that visits with the lowest risk of adverse events from traditional NSAIDs are increasingly including the receipt of their considerably more expensive counterparts jeopardizes the cost-effectiveness of COX-2 inhibitors and may be applicable to the adoption of other innovative therapies such as newer antihypertensives (eg, angiotensin 2 receptor blockers) and antiplatelet agents (eg, adenosine diphosphate receptor blockers). Efforts to focus COX-2 inhibitor use to settings of clear clinical benefit offers one means of reducing prescription drug expenditures without compromising the quality of patient care.

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