Over and Under-utilization of Cyclooxygenase-2 Selective Inhibitors by Primary Care Physicians and Specialists

The Tortoise and the Hare Revisited

Brian D. De Smet, Pharm D, MS,[1,2] A. Mark Fendrick, MD,[3,4] James G. Stevenson, Pharm D,[1,2] Steven J. Bernstein, MD, MPH[3,4,5]

[1]Department of Pharmacy Services, University of Michigan Hospitals and Health Centers, Ann Arbor, MI, USA; [2]Department of Clinical Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI, USA; [3]Department of Internal Medicine, School of Medicine, University of Michigan, Ann Arbor, MI, USA; [4]Department of Health Management & Policy, School of Public Health, University of Michigan, Ann Arbor, MI, USA; [5]Center for Practice Management and Outcomes Research, VA Ann Arbor Healthcare System, Ann Arbor, MI, USA.

OBJECTIVES: To compare prescribing trends and appropriateness of use of traditional and cyclooxygenase-2 selective (COX-2) nonsteroidal anti-inflammatory drugs (NSAIDs) by primary care physicians (PCPs) and specialists.

DESIGN: Retrospective cohort study.

PATIENTS: One thousand five hundred and seventy-six adult patients continuously enrolled for at least 1 year with an independent practice association of a University-associated managed care plan who were started on a traditional NSAID or a COX-2 inhibitor from 1999 to 2002 and received at least 3 separate medication fills.

MEASUREMENTS: Physician specialty was identified from office visits. Appropriateness of utilization was based on gastrointestinal risk characteristics.

RESULTS: Primary care patients were younger and less likely to have comorbid conditions. Despite similar GI risk, COX-2 use among patients seen by PCPs was half that of patients seen by specialists (21% vs 44%, $P<.001$). While PCPs overused cyclooxygenase-2-specific inhibitors (COX-2s) less often than specialists (19% vs 41%, $P<.001$), they also tended to underuse COX-2s in patients who were at increased GI risk (46% vs 32%, $P=.063$). This represents a 3-fold and 8-fold difference in overuse versus underuse for PCPs and specialists, respectively.

CONCLUSIONS: Using COX-2s as a model for physician adoption of new therapeutic agents, specialists were more likely to use these new medications for patients likely to benefit but were also significantly more likely to use them for patients without a clear indication. This study demonstrates the tension between appropriate adoption of innovative therapies for those individuals who would benefit from their use and those individuals who would receive no added clinical benefit but would incur added cost and be placed at increased risk.

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Prescription drug costs continue to escalate at a much higher rate than other medical services.[1] A substantial portion of these costs is associated with the introduction of new, costly medications. The uptake of these new medications is partially driven by pharmaceutical companies targeting specialist physicians to become early adopters and promoters of their drugs in the hope that these physicians will help disseminate information on their use to primary care physicians (PCPs) and trainees.

Although specialists may provide more appropriate care for patients presenting with conditions in their specialty then generalists,[2–5] these patients often receive more expensive medications without additional benefits.[4,5] One such group of medications is the cyclooxygenase-2-specific inhibitors (COX-2s), which were developed to provide similar pain relief as traditional non-steroidal anti-inflammatory drugs (NSAIDs) but with a reduced risk of gastrointestinal (GI) toxicity. Given the equal efficacy and the higher cost of COX-2s when compared with traditional NSAIDs, their use was recommended for individuals at risk for NSAID-related adverse GI events. While the appropriateness of COX-2s has been described, the differential rate of adoption and appropriateness of use by specialists and PCPs has not been reported. Accordingly, the study's objectives were to assess the difference between PCPs and specialists in their (1) rate of adoption of COX-2 selective inhibitors; (2) underuse of COX-2s among high GI risk patients; and (3) overuse of COX-2s among low GI risk patients

METHODS

We conducted a retrospective cohort study on patients enrolled with one independent practice association (IPA) of a mid-western University-associated managed care plan.

Study Population

We identified 38,695 managed care members age 18 or older who filled prescriptions for NSAIDs or NSAID combinations between January 1, 1999 and December 31, 2002. We then restricted the population to those patients who were continuously enrolled in the health care plan for at least 11 months before their first NSAID prescription, were chronic NSAID users (i.e., at least 3 prescriptions within any calendar year) and had seen an IPA physician during the measurement period.

Data Elements

De-identified data obtained from the university health system's and managed care organization's data warehouses included

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Address correspondence and requests for reprints to Dr. Bernstein, Department of Internal Medicine, University of Michigan, 300 North Ingalls Building, Room 7E14, Ann Arbor, MI 48109-0429 (e-mail: sbernste@umich.edu).

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patient age, gender, and clinical history. Medications included NSAIDs, GI protective agents (proton pump inhibitors (PPIs), and misoprostol), and drugs that increased the risk of GI complications on NSAIDs (glucocorticoids, antiplatelet, and anticoagulant drugs). Data were compiled on a yearly basis.

Based on the patient's claims data and electronic problem summary list, patients were classified as being at an increased risk for a GI complication (history of upper GI bleed, peptic or duodenal ulcer; co-therapy with an anticoagulant or corticosteroid; or age 70 years or older) or at normal to low risk of a GI complication.[6–8] The study was approved by the University of Michigan Institutional Review Board.

Identifying New NSAID Prescriptions and Prescriber Specialty

Patients were considered to have started an NSAID in a measurement year if they had not received a prescription NSAID within the previous 335 days. Nonsteroidal anti-inflammatory drug medications were classified as either a traditional NSAID or a COX-2-specific medication. If a patient received a prescription for both a traditional NSAID and a COX-2-specific medication in the same year, they were classified as being on a COX-2 medication.

Physicians were classified as being either a PCP (i.e., physicians specializing in Family Medicine or General Internal Medicine) or a specialist (i.e., rheumatologist, orthopedic surgeon, or physiatrist). If a patient saw only a PCP or only a specialist during the measurement year, the patient was assigned to that group; however, if a patient was treated by both a PCP and a specialist in the same year, the patient was assigned to the specialist group because patients naturally "progress" from PCP to specialist. There were a total of 175 PCPs and 111 specialists who wrote first NSAID prescriptions for patients in this study.

Defining Underuse and Overuse of COX-2s

Patients were divided into low- and high-risk groups based on their risk for an NSAID related GI complication. Patients at high risk, who require NSAID therapy, receive significant benefit from using either a COX-2 inhibitor or by combining a gastroprotective medication with a traditional NSAID. Therefore, in high-risk patients the use of a traditional NSAID without a gastroprotective agent was considered *underuse* of a COX-2. Conversely, patients at no or low risk of a GI complication from NSAIDs would receive little benefit from a COX-2 and prescribing a COX-2 for such a patient was considered *overuse*.

Analysis

We compared characteristics of patients seen by PCPs to those seen by specialists. Dichotomous variables were analyzed using Pearson's χ^2-test. Ordinal and categorical variables were compared with the Mann-Whitney rank-sum test. To see which variables were predictive of COX-2 utilization and overuse/underuse, we performed bivariate comparisons of all demographic variables, including prescriber type, against type of NSAID and appropriateness of the prescription. Multiple logistic regression was used to examine differences between PCP and specialists for both NSAID utilization and overuse/underuse of a COX-2 by forcing the prescriber variable into each model. Data were analyzed using STATA, release 8.0, College Station, TX.

RESULTS

The characteristics of the 1,576 patients started on a traditional NSAID or a COX-2 inhibitor are shown by physician specialty in Table 1. Women comprised 58% of the patients. Primary care patients were younger than those seen by a specialist and were less likely to be taking either a glucocorticoid or an anticoagulant compared with those cared for by specialists.

Utilization

In 1999, the first year COX-2s were available, 28% of NSAID prescriptions received by patients seen by a specialist were for a COX-2 compared with 15% of the prescriptions received by patients seen only by PCPs. Cyclooxygenase-2 prescribing peaked at 58% of NSAID prescriptions for patients seen by specialists in 2000 and at 31% for PCPs in 2001. By 2002, COX-2 prescribing decreased to 35% and 16% for specialists and PCPs, respectively. Over the 4-year period, more than twice as many patients seeing specialists were taking a COX-2 medication than those cared for only in primary care (44% vs 21%, $P<.001$) despite similar GI risk between the 2 groups.

Multivariate analysis showed that 6 variables were predictors of prescribing a COX-2 including a diagnosis of rheumatoid arthritis (odds ratio [OR] 2.54, 95% Confidence Interval

Table 1. Characteristics of 1,576 Patients Started on a Traditional or COX-2 Selective NSAID, by Physician Specialty (1999–2002)

Patient Characteristic	Primary Care Provider $n=1,091$	Specialist $n=485$	P value
Age (years), median	46	49	< .001
Age group			< .01
< 45 years old	48%	39%	
45–54 years old	25%	25%	
55–64 years old	15%	19%	
≥65 years old	12%	17%	
Gender (Female)	59%	56%	.35
Musculoskeletal diagnoses			
Rheumatoid arthritis	1%	6%	< .001
Osteoarthritis	10%	31%	< .001
Other musculoskeletal pain	38%	81%	< .001
History of gastrointestinal problems			
Gastroesophageal reflux disease	14%	14%	.79
Gastric or duodenal ulcer	8%	6%	.45
Upper gastrointestinal bleed	6%	5%	.55
High risk for a gastrointestinal complication from an NSAID	11%	14%	.19
History of vascular disease			
Coronary artery disease	10%	17%	< .001
Other atherosclerosis	23%	26%	.29
Peripheral arterial disease	1%	3%	.10
Diabetes mellitus	6%	7%	.84
Hypertension	23%	23%	.77
Gastrointestinal protective medications			
Proton pump inhibitor	14%	14%	.81
Misoprostol	0%	0%	.99
Other medications			
Glucocorticoids	0%	2%	< 0.001
Anticoagulants	0%	1%	.03

NSAID, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2.

Table 2. Appropriateness of Traditional and COX-2 Specific NSAID Prescribing given a Patient's Risk for A Gastrointestinal Complication While on an NSAID, by Physician Specialty

GI Risk	NSAID Prescribed	Total	*n* (%)		*P*-value*
			Primary care provider	Specialist	
Low	Traditional NSAID	1,029 (74%)	783 (81%)	246 (59%)	< .001
	Cox-2	*358 (26%)*	*185 (19%)*	*173 (41%)*	
High	NSAID+GPA or COX-2	111 (59%)	66 (54%)	45 (68%)	.06
	Traditional NSAID alone	*78 (41%)*	*57 (46%)*	*21 (32%)*	

**Comparing PCP and specialist.*
Text in italics represents inappropriate prescribing practice. COX-2, cyclooxygenase-2 selective; NSAID, nonsteroidal anti-inflammatory drugs; PCP, primary care physicians.

[CI] 1.24, 5.22), osteoarthritis (OR 2.49, 95% CI 1.78, 3.48), other musculoskeletal pain (OR 1.91, 95% CI 1.44, 2.53), gastroesophageal reflux disease (OR 1.92, 95% CI 1.36, 2.71), and age (increasing from an OR 1.82 for patients 45 to 54 years old to an OR 2.93 for patients age 65 years or older compared with patients younger than 45 years old). In addition, seeing a specialist was associated with an almost 2-fold increase in use of a COX-2 (OR 1.92, 95% CI 1.45, 2.54).

COX-2 Underuse

Patients at an increased risk of an NSAID-related GI complication would probably benefit from being prescribed either a COX-2 or a traditional NSAID with a gastroprotective agent. While there was no temporal pattern of underuse of COX-2s, over 40% (n=78) of patients at high GI risk were prescribed neither treatment (see Table 2). Primary care physicians tended to underuse COX-2s more often than specialists did (46% vs 32%, P=.063).

Multivariate analysis demonstrated that among patients at high risk for a GI complication, there was less underuse of COX-2s for those patients with gastroesophageal reflux disease (OR 0.25, 95% CI 0.16, 0.57) and more underuse for patients with diabetes (OR 3.87, 95% CI 1.30, 11.5). There was no difference by physician specialty.

COX-2 Overuse

As most patients (88%) were at low risk of a GI complication on NSAIDs, a larger problem with respect to appropriateness was prescribing COX-2s for patients who would receive limited benefit but would incur extra cost. More than one-quarter of low risk patients received COX-2s (see Table 2).

The trend in overuse of COX-2s among patients at low risk of GI complications was similar to the utilization trend with specialists peaking at 54% in 2000 compared with 31% among PCPs in 2001. By 2002, overuse had decreased to 35% and 14% for patients seen by specialists and PCPs, respectively. This decrease was associated with the institution of prior authorization criteria for COX-2 selective inhibitors within the managed care plan. Over the 4-year period, PCPs were less likely to overuse COX-2s compared with specialists (19% vs 41%, P<.001).

Multivariate analysis demonstrated that 5 variables were significant predictors of overuse: a diagnosis of osteoarthritis (OR 2.78, 95% CI 1.90, 4.07), other musculoskeletal pain (OR 1.89, 95 CI 1.40, 2.58), or gastroesophageal reflux disease (OR 1.91, 95% CI 1.29, 2.82); increasing age (i.e., compared with patients younger than age 45, those who were older had a greater risk of overuse ranging from an OR 1.78 (95% CI 1.27, 2.51) for patients aged 45 to 54 years old to an OR 3.25 (95% CI 1.90, 5.55) for those age 65 or older); and being seen by a specialist (OR 2.08, 95% CI 1.54, 2.82).

DISCUSSION

The most appropriate ways to utilize innovations in medicine is an area open to much debate. Early adopters of medical innovations are more likely to be specialist physicians.[9,10] This makes sense because specialists have advanced training and education in a rather narrow area of medicine compared with the average internist. Specialists have more understanding of a limited number of diseases and are the ones that are performing the diagnostic and therapeutic procedures upon the most difficult to treat patients. They are often among the key opinion leaders in their field and, as such, may feel responsible for pioneering new innovations because of their extended credentials. However, new innovations often lack scientific validation with regard to the clinical scenarios that would best call for their use or application. Newer therapies may not always be better than existing therapies and may lead to added cost, and in instances unexpected adverse clinical events.

Regarding the COX-2 inhibitors, the initial decision of whether or not to use them on a wide scale should have largely been focused on whether the purported GI safety advantage was worth the substantial incremental cost compared with equally efficacious traditional NSAIDs. Results from this study suggest that cost was a less influential factor in the decision making process for specialists. The appeal of a "safer" drug accompanied by heightened promotional efforts appears to have overshadowed the appropriate use of these medications by specialists who were apparently more concerned about GI risk. Primary care physicians less frequently prescribed COX-2s compared with specialists when considering preexisting GI risk factors, especially among patients at low GI risk where the use of the more expensive COX-2 agents has little added benefit for the increased cost. Although we evaluated a convenience sample of patients from a single Mid-western managed care plan, our results are consistent with Sebalt's report that among Canadian patients with osteoarthritis 39% of COX-2 prescriptions were for patients that had no identified GI risk factors and 56% of traditional NSAID prescriptions were for patients that had at least 1 GI risk factor (where concurrent gastroprotection or a COX-2 would be recommended).[11,12] Given current concerns regarding a possible class effect of COX-2s on cardiovascular adverse events, the issue has shifted from cost to safety.[13–15]

There are several limitations in this study. First, we designated patients as receiving care from a PCP or specialist based on the physicians they saw and not by which physician wrote their prescriptions. We believe this better reflects who was managing the patient. Second, by requiring 3 NSAID prescriptions in a calendar year to be considered a chronic user and not having information on over-the-counter products, we underestimate the extent of the problem. Third, since the only information we had for prescribing physicians was their specialty, without a unique physician identifier, we cannot statistically adjust for clustering of patients by physician. However, given that there were 286 different physicians who wrote a first NSAID prescription for the 1,576 patients in this study, we suspect this would not significantly alter the findings.

This study demonstrates the tension between appropriate adoption of innovative therapies for those individuals who would benefit from their use and those individuals who would receive no added clinical benefit but would incur added cost and be placed at increased risk. Those in positions of authority and influence need to exercise prudence with respect to adopting new medications and technologies until their appropriate place in therapy is established. The burden of proof should shift from physicians feeling they need to defend a decision not to prescribe new products to one where they can say to pharmaceutical companies "show me the study" proving your product is safe, cost-effective, and not simply another "me-too" drug.

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