

Prescribing COX-2s for Patients New to Cyclo-oxygenase Inhibition Therapy

Emily R. Cox, PhD; Brenda Motheral, PhD; Mark Frisse, MD*;
Andrew Behm, PharmD; and Doug Mager, BS

Objectives: To profile the pattern of cyclo-oxygenase 2 inhibitor (COX-2) use, including length of therapy, medical conditions treated, and gastrointestinal (GI) risk profile of users.

Study Design: Descriptive retrospective analysis of medical and prescription claims data from a large preferred provider organization in the Midwest.

Methods: During an index period of January through May 31, 2000, patients new to COX-2 therapy were evaluated 365 days before and after their first prescription. Among the inclusion criteria, patients had to have no previous use of COX-2 therapy, be at least 18 years of age, and be continuously eligible during the entire study period.

Results: Of the more than 300 000 members with at least 1 day of coverage in the index window, 1312 members met the inclusion criteria. The average age of COX-2 users was 49.5 years (SD = 11.4) and 60% were female. The number of days' supply of COX-2 agent obtained by members was highly skewed, with a mean of 116 days (SD = 119.5) and a median of 60 days. The medical conditions associated with COX-2 use included a variety of musculoskeletal conditions, the most common being low back pain (22%) and osteoarthritis (18%). Approximately 19% of members did not have a diagnosis associated with COX-2 use. Sixty-five percent of those new to COX-2 therapy did not have an indication of being at risk for GI events, and 68% had no indication for trying a lower-cost nonselective nonsteroidal anti-inflammatory drug (NSAID) prescription prior to beginning COX-2 therapy. Taken together, 45% did not have a GI risk factor or prior use of nonselective NSAID prescription therapy.

Conclusions: These findings suggest that opportunities exist to encourage the cost-effective prescribing of COX-2 therapy. Possible methods include implementation of step therapy, academic detailing, and physician education programs, among others.

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From 1999 to 2000, the per member per year costs for the drug class analgesic anti-inflammatories grew by 37.9%, the highest rate of growth among the top 25 therapy categories, as measured by Express Scripts' *Drug Trend Report*.¹ Contributing to this growth was the introduction of the newer, more expensive cyclo-oxygenase-2 (COX-2) specific inhibitors, whose combined market share grew by approximately 40% from 1999 to 2000.¹ The first COX-2 inhibitor approved in the United States was celecoxib (Celebrex)

in December 1998 and the second, rofecoxib (Vioxx), entered the market in May 1999. Valdecoxib (Bextra) was approved by the US Food and Drug Administration (FDA) in November 2001.

All three COX-2 therapies are approved for relief of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), and for the treatment of primary dysmenorrhea. Celebrex and Vioxx are also approved for the management of acute pain in adults. Additionally, Celebrex is approved as adjuvant treatment of familial adenomatous polyposis. The COX-2 specific inhibitors and nonselective nonsteroidal anti-inflammatory drugs (NSAIDs; eg, ibuprofen, naproxen) have shown similar clinical efficacy at equipotent doses for the management of acute pain and other conditions associated with pain.²⁻¹⁵

Pharmacologically, COX-2 inhibitors are distinct from nonselective NSAIDs because of their ability to selectively inhibit the COX-2 pathway.¹⁶ Nonselective NSAIDs inhibit both COX-1 and COX-2. Inhibition of COX-1 is associated with gastrointestinal (GI) toxicity,⁵ whereas COX-2 inhibition leads to relief of pain and inflammation. The GI toxicity associated with COX-1 inhibiting agents ranges from symptoms such as nausea, dyspepsia, anorexia, abdominal pain, flatulence, and diarrhea, to potentially life-threatening complications such as upper GI bleeding, perforation, and gastric outlet obstruction.¹⁶

It was thought that newly developed drugs designed to block COX-2 but not COX-1 would have anti-inflammatory properties but would avoid the ulcers and other GI events associated with COX-1 inhibition. Two large

From the Office of Research and Planning, Express Scripts, Inc., Maryland Heights, Mo. *Dr. Frisse is now Vice President, First Consulting Group, Chicago, Ill.

Address correspondence to: Emily R. Cox, PhD, Express Scripts, Inc., 13900 Riverport Drive, Maryland Heights, MO 63043. E-mail: ecox@express-scripts.com.

trials designed to test this theory have been conducted: the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial¹⁷ and the Celecoxib Long-Term Arthritis Safety Study (CLASS) trial.¹⁸ In the VIGOR trial, the rate of complicated confirmed upper GI events (ie, perforation, gastric or duodenal ulcer, obstruction, and bleeding) was significantly lower in the rofecoxib group compared with the naproxen group (0.52% vs 1.22%; $P < .005$).¹⁷ However, the CLASS trial, in which celecoxib was compared with traditional NSAIDs (ie, ibuprofen and diclofenac), did not show a statistically significant difference in the rate of ulcer perforation, gastric outlet obstruction, or upper GI bleeding between celecoxib and nonselective NSAIDs (0.76% vs 1.45%; $P = .09$).¹⁸ Although the rate of serious GI complications observed in these studies was low (< 2%), the absolute number of patients affected is large considering the number of individuals currently taking NSAIDs. With an estimated 13 million Americans taking NSAIDs on a regular basis, annual estimates of hospitalization costs due to serious GI complications exceed \$1 billion.¹⁹

Both rofecoxib and celecoxib have been found to be associated with significantly reduced mild-to-moderate GI adverse events (event rates for rofecoxib compared with naproxen²⁰ = 23.5% vs 25.5%, $P = .02$; celecoxib compared with nonselective NSAID¹⁸ = 31.4% vs 36.8%, $P \leq .05$).

One clearly distinguishing feature between COX-2s inhibitors and nonselective NSAIDs is their cost. In 2001, the average wholesale price per prescription was approximately \$98 for Celebrex and \$86 for Vioxx, compared with \$29 for generic nonselective NSAIDs.²¹ Due in part to the cost difference, many researchers question the widespread use of COX-2s based on symptom benefit alone,^{22,23} particularly given that mild symptoms do not correlate well with serious adverse events (perforation, obstruction, ulceration, bleeding) and are often managed clinically with histamine-2 receptor antagonists (H_2 s) and proton pump inhibitors (PPIs). As a result, some researchers recommend that COX-2s be reserved for those patients at high risk for GI adverse events,²⁴ and formal guidelines have been developed to reflect this advice.^{25,26}

The rapid increase in the use of the more expensive COX-2 therapies, coupled with their comparable clinical efficacy to traditional NSAIDs, led to a series of research questions surrounding the use of COX-2s. The goal of our study was to answer these questions:

- What is the pattern of COX-2 use with respect to patient demographics and length of therapy?
- What conditions are COX-2s being used to treat?
- Are these agents being reserved for patients at risk for GI-related events?

METHODS

Medical and prescription claims data from a large preferred provider organization in the Midwest were used to evaluate diagnostic conditions and patterns of use among new COX-2 users. The prescription copay structure varied across members, however. More than 90% of sample members had a 3-tier benefit structure with first-tier co-pays varying from \$8 to \$10, second tier from \$15 to \$20, and third tier from \$25 to \$30. COX-2s were on the third tier, and no other restrictions regarding their use were in place during the time of evaluation (ie, step therapy or prior approval).

New COX-2 users were defined as patients with a prescription claim for a COX-2 during the index window January 1, 2000, to May 31, 2000, and with no COX-2 claim during the 12 months prior to the first claim in the index window. Patient's prescription and medical claims were evaluated 365 days before and 365 days after the index prescription (eg, the first prescription in the index window). Other study inclusion criteria were that patients had to be at least 18 years of age and continuously eligible during the study period.

The COX-2 prescription claims were identified using the generic product identifier (GPI; First Databank [Medispan], Indianapolis, Ind) code beginning "661005." The GPI is a 14-character code consisting of a hierarchy of 7 subsets, each providing more specific information about a drug product. The total days' supply of COX-2 therapy was calculated as the sum of the days' supply field for all COX-2 claims in the 365 days after and including the index prescription.

Medical Conditions

Medical conditions were evaluated using the primary, secondary, and tertiary International Classification of Diseases (ICD-9) fields. **Table 1** outlines the diagnoses considered to be associated with COX-2 use, including how they were defined and measured. Medical conditions were rank ordered with FDA-approved indications ranked highest, followed by non-FDA approved, but possible indications for use. Patients were assigned to a diagnosis hierarchically. For example, patients with more than one of the diagnoses listed were grouped in the diagnosis category higher on the list.

Risk Factors

Prescription and medical claims data were used to identify members with risk factors for NSAID-related GI events. These criteria were adapted from the literature of established and possible risk factors of NSAID-associated GI ulcer.²⁷⁻²⁹ The risk factors used in this study and how they were defined and measured are

Table 1. Diagnoses Associated with COX-2 Use and Method of Identification

Diagnosis	Code	Definition	Percent Meeting Criteria
Osteoarthritis	ICD-9 = 715XX, 7210X, 7213X, or 7219X	a	18.4
Rheumatoid arthritis	ICD-9 = 7140X, 7141X, 7142X, or 7149X; or GPI beginning "6629," "6628," "6625," "13000020," or "52500060"	a	2.6
Psoriatic arthritis	ICD-9 = 6960X	a	0.2
Dysmenorrhea	ICD-9 = 6253X	a	1.1
Low back pain	ICD-9 = 7201X, 7202X, 7208X, 7209X, 7214X, 7221X, 7225X, 7226X, 7227X, 7228X, 7229X, or 724XX	a	21.8
Other and unspecified arthropathies, knee or other joint derangement, other and unspecified disorders of the joint	ICD-9 = 716XX, 717XX, 718XX, or 719XX	a	19.5
Cervical disc disorders	ICD-9 = 7220X, 7224X	a	0.7
Dislocations	ICD-9 = 830XX through 839XX	a	0.1
Sprains and strains of joints and adjacent muscles	ICD-9 = 840XX through 848XX	a	2.8
Disorders of the muscles and tendons and their attachments, and of other soft tissues	ICD-9 = 725XX through 729XX	a	6.4
Osteopathies, chondropathies, and acquired musculoskeletal deformities	ICD-9 = 730XX through 739XX	a	1.8
Carpal tunnel	ICD-9 = 3540X	a	0.4
Fractures	ICD-9 = 800XX through 829XX	a	0.3
Abdominal pain	ICD-9 = 7890X	a	2.7
Hospital stay	Revenue codes = 100-139, 140-149, 150-169,190-219	b	0.9
Cervicalgia	ICD-9 = 7231X	a	0.2
Vaginismus	ICD-9 = 6251X, 6262X	a	0.2
Headache	ICD-9 = 7840X	a	1.1
Organ transplant	ICD-9 = V42, V43	a	0.2
None of the above			18.7

n = 1312.

a = 365 days before or 120 days after the index prescription.

b = 2 or more days' inpatient hospital stay occurring 365 days before or 120 days after the index prescription.

COX-2 indicates cyclo-oxygenase 2 inhibitor; GPI, generic product identifier; ICD-9, *International Classification of Diseases, 9th Edition*.

presented in **Table 2**. Risk for GI-related events was defined as any one of the following factors: history of a GI event; age 60 years or older; recent use of anticoagulant or corticosteroid agents; and higher doses of COX-2 therapy. History of a GI event included diagnosis of gastric, duodenal, or peptic ulcers; *Helicobacter pylori* infection; GI hemorrhage; and evidence of an endoscopy. Prior use of gastroprotective agents (ie, PPIs and H₂ blockers) was also included as a GI risk factor given recent evidence in the literature suggesting that use of these agents may serve as a proxy for GI

risk.^{30,31} Although not established risk factors, we also included acid-related diagnoses such as gastroesophageal reflux disease, heartburn, and esophagitis, including ulceration or perforation of the esophagus. These factors were included to be as generous as possible in identifying individuals as possible at risk for GI events, recognizing the limitations of claims data and the time over which we evaluated GI risk. As a sensitivity analysis, and because of the lack of specificity around the age criteria, we also included estimates of GI risk using age ≥ 65 years.

Table 2. Gastrointestinal Risk Factors and Method of Identification

GI Risk Factor	Code	Definition	n (%) Meeting Criteria
Advanced age: criteria 1		Age \geq 60 calculated as of January 1, 2000, from eligibility file	247 (18.8)
Advanced age: criteria 2		Age \geq 65 calculated as of January 1, 2000, from eligibility file	89 (6.8)
History of GI event			216 (16.5)*
Ulcer; <i>H pylori</i> ; endoscopy; iron deficiency anemia secondary to blood loss; or GI hemorrhage including melena	ICD-9 = 531XX, 532XX, 533XX, 534XX, 04186, 2800X, or 578XX or procedure code = 43200 through 43259, or GPI beginning "4999"	Diagnosis or procedure in previous 12 months or at least one prescription claim in previous 12 months	58 (4.4)
Prior use of misoprostol, H ₂ , PPI, or sucralfate	GPI beginning "4920," "4927," "4930," or "4925"	\geq 120 days supply in previous 12 months	148 (11.3)
Gastritis and duodenitis	ICD-9 = 535XX	Diagnosis in previous 12 months	24 (1.8)
Esophagitis; perforation or ulcer of esophagus; GERD; or heartburn	ICD-9 = 5301X, 5302X, 5304X, 5308X, or 7871X	Diagnosis in previous 12 months	62 (4.7)
Concomitant use of corticosteroid agents	GPI beginning "22"	2 or more claims 180 days before or after index prescription	76 (5.8)
Concomitant use of anticoagulant agents	GPI beginning "8320"	2 or more claims 180 days before or after index prescription	33 (2.5)
Higher doses of COX-2s: calculated with index window		> 400 mg for celecoxib and > 50 mg/d for rofecoxib	8 (0.6)
Percent with any risk factor		Subjects meeting at least one of the above criteria	466 (35.5)*
Percent with any risk factor		Subjects meeting at least one of the above criteria	356 (27.1)*

n = 1312.

*Percentages are not additive because some individuals had 1 or more risk factors.

COX-2 indicates cyclo-oxygenase 2 inhibitor; GERD, gastroesophageal reflux disease; GI, gastrointestinal; GPI, generic product identifier; H₂, histamine-2 receptor antagonist; ICD-9, *International Classification of Diseases, 9th Edition*; and PPI, proton pump inhibitor.

RESULTS

Of the 319 263 members with at least 1 day of enrollment during the index window, 5561 had a COX-2 prescription claim. After screening for eligibility and age, 2450 members remained. An additional 1138 were excluded due to prior use of a COX-2, resulting in a final sample size of 1312.

Sample Demographics and Patterns of Use

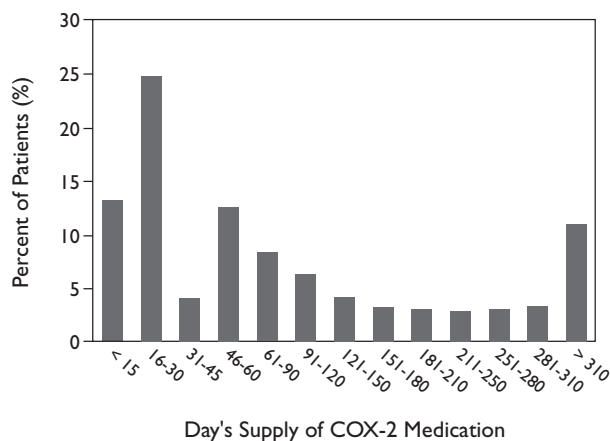
Approximately 60% of those new to COX-2 therapy were female; the mean age was 49.5 years (SD = 11.4). The days' supply among new COX-2 users during the 365-day follow-up was highly skewed (**Figure**). The

mean days' supply was 116 days (SD = 119.5) and the median was 60 days.

Medical Conditions

Approximately 19% (n = 245) of members had no medical condition that would indicate the need for a COX-2 inhibitor (Table 1). The diagnosis representing the largest proportion of new COX-2 users was low back pain (22%). Next were diagnoses related to joint pain and inflammation including OA (18%) and joint derangements and other unspecified disorders of the joint (20%). Other conditions related to COX-2 use included various disorders of the muscle tissue and soft tissue, including sprains and strains (3%), disorders of

Figure. Distribution of COX-2 Supply Among New Users (n = 1312) During 365-Day Follow-Up



the muscles and tendons and their attachments (6%), and RA (3%).

Risk Factors

Table 2 profiles the percent of members meeting each of the GI risk factor criteria and the percent with 1 or more risk factor. Among individuals new to COX-2 therapy, 18.8% met the age criterion of being at least 60 years. Increasing the age criterion to a minimum of 65 years decreased the absolute percentage meeting the criteria by 12 percentage points to 6.8%. Approximately 17% had a history of GI problems, the vast majority of which represented prior use of gastroprotective agents. Approximately 6% and 3%, respectively, had recent use of corticosteroid agents or anticoagulant agents.

Overall, using the age criterion of a minimum of 60 years, 65% of persons new to COX-2 therapy had no evidence of being at risk for NSAID-related GI problems. Using the age criterion of a minimum of 65 years, 73% of those new to COX-2 therapy had no evidence of being at risk for NSAID-related GI problems.

Prior Use of Nonselective Nonsteroidal Anti-inflammatory Drug Therapy

Approximately 68% of new COX-2 users did not have a claim for a nonselective NSAID during the 1 year prior to beginning their COX-2 therapy. The likelihood of using a nonselective NSAID prior to COX-2 use was not significantly different among those with and without a GI risk factor ($\chi^2 = 1.07, P = .302$). Taken together, approximately 45% of new COX-2 users did not have a GI risk factor or prior use of a nonselective NSAID agent.

DISCUSSION

The profile of COX-2 use within our sample was for predominantly short-term treatment of a variety of musculoskeletal conditions. Such individuals are often not at risk for GI events, or have not tried a lower-cost nonselective NSAID agent prior to beginning COX-2 therapy. These findings suggest the need for more cost-effective prescribing of COX-2 medications among those new to therapy. This conclusion is based on findings of the sensitivity of COX-2 cost-effectiveness models to assumptions regarding the underlying GI risk of the modeled population,³²⁻³⁴ and no evidence to suggest that COX-2s are cost effective in the short-term treatment of pain. When cost-effectiveness models evaluate the sensitivity of results to assumptions regarding GI risk, incremental costs per event avoided go beyond that considered economically acceptable^{32,34} or differences in total expected costs between COX-2s and nonselective NSAIDs are practically indistinguishable.³³

Several study limitations may limit generalizability of the study findings. The data represent only one plan's experience, and COX-2 prescribing patterns could vary depending on numerous factors including physician incentives and plan design. Limitations of medical claims data, particularly to identify specific diagnoses, are also recognized.³⁵ Diagnoses associated with COX-2 use or GI risk may have been missed because of under-coding. We attempted to overcome these limitations through inclusion of gastroprotective agent therapy identified using prescription claims data, which has been shown to be a reliable and valid source of data compared with medical claims data.^{36,37} The time during which we evaluated individual history of GI events was limited to 365 days. We recognize that a GI event could have occurred prior to this look-back period. However, we were generous in our definition of GI risk (ie, meeting any one criteria), possibly overstating the percent with GI risk. Further research, using a longer look-back period or medical record review, would need to be conducted to determine the extent of false-negative or false-positive identification of risk.

The conditions for which COX-2s appeared to be used included a variety of musculoskeletal conditions. Although COX-2s are indicated for acute pain, the fact that close to 1 in 4 new COX-2 users appeared to be prescribed such therapy for the treatment of low back pain was a surprising finding. Etiology of low back pain is often difficult to determine, and the manifestations can include both inflammatory and noninflammatory pain. Some proportion of COX-2 therapy is likely for low back pain associated with OA; however, further analysis would be needed to determine the extent of

OA within this diagnosis category. Approximately 20% of members did not have a diagnosis that would be an indication for COX-2 use, which could be related to the limitations of medical claims data discussed earlier, or use of COX-2 inhibitors in dental practice, data not captured in our medical claims database.

Forty-five percent of new COX-2 users—individuals with no GI risk or prior traditional NSAID use—were given a COX-2 inhibitor as first line-therapy when lower-cost nonselective NSAIDs might have been the most cost-effective approach. The premise of this conclusion rests on the wealth of research evaluating predictors of NSAID-associated GI complications, no evidence of superior clinical efficacy of COX-2s, and no evidence of the cost effectiveness of COX-2s in patients not at risk for GI events. The research on predictors of NSAID-related GI events have resulted in a generally accepted list of factors thought to significantly increase a patient's risk of developing an NSAID-related GI ulcer.^{27-29,38-40} While the presence of any 1 risk factor is an important determinant in predicting overall GI risk, the presence of more than 1 factor has also been shown to increase a patient's risk for GI toxicity. Silverstein and colleagues noted that among the 4 risk factors found to be significantly related to the risk of serious upper GI complications, patients with no risk factor have a 0.4% risk for having a serious GI complication, those with any 1 risk factor have ~1% risk, and those with all 4 risk factors a 9% risk.⁴¹

The evidence of GI risk should also take into consideration the fact that more than half of the patients who were new to COX-2 therapy obtained at most a 60 days' supply of therapy during the 1-year follow-up. This pattern of use is not unlike that observed in studies of OA patients prescribed nonselective NSAIDs—half of the patients on aspirin, ibuprofen, naproxen, or piroxicam had discontinued therapy after 66, 53, 51, and 120 days, respectively.⁴²

With regard to duration of therapy and the risk of nonselective NSAID-related GI adverse events, whereas the relative risk of adverse GI events is greatest within the first month of therapy,⁴⁰ findings from the Arthritis, Rheumatism, and Aging Medical Information System database (ARAMIS) suggest that the risk of GI bleed remains constant during a 10-year follow-up.²⁸ The ARAMIS findings indicated that patients taking NSAIDs for 5 years have a 5-times greater risk of bleeding than do patients taking NSAIDs for 1 year. The bleeding risk for individuals undergoing NSAID therapy for 3 months was one quarter that for individuals taking NSAIDs for 1 year. The degree of GI risk associated with short-term NSAID use is an important issue for further research, given the large amount of short-term COX-2 use.

The high proportion of COX-2 use by persons with no evidence of GI risk or trial of nonselective NSAID, together with the substantial amount of short-term use, suggest that steps could be taken to encourage more cost-effective prescribing of COX-2 agents. Ways in which plans can encourage the cost-effective prescribing of COX-2s include programs such as step therapy, prior approval, and academic detailing. Step therapy is a program designed to manage the use of select or first-line therapies (ie, nonselective NSAIDs) before alternative or second-line therapies (ie, COX-2s) are covered. These programs are typically automated at the point of service. The limitation of step therapy for NSAIDs is that this strategy does not take into consideration the GI risk profile of the patient.

Prior authorization requires that approval for the product be given prior to prescribing the product. The criteria for determining approval can vary, but in the case of COX-2s, could include the generally agreed upon list of established risk factors.²⁷ Prior approval has the advantage of ensuring that these high-cost products are reserved for patients at risk for NSAID-related GI events; however, plans would have to balance program costs carefully against the potential savings given the high volume of calls that such a program could generate. To overcome the limitations of both step therapy and prior approval for this therapy class, some plans have used a combination of step therapy and prior approval using an automated process at the point of service.

An example of a combined step therapy–prior approval program was described by Tucker and colleagues.⁴³ Their step therapy component included prior use of nonselective NSAIDs and the prior approval component included checks for GI risk (ie, prior use of a gastroprotective agent or other ulcer treatment, or anticoagulant or antiplatelet therapy).⁴³ Other criteria could also be automated, including patient age and use of corticosteroids. When implementing prior approval programs for COX-2s, plan administrators should be aware that the age selected as the criterion for increased GI risk is important in determining the overall percent of members who would be affected by these programs. Our results varied by approximately 8 percentage points when the age criterion was 60 versus 65 years. There is no definitive age at which a person suddenly is at risk for an NSAID-related GI event; rather, findings suggest that the relationship between GI risk and age is linear, increasing steadily by ~4% per year increase in age.²⁸

Evidence that plans are implementing academic detailing or physician education programs for COX-2s has also appeared in the literature.²⁵ Treatment guidelines based on The Standardized Calculator of Risk for

Events (SCORE) criteria were disseminated among physicians of a northern California HMO and reinforced through academic detailing by drug education pharmacists. SCORE is an instrument designed to estimate an individual's risk for serious NSAID-induced GI toxicity (eg, stomach ulcer or bleeding ulcer).^{44,45} It is based on 6 criteria: age, self-reported health status, diagnosis of RA, use of oral corticosteroids, hospitalization for a stomach or intestinal problem or prior history of stomach ulcer, and history of GI side effects (heartburn, stomach pain, nausea, vomiting) when taking NSAIDs. SCORE was developed by researchers at Stanford University using data from ARAMIS.⁴⁵

These examples are just some of the steps plan sponsors are taking to encourage the cost-effective use of COX-2 therapy. As more health plans move toward adoption of these programs, research should be conducted to ensure that the risk identification tools avoid false-negative results (ie, those with risk are identified as not having risk) and false-positive results (ie, those without risk are identified as having risk). Such research is critical to the provision of quality, cost-effective healthcare.

REFERENCES

1. Teitelbaum F, Martinez R, Parker A, Kolling B, Svirnovskiy Y. 2000 Drug Trend Report. Maryland Heights, Mo: Express Scripts, Inc; June 2001.
2. Celebrex [package insert]. Skokie, Ill: G.D. Searle & Co; April 24, 2000.
3. Vioxx [package insert]. Whitehouse Station, NJ: Merck & Co; July 2000.
4. Bensen WG, Fiechtner JJ, McMillen JJ, et al. Treatment of osteoarthritis with celecoxib, a cyclo-oxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc.* 1999;74:1095-1105.
5. Simon LS, Weaver AL, Graham DY, et al. Anti-inflammatory and upper gastrointestinal effects of celecoxib in rheumatoid arthritis: a randomized controlled trial. *JAMA.* 1999;282:1921-1928.
6. Emery P, Zeidler H, Kvien TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomized double-blind comparison. *Lancet.* 1999;354:2106-2111.
7. Dougados M, Behier MJ, Jolchine I, et al. Efficacy of celecoxib, a cyclo-oxygenase 2-specific inhibitor, in the treatment of ankylosing spondylitis. *Arthritis Rheum.* 2001;44:180-185.
8. Acevedo E, Castaneda O, Ugaz M, et al. Tolerability profiles of rofecoxib (Vioxx) and Arthrotec. *Scand J Rheumatol.* 2001;30:19-24.
9. Day R, Morrison B, Luza A, et al. A randomized trial of the efficacy and tolerability of the COX-2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. *Arch Intern Med.* 2000;160:1781-1787.
10. Saag K, Van Der Heijde D, Fisher C, et al, for the Osteoarthritis Studies Group. Rofecoxib, a new cyclo-oxygenase 2 inhibitor, shows sustained efficacy, comparable with other non-steroidal anti-inflammatory drugs. *Arch Fam Med.* 2000;9:1124-1134.
11. Cannon GW, Caldwell JR, Holt P, et al, for the rofecoxib phase III protocol 035 study group. Rofecoxib, a specific inhibitor of cyclo-oxygenase 2, with clinical efficacy comparable with that of diclofenac sodium. *Arthritis Rheum.* 2000;43:978-987.
12. Malmstrom K, Daniels S, Kotey P, et al. Comparison of rofecoxib and celecoxib, two cyclo-oxygenase-2 inhibitors, in postoperative dental pain: a randomized, placebo- and active-comparator-controlled clinical trial. *Clin Ther.* 1999;21:1653-1663.
13. Morrison BW, Christensen S, Yuan W, et al. Analgesic efficacy of the cyclo-oxygenase-2-specific inhibitor rofecoxib in post-dental surgery pain: a randomized, controlled trial. *Clin Ther.* 1999;21:943-953.
14. Morrison BW, Daniels SE, Kotey P, et al. Rofecoxib, a specific cyclo-oxygenase-2 inhibitor, in primary dysmenorrhea: a randomized controlled trial. *Obstet Gynecol.* 1999;94:504-508.
15. Reicin A, Brown J, Jove M, et al. Efficacy of single-dose and multidose rofecoxib in the treatment of post-orthopedic surgery pain. *Am J Orthop.* 2001;30:40-48.
16. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclo-oxygenase-2. *N Engl J Med.* 2001;345:433-442.
17. Bombadier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med.* 2000;343:1520-1528.
18. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *JAMA.* 2000;284:1247-1255.
19. Singh G, Ramey DR. NSAID induced gastrointestinal complications: the ARAMIS perspective—1997. *J Rheumatol.* 1998;25(suppl 51):8-16.
20. Langman MJ, Jensen DM, Watson DJ, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. *JAMA.* 1999;282:1929-1933.
21. Teitelbaum F, Martinez R, Parker A, Kolling B, Svirnovskiy Y. 2001 Drug Trend Report. St. Louis, Mo: Express Scripts, Inc; 2002.
22. Lichtenstein DR, Wolfe MM. COX-2-selective NSAIDs: new and improved? *JAMA.* 2000;284:1297-1299.
23. Peterson WL, Cryer B. COX-1-sparing NSAIDs—is the enthusiasm justified? *JAMA.* 1999;282:1961-1963.
24. McCarthy DM. Prevention and treatment of gastrointestinal symptoms and complications due to NSAIDs. *Best Pract Res Clin Gastroenterol.* 2001;15:755-773.
25. Bull SA, Conell C, Campen DH. Relationship of clinical factors to the use of COX-2 selective NSAIDs within an arthritis population in a large HMO. *J Manage Care Pharm.* 2002;8:252-258.
26. National Institute for Clinical Excellence. Guidance on the use of cyclo-oxygenase (COX) II selective inhibitors, celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. Technology Appraisal Guidance No. 27. London: National Institute for Clinical Excellence; July 2001. Available at: <http://www.nice.org.uk>. Accessed July 18, 2003.
27. Wolfe MM, Lichtenstein DR, Singh G. Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. *N Engl J Med.* 1999;340:1888-1899.
28. Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med.* 1998;105:31S-38S.
29. McCarthy D. Nonsteroidal anti-inflammatory drug-related gastrointestinal toxicity: definitions and epidemiology. *Am J Med.* 1998;105:31S-38S.
30. Wolfe F, Anderson J, Burke TS, Arguelles LM, Pettitt D. Gastroprotective therapy and risk of gastrointestinal ulcers: risk reduction by COX-2 therapy. *J Rheumatol.* 2002;29:467-473.
31. Garcia Rodriguez LA, Hernandez-Diaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. *Epidemiology.* 2001;12:570-576.
32. Fendrick AM, Bandekar RR, Chernew ME, Scheiman JM. Role of initial NSAID choice and patient risk factors in the preven-

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- tion of NSAID gastropathy: a decision analysis. *Arthritis Care Res.* 2002;47:36-43.
- 33. Chancellor JVM, Hunsche E, de Cruz E, Sarasin FP.** Economic evaluation of celecoxib, a new cyclo-oxygenase 2 specific inhibitor, in Switzerland. *Pharmacoeconomics.* 2001;19(suppl 1):59-75.
- 34. Zabinski RA, Burke TA, Johnson J, et al.** An economic model for determining the costs and consequences of using various treatment alternatives for the management of arthritis in Canada. *Pharmacoeconomics.* 2001;19(suppl 1):49-58.
- 35. Motheral BR, Fairman KA.** The use of claims databases for outcomes research: rationale, challenges, and strategies. *Clin Ther.* 1997;19:346-366.
- 36. Tamblyn R, Lavoie G, Petrella L, Monette J.** The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Québec. *J Clin Epidemiol.* 1995;48:999-1009.
- 37. Kirking DM, Ammann MA, Harrington CA.** Comparison of medical records and prescription claims files in documenting prescription medication therapy. *J Pharmacoepidemiol.* 1996;5(1):3-15.
- 38. Fries JF.** A scoring system that identified high-risk patients: NSAID gastropathy: epidemiology. *J Musculoskel Med.* 1991;8(2):21-28.
- 39. Fries JF, Williams CA, Bloch DA, Michel BA.** Nonsteroidal anti-inflammatory drug-associated gastropathy: incidence and risk factor models. *Am J Med.* 1991;91:213-222.
- 40. Gabriel SE, Jaakkimainen L, Bombardier C.** Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. *Ann Intern Med.* 1991;115:787-796.
- 41. Silverstein FE, Graham DY, Senior JR, et al.** Misoprostol reduced serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. *Ann Intern Med.* 1995;123:241-249.
- 42. Scholes D, Stergachis A, Penna PM, Normand EH, Hansten PD.** Nonsteroidal antiinflammatory drug discontinuation in patients with osteoarthritis. *J Rheumatol.* 1995;22:708-712.
- 43. Tucker G, Moore A, Avant D, Monteiro M.** A cost analysis of four benefit strategies for managing a COX-II inhibitor. *J Managed Care Pharm.* 2001;7:224-227.
- 44. Singh G, Terry R, Ramey DR, Triadafilopoulos G, Brown BW.** GI SCORE: a simple self-assessment instrument to quantify the risk of serious NSAID-related GI complications. *Arthritis Rheum.* 1997;40(suppl):S93.
- 45. Singh G, Triadafilopoulos G.** Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol.* 1999;26(suppl 56):18-24.