

COX-2-Specific Inhibitors: Prescribing Patterns in a Large Managed Care Health System and Strategies to Minimize Costs

Rick A. Weideman, PharmD, BCPS; Kevin C. Kelly, PharmD, BCPS; Catherine L. Kelley, PharmD, BCPS; and Byron Cryer, MD

Objective: To determine the relative costs associated with the exclusive use of celecoxib versus rofecoxib in a large managed care system.

Study Design: A retrospective review of all calendar year 2000 prescriptions dispensed for celecoxib and rofecoxib in the Veterans Affairs (VA) system.

Methods: The primary data points included drug strength, quantity dispensed, and days supply for the prescription. The cost minimization model described in *Federal Practitioner* (1999;16[4]:41-44) was used to calculate the cost savings. The mean once-daily dosing rates and their 95% confidence intervals were determined by binomial data analysis. Calendar year 2001 utilization and cost projections were derived by linear regression trend analysis.

Results: Current VA system costs per dose are celecoxib 100 mg \$0.66; celecoxib 200 mg \$1.32; rofecoxib (12.5 or 25 mg) \$1.32; rofecoxib 50 mg \$2.14. During calendar year 2000, the VA spent \$13.8 million and \$4.2 million on celecoxib and rofecoxib, respectively. The percentage of once-daily or less than once-daily dosing was celecoxib 100 mg (17%), celecoxib 200 mg (67%), celecoxib overall (49%), rofecoxib 12.5 mg (86%), rofecoxib 25 mg (94%), rofecoxib 50 mg (100%), and rofecoxib overall (93%). Based on current utilization, if all celecoxib prescriptions were changed to rofecoxib, the VA would have realized annual cost savings of \$2.1 million in calendar year 2000. In calendar year 2001, projected cost savings could total \$5.2 million. This potential savings is largely due to the high prevalence of twice-daily celecoxib dosing.

Conclusion: The results of the cyclooxygenase-2 cost minimization analysis provide a compelling argument for the preferred use of rofecoxib in the VA system, and potentially in other managed care systems.

(*Am J Manag Care* 2002;8:869-877)

either prescribed or over the counter.¹ Seventy percent of individuals over the age of 65 use NSAIDs weekly.² The widespread use of NSAIDs is, in large part, attributed to the high prevalence of osteoarthritis and rheumatoid arthritis, conditions for which NSAIDs are effective. Despite their effectiveness, however, use of NSAIDs is associated with a broad spectrum of untoward reactions, most notably, significant upper gastrointestinal (GI) events.

The primary mechanism thought to be responsible for NSAID-induced GI events is inhibition of the enzyme cyclooxygenase (COX)-1 in the GI tract. Inhibition of COX-1 leads to a reduction of protective gastrointestinal mucosal prostaglandins and therefore potentially increases GI injury. Nonsteroidal anti-inflammatory drugs that selectively inhibit COX-2 have the benefit of reducing inflammation to an extent comparable to nonselective NSAIDs while having a much lower rate of ulceration and untoward GI events, a property that is largely a consequence of their lack of inhibition of the gastroprotective COX-1 isoform. Although several NSAIDs have been suggested to be COX-1 sparing, the 2 most common agents accepted as COX-2-specific inhibitors are celecoxib and rofecoxib.

Celecoxib received US Food and Drug Administration (FDA) approval for marketing in December 1998 and rofecoxib received approval in May 1999.

From the Veterans Affairs Health Care System, Dallas, Tex (RAW, KCK, BC); the Veterans Affairs Pharmacy Benefits Management at Hines, Ill (CLK); and the Department of Medicine, University of Texas Southwestern Medical School, Dallas, Tex (BC).

This study was funded by the VA Health Care System through existing intramural funds.

Address correspondence to: Rick A. Weideman, PharmD, BCPS, Department of Veterans Affairs, North Texas Health Care System, 4500 South Lancaster Road, Dallas, TX 75216. E-mail: Rick.Weideman@med.va.gov.

Worldwide, nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed more frequently than any other group of medicines. It is estimated that during the course of a year nearly 1 in 5 Americans will be treated with an NSAID,

Since that time, prescriptions for these COX-2-specific inhibitors have markedly increased, either through substitution of existing prescriptions for traditional NSAIDs or through expanding the NSAID market by attracting clinicians to prescribe these agents to patients who had previously not been prescribed NSAIDs because of their perceived risk for NSAID-induced GI events (RAW, unpublished data, 2001). Indeed, numerous studies, showcased in package inserts, have described a decreased incidence of endoscopic ulcers for celecoxib and rofecoxib while providing similar efficacy compared with nonselective NSAIDs; however, celecoxib and rofecoxib are more expensive than many traditional NSAIDs. Accordingly, new and recurring prescriptions for COX-2-specific inhibitors have had a major impact on drug formularies in most healthcare systems, including that of the Veterans Affairs (VA), the nation's largest integrated healthcare system.

Most managed care organizations have instituted algorithms for the appropriate prescribing of COX-2-specific inhibitors, to some extent as an attempt to control the cost impact that these agents might have on formulary budgets. Many current algorithms for the prescribing of COX-2 inhibitors are focused on restricting the use of celecoxib and rofecoxib to patients who are at high risk for NSAID-induced GI events. Despite such guidelines, prescriptions for COX-2-specific inhibitors have continued to rise, as has their cost impact on drug formulary budgets. And, prescriptions for these agents will likely continue to increase in the future. Accordingly, additional approaches to minimize the formulary cost impact of COX-2-specific inhibitors are needed.

One approach to reduce a medication's formulary cost impact is to evaluate postmarketing drug utilization patterns and to use that data to refine prescribing guidelines. Because COX-2-specific inhibitors have been clinically available for almost 2 years, we believed that extensive utilization information on these agents would be available through an analysis of accumulated data in a large managed care network such as the VA healthcare system. We therefore performed a cost analysis based on national medication utilization patterns of COX-2-specific inhibitors in the VA and compared those observations with a utilization calculation model that estimates the frequency and costs of drug utilization.³ Each of these methods of analysis incorporates drug costs, drug utilization patterns, dose unit strength information, and frequency of dosing to assess systemwide impact of products within a drug class. As with all cost minimization analyses,

safety and efficacy of the agents are assumed to be equivalent and the products are assumed to be treating the same diseases equally. Equivalence in safety and efficacy is ideally determined by rigorous scientific studies.

Currently, debate is ongoing regarding the efficacy and safety similarities, or differences, between COX-2 inhibitors.⁴⁻⁸ Studies have suggested superiority of one agent over another for safety⁶ and efficacy⁷ and other studies maintain comparable safety⁷ and efficacy.⁸ However, many managed care organizations, including the VA, have criteria⁹ that do not differentiate among these agents. Thus, in practice, these agents are considered equivalent and therefore meet the criteria for a cost minimization analysis.

.....
METHODS

Nationwide use of COX-2-specific inhibitors in the VA health system was evaluated by reviewing dispensing data for these agents in calendar year 2000. This information was provided by the VA Pharmacy Benefits Management group, located in Hines, Ill. This group, in addition to many other functions, collects data on all national VA prescriptions dispensed.

Data collection for every COX-2 NSAID prescription included a scrambled unique patient identifier; the drug product name and strength (eg, "celecoxib 100 mg" or "rofecoxib 12.5 mg"); the total unit (tablet or capsule) quantity dispensed; the total days' supply; and the cost per dispensed unit at the time the prescription was dispensed. Using these data, we calculated the frequency of dosing of celecoxib and rofecoxib and the cost impacts these dosing patterns had on the VA system.

We also calculated medication utilization patterns by using a model that estimates frequency of drug utilization, as previously described by Weideman et al.³ Rather than calculating frequency of dosing based on a review of thousands of individual prescriptions, this model uses the national average number of units per day dispensed for each dosage form of celecoxib and rofecoxib to estimate mean percentages (and binomial confidence intervals) of once-daily dosing for these COX-2 NSAIDs according to the method described by Zar.¹⁰ Each method of depicting frequency of dosing, that is either by calculation or by estimation through modeling, produces nearly identical results, as will be shown below in the Results section.

Systemwide costs of celecoxib and rofecoxib were then calculated for calendar year 2000. Next, we

projected the nationwide VA formulary costs of switching to a celecoxib-exclusive or a rofecoxib-exclusive formulary in calendar year 2000. To perform these projections, we assumed that under a single product exclusive formulary, the distribution and frequency of products dispensed at a given dosage strength (eg, percent of total prescriptions of celecoxib dispensed at 100 mg and 200 mg at frequencies of dosing of daily, twice daily, etc) would maintain current proportions.

Finally, based on calendar year 2000 utilization patterns, we projected the national VA COX-2 NSAID utilization and costs for calendar year 2001. These calculations were based on the cumulative treatment days for celecoxib and rofecoxib and assumed the same linear rate of growth for both agents in 2001 as was observed in 2000. Specifically, we used linear regression of the monthly rate of increase over 1 year in utilization of each product during calendar year 2000 to obtain calendar year 2001 utilization and cost estimates.

RESULTS

Table 1 demonstrates 2001 VA system costs and average wholesale price (AWP) per dose for the COX-2-specific inhibitors, celecoxib and rofecoxib.¹¹ Depending on the indication, celecoxib may be prescribed 100 mg twice daily, 200 mg once or twice

daily, or 400 mg twice daily; rofecoxib may be prescribed 12.5, 25, or 50 mg once daily. Thus, daily drug costs may be nearly identical or may vary widely depending on COX-2-specific inhibitor dose and frequency.

Among variables that could impact formulary costs of COX-2 inhibitors, frequency of dosing is one that could potentially have the greatest effect on overall costs. **Table 2** highlights differences in prescribing patterns for COX-2-specific inhibitors in the national VA health system. For example,

Table 1. Unit Cost of Celecoxib and Rofecoxib to VA and AWP (April, 2001)

Drug	VA Cost (\$)	AWP(\$)*
Celecoxib		
100 mg	0.66	1.49
200 mg	1.32	2.52
Rofecoxib		
12.5 mg	1.32	2.52
25 mg	1.32	2.52
50 mg	2.14	3.68

VA indicates Veterans Affairs; AWP, average wholesale price.
*2001 Drug Topics Red Book¹¹

Table 2. Dispensing Data for COX-2 Inhibitors in National VA System

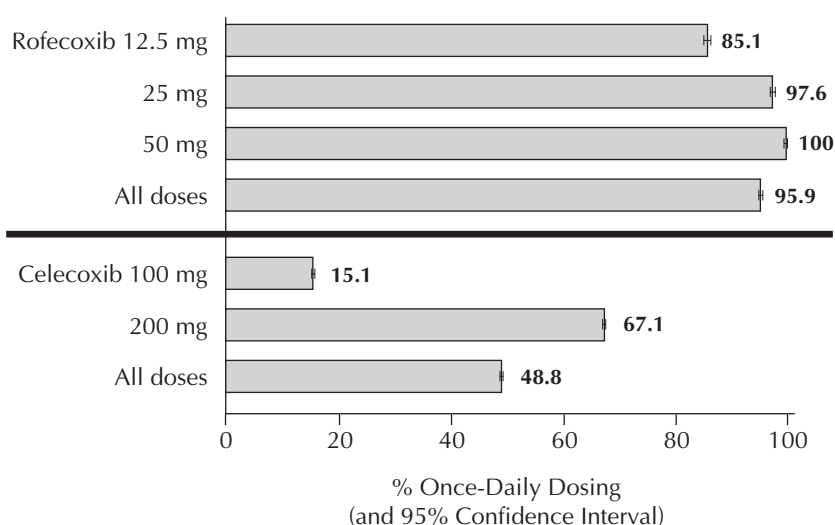
Drug	Total Units	Percent of Product Dispensed at a Given Strength (%)	Treatment Days	Average Units/Day	Frequency of Dosing			
					Less Than Once Daily (%)*	Once Daily (%)	Twice Daily (%)	More Than Twice Daily (%)
Celecoxib								
100 mg cap	5 076 439	35	2 746 267	1.85	0	17	81	2
200 mg cap	6 717 847	65	5 056 180	1.33	0	67	32	1
Rofecoxib								
12.5 mg tab	508 540	15	442 707	1.15	1	85	13	1
25 mg tab	2 199 117	74	2 146 543	1.02	8	86	6	0
50 mg tab	178 904	11	300 880	0.59	80	20	0	0

COX-2 indicates cyclooxygenase-2; VA, Veterans Affairs; cap, capsules; tab, tablets.

*The "Less Than Once Daily" column should be added to the "Once Daily" column since it likely reflects split tablets taken once daily.

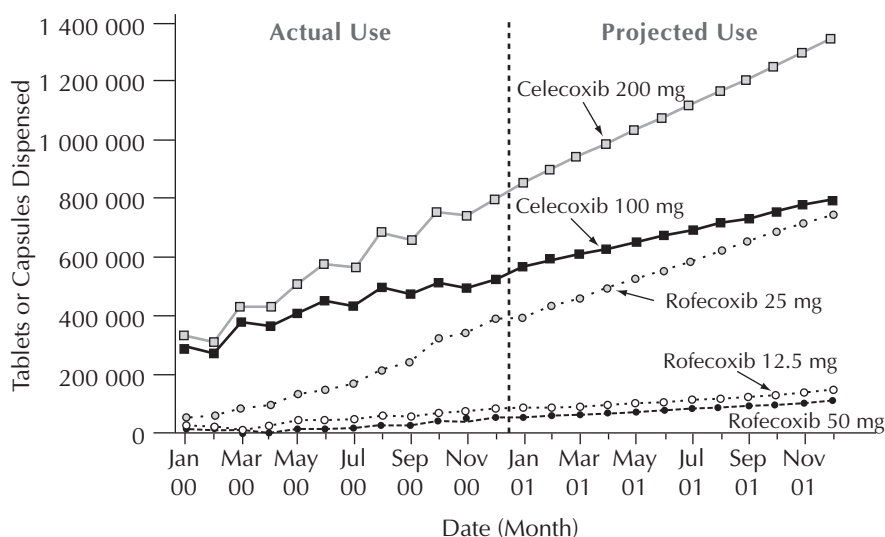
COST CONTROL

Figure 1. Frequency of Drug Utilization



Using the national average number of units per day dispensed for each dosage form of celecoxib and rofecoxib, mean percentages (and binomial confidence intervals) of once-daily dosing of celecoxib and rofecoxib were estimated.

Figure 2. Actual and Projected Number of Tablets or Capsules of Cyclooxygenase-2 Inhibitors Dispensed Monthly Throughout the National Veterans Affairs System



Actual use data are for calendar year 2000 and projected use data are for calendar year 2001.

35% of the prescriptions for celecoxib were dispensed for the 100-mg strength whereas 65% were for the 200-mg strength. Rofecoxib 12.5-, 25-, and 50-mg tablets accounted for 15%, 74%, and 11% of dispensed rofecoxib tablets, respectively. The percentage of each COX-2-specific inhibitor dose that was dispensed once daily, twice daily, less than once daily, and more than twice daily is also shown in Table 2. For each dosage strength the percentage of multiple daily dosing was as follows: celecoxib 100 mg (83%), celecoxib 200 mg (33%), celecoxib overall (51%), rofecoxib 12.5 mg (14%), rofecoxib 25 mg (6%), rofecoxib 50 mg (0%), and rofecoxib overall (7%).

Estimation of COX-2 NSAID utilization by modeling, expressed as the percent of once-daily use of celecoxib and rofecoxib (mean \pm 95% confidence intervals), produced results shown in **Figure 1**. The two methods will differ when there are prescriptions with less than 1 unit per day, more than 1 unit but less than 2 units per day, and more than 2 units per day. The average units per day method includes these prescriptions because they were really dispensed, but the manual method might exclude them, or put them in the wrong category of qd or bid. Thus, the average units per day method is the correct method for use in cost analyses. It is important to note the similarity of the manually calculated once-daily utilization rates (Table 2) and the estimated frequen-

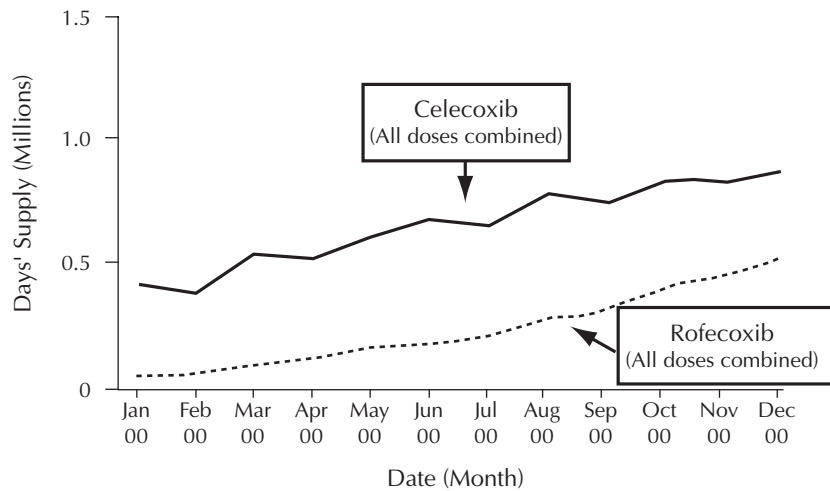
cy of once-daily utilization as shown in Figure 1. It should also be noted that the confidence intervals are narrow for each dose of celecoxib and rofecoxib in the modeling estimate due to the large sample size (Figure 1). The nearly identical results between the 2 methods of analysis and the tight confidence intervals derived from the model support and validate assessment of drug utilization frequency by estimation through modeling.

In calendar year 2000, VA national expenditures for COX-2-selective agents totaled \$18 million. Celecoxib and rofecoxib accounted for \$13.8 million and \$4.2 million, respectively. The national VA contract price per tablet or capsule of each drug has decreased since the time of data collection for this study. For the purpose of meaningful future cost projections, current prices are used in our calculations. Thus, using current prices, total costs for calendar year 2000 would have been \$16.2 million dollars, celecoxib accounting for \$12.2 million and rofecoxib comprising the remaining \$4 million.

To project future formulary COX-2 costs, we assessed the rates of change in the number of tablets or capsules (units) of rofecoxib and celecoxib in calendar year 2000. Figure 2 illustrates the number of units dispensed for each strength of celecoxib and rofecoxib during calendar year 2000 and their future projected use in calendar year 2001 derived by linear regression trend analysis. In 2000, units increased by an average of approximately 65 000 and 41 000 per month for celecoxib and rofecoxib (all doses combined), respectively. As a basis for our calendar year 2001 projections of COX-2 NSAIDs usage and costs, we applied the rate of increase for each dose of celecoxib or rofecoxib in calendar year 2000 (ie, the linear regression slopes) to our estimates for dispensing rates in calendar year 2001 (see Figure 2 "Projected Use").

The "days' supply" is a surrogate marker for the number of prescriptions written. Because prescriptions are written for variable lengths ("days' supply"), for example 30, 60, or 90 days, totaling the days' supply for each prescription for celecoxib or

Figure 3. Total Days' Supply of Tablets or Capsules of Cyclooxygenase-2 Inhibitors Dispensed Monthly Throughout the National Veterans Affairs System

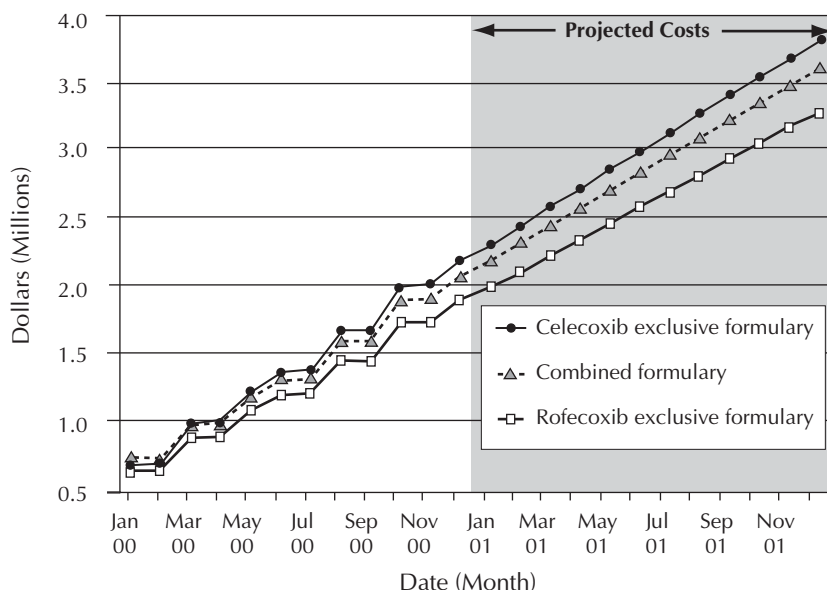


"Days' supply" is a surrogate for the number of prescriptions written. During calendar year 2000, days' supply increased by approximately 44 000 and 46 000 per month for celecoxib and rofecoxib, respectively.

rofecoxib at their various strengths provides a method of comparing rates of growth of COX-2 NSAIDs that is more accurate than comparing the numbers of prescriptions written for each agent. Figure 3 clearly shows that the days' supply of each agent had almost identical growth rates. In 2000, the average monthly days' supply increased by approximately 44 000 and 46 000 per month for celecoxib and rofecoxib, respectively. Thus, the higher rate of growth for celecoxib units is largely due to the higher rate of multiple daily dosings of celecoxib compared with rofecoxib, and not due to a higher rate of growth in the number of new prescriptions for celecoxib in the national VA system.

Based on current prices, Figure 4 illustrates 3 cost scenarios for both actual tablet/capsule use of COX-2 inhibitors (calendar year 2000) and their projected use (calendar year 2001). Results for calendar year 2000 are first described, in descending order of cost. One scenario is the exclusive use of celecoxib. Another scenario is the nonexclusive use of COX-2s, allowing both celecoxib and rofecoxib to be used in the VA system as is currently practiced. A third scenario describes the exclusive use of rofecoxib. The mixed COX-2 NSAID calendar year 2000 formulary costs seen in Figure 4 reflect costs calculated based on actual usage in calendar year 2000. Cost differences between a mixed formulary and a

Figure 4. Actual and Projected Monthly Costs for Cyclooxygenase-2 Inhibitors in the National Veterans Affairs System



The costs of the combined celecoxib and rofecoxib formulary in calendar year 2000 were actual costs, corrected to Veterans Affairs pricing as of April 2001. Costs for calendar year 2001 and costs of celecoxib-exclusive or rofecoxib-exclusive formularies were projected for both 2000 and 2001.

celecoxib-exclusive formulary in calendar year 2000 would not have differed greatly because most of the current COX-2 prescribing was for celecoxib. Because celecoxib and rofecoxib have similar unit costs, similar rates of growth of new prescriptions, but vary in their dosage frequency, differences in exclusive formulary costs would be mostly attributable to differences in frequency of prescribing of celecoxib and rofecoxib. Exclusive use of rofecoxib in calendar year 2000, based on current prices, could have resulted in a savings of \$2.1 million.

In 2001, with celecoxib as the exclusive COX-2 NSAID, formulary costs were estimated to total \$36.7 million. During this same period, mixed COX-2 NSAID formulary costs were projected to cost the national VA system \$34.7 million. The exclusive use of rofecoxib would be estimated to cost \$31.5 million in calendar year 2001. Thus, over 2001 the national VA healthcare system, with a celecoxib-exclusive formulary, would increase expenditures by \$2 million over projected expenditures for our currently combined use. In contrast, a rofecoxib-exclusive formulary would decrease expenditures by \$3.2 million over projected expenditures for our current-

ly combined use. Among the various discussed scenarios, the maximum potential cost difference in calendar year 2001 is estimated to be \$5.2 million. Additionally, some facilities may be using half-tablets of rofecoxib 25 mg to save costs on the 12.5-mg tablet. Continuing this practice would result in a 50% savings on 12.5-mg doses. If the VA system used only half-tablets of the 25-mg rofecoxib to dispense a 12.5-mg dose, the VA would save an additional \$2 million in calendar year 2001. Thus, the grand total possible savings from exclusive rofecoxib formularies with tablet splitting would be in excess of \$7 million, given projected calendar year 2001 dispensing rates.

One final comparison involved using AWP for celecoxib and rofecoxib. In the current study we reported VA system-contracted costs for COX-2 inhibitors. However, because drug costs in managed care agencies outside of the VA system differ from our costs, we have also calculated the cost per patient-year for each COX-2 agent using AWP costs to assist readers in managed care settings. Using AWP, if the differences in rates of COX-2 NSAID utilization were similar to differences in the VA, the average cost per patient-year in non-VA agencies would be \$1174 and \$934 for celecoxib-exclusive and rofecoxib-exclusive formularies, respectively. Thus, with rofecoxib-exclusive formularies, \$240 per patient-year would be saved for every patient receiving a COX-2 inhibitor when compared with the costs of celecoxib-exclusive formularies.

DISCUSSION

In older patient populations, such as in the VA system, arthritis is a common chronic condition affecting approximately 50% of adults older than 65 years.¹² Among the various forms of arthritis in the United States, osteoarthritis is the most common

and affects more than 20 million patients.¹² Nonsteroidal antiinflammatory drugs are the principal form of therapy used in most osteoarthritis patients. Data from therapeutic trials of osteoarthritis indicate that COX-2-specific inhibitors are as effective as, but not more effective than, non-specific NSAIDs.¹³⁻¹⁵ The advantage that COX-2 NSAIDs offer over nonselective NSAIDs is that they have less potential to cause serious upper GI adverse events.^{16,17} However, use of COX-2 inhibitors is associated with higher financial costs when compared with traditional NSAIDs such as naproxen and ibuprofen. Costs favor generic NSAIDs in patients at low risk for NSAID-induced gastropathies.¹⁸ For example, the cost to the VA system for ibuprofen is approximately \$0.01 per tablet compared with \$1.32 for equivalent doses of celecoxib or rofecoxib. When products of similar efficacy are associated with dramatic cost differences, these differences are met with a high degree of scrutiny by pharmacy benefits managers (PBMs) who attempt to provide patients with appropriate and effective medications at a reasonable cost to the system.

Depending on the dose of COX-2 inhibitor prescribed, the per-dose costs of celecoxib and rofecoxib may be identical, as seen in Table 1. However, the range of their costs can also vary considerably. Total daily treatment costs for COX-2-specific inhibitors can fluctuate depending on the daily frequency of their administration and the dose required to achieve therapeutic efficacy. For example, one of the current FDA-approved indications for COX-2 inhibitors is for the treatment of osteoarthritis at doses of celecoxib 100 mg twice daily or 200 mg daily, and of rofecoxib 12.5 or 25 mg daily.¹⁹ Only celecoxib is currently approved for the treatment of rheumatoid arthritis at a dose of 200 mg twice daily¹⁹ or for the management of patients with familial adenomatous polyposis at a dose of 400 mg twice daily.¹⁹ Both agents are approved for the acute treatment of pain, celecoxib at a dose of 400 to 600 mg on the first day followed by 200 mg twice daily on subsequent days, and rofecoxib at a dose of 50 mg once daily.

Data related to treating osteoarthritis with celecoxib and rofecoxib have suggested that the 2 agents would have equivalent efficacy.⁸ In contrast, data from another study suggested the superiority of one agent over the other with regard to efficacy.⁷ Despite the different FDA-approved indications, it is reasonable to expect that most providers are using these medications interchangeably depending on the formulary status where they practice. Given perceived

similarity in efficacy, but potentially varying daily costs, cost minimization analysis can assist pharmacy benefits managers in their assessments of similar medications within a class.

Another important component of drug cost analysis is to have utilization data available based on the accumulated experience of a particular healthcare system. The need for utilization data requires that PBMs and drug formulary committees initially make multiple agents available on either a formulary or nonformulary basis so that they can later assess patterns of medication usage. Product information contained within the package insert and data from clinical studies are often helpful in determining optimum medication doses; however, these data do not always reflect the way the medications may be prescribed by clinicians or used by patients in actual clinical practice. Thus, gathering actual patient use data from accrued clinical experience, as we have done in the current study, can prove to be extremely helpful in conducting cost analyses.

In our healthcare system, celecoxib has comprised the larger share of our expenses for COX-2-specific inhibitors. During calendar year 2000, the VA spent \$13.8 million on celecoxib and \$4.2 million on rofecoxib. The disparity is, in part, due to the order in which these medications were introduced to the US market, because medications first to market often garner the larger proportion of market share. However, as demonstrated in the current study, a large component of the disparity in VA costs for celecoxib and rofecoxib is primarily due to the high prevalence of multiple daily dosing of celecoxib. More than 50% of celecoxib prescriptions are written for multiple daily dosing whereas, overall, only 7% of rofecoxib prescriptions are written for multiple daily dosing. It is possible that differences in serum half-lives may, in part, explain the differences in dosing frequency among these agents. Celecoxib has a half-life of approximately 11 hours, whereas rofecoxib has a half-life of approximately 17 hours.^{20,21} Thus to achieve the desired therapeutic efficacy in many instances, such as in osteoarthritis, celecoxib may need to be prescribed twice daily whereas rofecoxib might only require once-daily dosing,^{13,15} as suggested by our data in the current study. Another possibility is that patients unresponsive to celecoxib 200 mg daily may be increased to twice-daily dosing as an alternative to a medication change.

The data in Table 2 indicate that rofecoxib 50 mg is dosed less frequently than once daily in 80% of prescriptions for this dose. However, it is unlikely

that patients are taking rofecoxib 50 mg less frequently than once daily. It is probable that the 0.59 ratio reflects the fact that the rofecoxib 50-mg tablet is being broken in half and taken at a daily dose of 25 mg per day. If such a practice were to hypothetically occur with 100% of dispensed rofecoxib 50-mg tablets, this would yield an average of 0.50 units per day. The fact that the national VA system data on rofecoxib 50 mg demonstrated an average number of dispensed units per day of 0.59 suggests that, indeed, most dispensed rofecoxib 50-mg tablets are being taken at a rate of a half tablet per day. Although we do not endorse the practice of pill splitting, our data provide strong evidence that this routine is common in our system and one that assists in reducing the formulary cost impact of COX-2-specific inhibitors. Unfortunately, a similar cost-cutting strategy is not feasible for celecoxib because all doses are dispensed as capsules.

Given the differences in frequency of dosing between the 2 competing COX-2-specific agents throughout the national VA healthcare system, exclusive use of rofecoxib in calendar year 2000, based on current prices, could have resulted in a savings of \$2.1 million or a 12% decrease in our formulary costs for COX-2-specific inhibitors. In calendar year 2001, if rofecoxib were the only COX-2 selective agent used in our system, the VA could have saved \$5.2 million. Another equally cost-effective alternative would be to limit the use of celecoxib to 200 mg once daily. This approach, however, may be more difficult to implement and manage than a one-product COX-2 formulary.

In all likelihood, prescriptions for COX-2 NSAIDs will continue to increase in the VA, as well as in other healthcare systems, and will continue to expand the overall NSAID market. If future rates of increase in utilization of COX-2 NSAIDs were to increase at the same rate as it has over the last year, the cost differences potentially realized by a systemwide VA formulary shift to only one of these agents would result in an even greater decrease (with a rofecoxib-exclusive formulary) or a greater increase (with a celecoxib-exclusive formulary) when compared with current expenditures (Figure 4).

Although the data presented in this study were exclusively VA utilization data, it is expected that utilization patterns of COX-2-specific inhibitors, specifically frequency of dosing, would not differ from those at other large managed care organizations. However, drug acquisition costs at healthcare systems outside of the VA health system are generally greater than the acquisition prices of drugs in the VA. For the sake of

this discussion, a reasonable estimated acquisition price standard for non-VA healthcare organizations is the AWP. When calculating costs for COX-2-specific inhibitors using the AWP (as of June 2001), a non-VA managed care organization that changed its preferred COX-2 selective inhibitor from celecoxib to rofecoxib would potentially realize a cost savings of \$240 per rofecoxib patient-year, assuming that differences in frequency of dosing of celecoxib and rofecoxib in non-VA managed care organizations are similar to those patterns in the VA system.

Because the patient population in the VA healthcare system is predominantly male, one might argue that drug utilization in the VA might not be able to be extrapolated to non-VA managed care systems. However, osteoarthritis, the most common form of arthritis, has no gender predilection.²² Thus, NSAID use for this condition is likely to be similar in men and women. With regard to most other conditions for which analgesics and anti-inflammatory agents might be prescribed, the veteran patient population is also likely to be representative of populations being prescribed analgesics such as NSAIDs, ie, older patients with chronic conditions.

As demonstrated by the analyses in the current study, cost minimization models can be a useful tool for PBMs and drug formulary committees as they consider first-line, or preferred, drug therapies among a drug class. The frequency of drug utilization model (Figure 1) allows simple visual inspection to determine if significant differences exist among products with regard to once-daily or multiple daily dosing. Not all patients, however, may respond to one drug in a class and some may require the use of other agents, possibly agents within the same drug class. Moreover, a patient being considered for a particular medication might not be a candidate for that prescription because of allergies or concerns for potential adverse reactions specific to the medication under consideration. Accordingly, formularies must be flexible when considering potential switches to exclusive or preferred drugs within a class to ensure that adequate patient care is maintained. These and other factors will need to be assessed if a drug formulary committee, based on cost analyses, is considering revising their formulary to have available only one COX-2-specific inhibitor.

.....
CONCLUSION

Given that celecoxib and rofecoxib are considered to be equally effective, and have similar safety

profiles, the results of the cost minimization model provide a compelling argument for the preferred use of rofecoxib in the VA system and potentially in other managed care systems.

Acknowledgments

We acknowledge the contributions of Bertis B. Little, PhD, Jim J. McCoy, PhD, Kevin Roberts, PharmD, Dwayne Snider, PhD, Bob Bulinski, BS, and Kristi Rushin, BA.

REFERENCES

1. Singh G, Triadafilopoulos G. Epidemiology of NSAID-induced GI complications. *J Rheumatol*. 1999;26(suppl 26):18-24.
2. Talley NJ, Evans JM, Fleming KC. Nonsteroidal anti-inflammatory drugs in the elderly. *Dig Dis Sci*. 1995;40:1345-1350.
3. Weideman RA, Porter LK, Roberts KW, Garrett SM. Minimizing drug expenditures. *Federal Practitioner*. 1999;16(4):41-44.
4. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA*. 2001;286:954-959.
5. White WB, Whelton A. Cardiovascular events and COX-2 inhibitors [letter]. *JAMA*. 2001;286:2811-2812.
6. Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM. Cyclooxygenase-2-specific inhibitors and cardiorenal function: A randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther*. 2001;8:85-95.
7. Geba GP, Weaver AL, Polis AB, Dixon ME, Schnitzer TJ. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee: A randomized trial. *JAMA*. 2002;287:64-71.
8. McKenna F, Weaver A, Fiechtner JJ, Bello AE, Fort JG. COX-2 specific inhibitors in the management of osteoarthritis of the knee: A placebo-controlled, randomized, double-blind study. *J Clin Rheumatol*. 2001;7:151-159.
9. VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel. Summary of the criteria for the non-formulary use of cyclooxygenase-2 (COX-2) inhibitors in high-risk veteran patients. Available at: <http://www.vapbm.org/criteria/cox2summary.pdf>. Accessed November 1, 2001.
10. Zar JH. *Biostatistical Analysis*. 2nd ed. Englewood Cliffs, NJ: Prentice-Hall; 1984:378-379.
11. *2001 Drug Topics Red Book*. Montvale, NJ: Medical Economics; 2001.
12. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum*. 1998;41:778-799.
13. Bensen WG, Fiechtner JJ, McMillen JJ, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc*. 1999 Nov;74(11):1095-1105.
14. Emery P, Zeidel H, Kvein TK, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: A randomized double blind comparison. *Lancet*. 1999;354:2106-2111.
15. Cannon GW, Caldwell JR, Holt P, et al. Rofecoxib, a specific inhibitor of cyclooxygenase-2, with clinical efficacy comparable with that of diclofenac sodium: Results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. Rofecoxib Phase III Protocol 035 Study Group. *Arthritis Rheum*. 2000;43:978-987.
16. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. *JAMA*. 2000;284:1247-1255.
17. Bombardier 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. Peterson WL, Cryer B. COX-1-sparing NSAIDs—Is the enthusiasm justified? *JAMA*. 1999;282:1961-1963.
19. Westley GJ, Schafer J, Sifton DW, eds. *Physician's Desk Reference*. 55th ed. Montvale, NJ: Medical Economics; 2001.
20. Davies NM, McLachlan AJ, Day RO, Williams KM. Clinical pharmacokinetics and pharmacodynamics of celecoxib: A selective cyclo-oxygenase-2 inhibitor. *Clin Pharmacokinet*. 2000;38:225-242.
21. Porras A, Ko A, Larson P, et al. Single and multiple dose pharmacokinetics of rofecoxib in healthy subjects [abstract]. *Clin Pharmacol Ther*. 2000;67:137.
22. Brandt KD. Osteoarthritis. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. *Harrison's Principles of Internal Medicine*. 14th ed. New York: McGraw Hill; 1995:1935-1941.