Prescriptions for Chronic High-Dose Cyclooxygenase-2 Inhibitors are Often Inappropriate and Potentially Dangerous

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OBJECTIVE: To describe the use of coxibs outside of licensed indications and recommended dosing ranges including rofecoxib 50 mg, valdecoxib 20 to 40 mg, and celecoxib 400 mg.

DESIGN: Cross-sectional study of coxib utilization in 2002 and 2003 and retrospective cohort analysis of new users.

PARTICIPANTS: Patients with known age and sex enrolled in Tennessee's Medicaid program.

MEASUREMENTS: The prevalence of coxib use by dose and duration, and the proportion of persons initially prescribed a high-dose coxib and indications for such use.

RESULTS: The estimated daily prevalence of nonaspirin prescription nonsteroidal anti-inflammatory drugs (NSAIDs) was 8.7% in 2002 to 2003 (45.7% coxibs). NSAID use peaked at age 65 to 74 with a prevalence of 19.8% (56.3% coxibs). Doses above the recommended daily dose for osteoarthritis accounted for 33.2% (95% confidence intervals [CIs] 32.4%, 33.9%) of celecoxib use, 14.9% (95% CI 14.4%, 15.5%) of rofecoxib use, and 52.2% (95% CI 50.6%, 53.8%) of valdecoxib use. Most of these prescriptions were for a month's supply. For new coxib users, 13.5% were given a month's supply for the highest dose category, and 28% refilled their prescriptions within 7 days of the end of the original prescription. Of these new chronic high-dose users, 17.2% had ischemic heart disease and 7.1% had heart failure.

CONCLUSIONS: A substantial portion of coxib prescriptions were for a month's supply at doses above those recommended for most chronic indications. New users were also prescribed high doses despite evidence for cardiovascular comorbidity. These prescribing patterns at doses outside licensed indications are both inappropriate and potentially dangerous.

KEY WORDS: cyclooxygenase-2 inhibitors; inappropriate; nonsteroidal anti-inflammatory drugs (NSAIDs); prescribing.
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The cyclooxygenase-2 (COX-2) selective inhibitors (coxibs), celecoxib (Celebrex®, Pfizer, New York, NY), rofecoxib (Vioxx®, Merck, Whitehouse Station, NJ), and valdecoxib (Bextra®, Pfizer), have been widely prescribed since their approval for use by the Food and Drug Administration (FDA) in 1998, 1999, and 2001, respectively. There is now good evidence that all 3 of these drugs increase the risk of cardiovascular events in a dose-dependent manner.[1–9] Although published data on dose-related adverse events were not available for all of these drugs at the time of licensure, strong dose-related adverse effects including hypertension, edema, and impaired renal function were observed with rofecoxib in the prelicensing efficacy trials,[10] and the excess in acute myocardial infarctions was first detected with the use of the 50 mg dose, twice the dose licensed for chronic use.[4,6] There is no published evidence that coxibs above the maximum recommended doses offer an additional benefit over lower, approved doses for chronic pain associated with arthritis.[11,12]

The FDA licenses drugs that have been demonstrated to be "safe and effective" in clinical trials. Although postmarketing experience may reveal unanticipated problems, additional adverse events may occur because drugs are used outside their licensed indications. Because prelicensing clinical trials cannot cover all relevant clinical situations, clinicians sometimes prescribe drugs in "off-label" dosages or indications. However, in the absence of evidence for superior efficacy, and because higher doses are associated with an increased risk of side effects, we question whether drugs should be prescribed above their recommended dose ranges.

We previously described frequent chronic use of rofecoxib at the 50 mg dose among Tennessee Medicaid recipients.[13] We evaluated whether these prescribing patterns continued despite early warnings of problems with these new drugs,[6,14,15] and labeling changes made by the FDA in April, 2002.[16] In the current study, we examined more recent data to determine coxib prevalence, dose, duration, and prescriptions for at-risk patients.

METHODS

Study Design and Data Sources

We performed a cross-sectional study and a retrospective cohort study of Tennessee Medicaid program enrollees in 2002 and 2003. The Institutional Review Boards of Vanderbilt University and the Tennessee State Department of Health approved this study.

The study population was drawn from the Tennessee Medicaid program also known as TennCare. The primary sources of data were the administrative files of the TennCare program (2001 to 2003) including enrollment, hospital, physician, and pharmacy files. The enrollment file identifies

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eligible persons, the coverage dates, and demographic information. The hospital and physician files include medical care visit dates and associated diagnoses coded by the International Classification of Diseases, Ninth Revision; Clinical Modification (ICD9-CM).[17] The pharmacy file contains information on reimbursed prescriptions for outpatients and nursing home residents, including drug dispensed, date, dosage, the number of pills, and the days of supply, which cannot exceed 30 days.

Eligible Subjects

To estimate the average daily prevalence of all nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), we determined the mid-year point prevalence. All persons enrolled in TennCare for at least 1 year on July 1, 2002 and July 1, 2003 were included if they had known age and sex in the administrative files, at least 1 year of prior enrollment, prescription drug benefits, and filled at least 1 prescription in the prior 365 days. Persons with any current NSAID prescriptions on those 2 dates were classified as prevalent users by specific drug, dose, and duration of use. New users were defined as persons continuously enrolled in TennCare for the 365 days before a coxib prescription who had received no coxib prescription in that time.

For prevalent NSAID users who were prescribed coxibs, we determined the daily dose of each coxib by multiplying the number of pills dispensed by the dosage prescribed (in milligrams) divided by the recorded days' supply. Each drug was then categorized by the daily dose as: starting dose, the highest recommended dose approved for osteoarthritis, the highest recommended dose approved for rheumatoid arthritis, and the highest recommended dose approved for other indications, according to the Physicians Desk Reference.[18] Some of these maximum recommended doses and indications differ in other countries. The distribution of doses clustered around pill dosages or a multiple of these dosages, which in turn corresponded to maximum daily dose recommendations. The daily doses and ranges are listed in Table 1. All prescriptions for a supply of at least 28 days were considered a month's supply.

New Users of Coxibs and Comorbidities

To identify new users of coxibs, we examined the first coxib prescription for each person during the 2 study years. We determined the initial dose, duration, and indication for each new coxib prescription user. The indication was identified from medical care encounters on the date of the first prescription and during the preceding 365 days. The diagnostic categories included, in the following hierarchy: (1) inflammatory arthritis including rheumatoid arthritis (ICD9-CM codes 714.0, 714.1, 714.2, 714.81), lupus (710.0), and other inflammatory arthritis (696.0, 710.1 to 710.9, 713.1, 713.7, 714.30 to 714.33, 714.4, 714.8, 714.89, 720.0), or none of these but a prescription for a disease-modifying anti-rheumatic drug (methotrexate, gold injections, auranofin, hydroxychloroquine, penicillamine, azathioprine, etanercept, infliximab, cyclosporine, sulfasalazine, leflunomide, and minocycline); (2) osteoarthritis (715.x, 721.x); (3) painful musculoskeletal conditions (710.x to 739.x); and (4) none of the above. Clinical indications were only provided for new users and not prevalent coxib users owing to the uncertainty in linking a particular diagnosis to the medication prescribed.

Patients were categorized by age (<14, 15 to 44, 45 to 64, 65 to 84, and <85 years), gender, and race (white, black, and all others). Important comorbidities of new coxib users were determined using the physician and hospital claims files as well as the pharmacy file to identify all persons who had an inpatient, emergency room, or outpatient encounter with the ICD9-CM–coded comorbidity of interest or prescription for specific medications in the prior 365 days.

Cardiovascular comorbidities included: ischemic heart disease (hospitalizations, emergency room visits, or other outpatient visits with diagnoses codes 410.X to 414.X or a prescription for nitrates), congestive heart failure and cardiomyopathy (425.x and 428.x or prescription for both digoxin and furosemide), and hypertension (401.x to 405.x or prescription for diuretics, ACE inhibitors, angiotensin receptor blockers, β-blockers, calcium channel blockers, or centrally acting antihypertensive agents). Cerebrovascular comorbidities included any ischemic stroke (433.x to 434.x, 436.x), hemorrhagic stroke (intracranial and subarachnoid [430.x and 431.x]), and transient ischemic attacks (435.x). Renal comorbidities included acute and chronic renal failure (584 to 587).

Statistical Analysis

The daily prevalence of NSAID use (and proportion coxibs) was estimated by calculating the number of individuals with a current NSAID prescription on July 1 of each year, divided by the eligible population on these dates. The population of NSAID users and the proportion who used coxibs were characterized with descriptive statistics including age, sex, race, and nursing home residence. We also determined the proportions and 95% confidence intervals (CIs) of prevalent coxib users who filled a coxib prescription at high dose (celecoxib 400 mg/day) (range 300 to 700 mg/day) indicated for rheumatoid arthritis not

Table 1. Defined Daily Dose Categories

Dose category (mg/day)	Celecoxib Daily Dose (Range)	Rofecoxib Daily Dose (Range)	Valdecoxib Daily Dose (Range)
Start dose	200 (<300)	12.5 (<18.75)	10 (≤15)
Maximum recommended dose osteoarthritis	200 (<300)	25 (18.75 to 37.5)	10 (≤15)
Maximum recommended dose rheumatoid arthritis	**400 (300 to 700)**	25 (18.75 to 37.5)	10 (≤15)
Maximum recommended dose other indications: indication and duration	800 (>700)	**50 (>37.5)**	**20–40 (>15)**
	Polyp prevention	Acute pain 5 days	Dysmenorrhea 5 days

Categories of interest (bolded) are the highest daily dose category for which there is no chronic indication (rofecoxib and valdecoxib) or limited indication (celecoxib).

osteoarthritis; rofecoxib 50 mg/day (>37.5 mg), indicated only for acute pain and specifically not recommended for long-term use; and valdecoxib 20 to 40 mg/day (>15 mg), recommended only for short-term indications including dysmenorrhea and acute pain. The duration of coxib use was determined by examining the distribution (median and interquartile range [IQR]) of the number of days these high-dose coxib users filled any coxib prescription in the preceding 365 days.

We determined new users of coxibs (no prescription in the previous 365 days) in each of the 2 study years, and restricted subsequent analyses to patients who received a high-dose coxib for at least 1 month. We then examined the indication for the incident prescription by examining claims in the prior year, and finally determined the proportion of these incident coxib prescriptions that were for patients who were 65 years of age or older, or had cardiovascular, cerebrovascular, or renal comorbidities of interest. All tabulations and statistical analyses were conducted using Stata, version 7.0 (Stata Corporation, College Station, Tex).

RESULTS

The average annual enrollment in TennCare of persons with pharmacy benefits and a full year of eligibility in 2002 to 2003 was 891,859 persons. The point prevalence of nonaspirin NSAIDs was 8.7% (95% CI 8.6%, 8.8%). Coxibs accounted for 45.7% (95% CI 45.3%, 46.1%) of total NSAID prescriptions and included an annual average of 15,632 (20.1%) celecoxib users, 16,033 (20.6%) rofecoxib users, and 3,789 (4.9%) valdecoxib users.

Nonsteroidal anti-inflammatory drug prevalence increased with age up to age 65 to 74 (19.8%), and then declined. The proportion of NSAIDs that were coxibs was substantial even among younger adults aged 15 to 44 (32.1%) and increased to 66.0% among those 85 years and older. Nonsteroidal anti-inflammatory drug prevalence was higher in women than men (9.9% vs 6.9%), whites than blacks (9.8% vs 5.3%), and among nursing home than community-dwelling enrollees (14.1% vs 8.6%). Coxib use was common in all these groups (Table 2).

Chronic High-Dose Coxibs

Of the 15,632 users of celecoxib, 33.2% (95% CI 32.4%, 33.9%) received a daily dose of 400 mg and 88.1% of these users had prescriptions written for at least 28 days. The proportion of celecoxib users prescribed doses of 800 mg/day was small, 0.4%. Of the 16,033 rofecoxib users, 14.9% (95% CI 14.4%, 15.5%) were prescribed the highest dose, 50 mg/day, and 83% of these persons received a month's supply. High-dose valdecoxib use was also common. Of the 3,789 valdecoxib users, 52.2% (95% CI 50.6%, 53.8%) had daily doses of 20 to 40 mg and 85.7% were for a month's duration. Of coxib users with at least a month's prescription duration, 21.8% had a diagnosis of ischemic heart disease, 9.8% congestive heart failure, and 70.9% a diagnosis of hypertension. In addition, 62.5% refilled their prescription within 7 days of the original prescription end, suggesting chronic use. Those who received a high dose for at least a month's supply had filled coxib prescriptions for a median of 240 days (IQR 117 to 344 days) in the prior 365 days, indicating chronic use of high doses.

Table 2. Average Prevalence of Nonaspirin Prescription NSAID Use and Proportion of those NSAID Prescriptions that were for 1 of the 3 Coxibs of Interest on July 1, 2002 and 2003 by Population Characteristics

Population Characteristics	Estimated Average Prevalence Nonaspirin Prescription NSAID Use (2002 to 2003)	Proportion of NSAID Prescriptions that were Coxibs (2002 to 2003)
N/N	77,647/891,859	35,454/ 77,647
Total % (95%CI)	8.7 (8.6, 8.8)	45.7 (45.3, 46.1)
Age (%)		
<15	0.4	3.9
15–44	6.4	32.1
45–64	18.3	47.3
65–74	19.8	56.3
75–84	18	62.1
≥85	14.8	66.0
Gender (%)		
Men	6.9	44.3
Women	9.9	46.3
Race (%)		
White	9.8	47.0
Black	5.3	37.2
Other	10.9	49.3
Nursing home (%)		
Yes	14.1	62.1
No	8.6	45.0

NSAID, nonsteroidal anti-inflammatory drug; CI, confidence interval.

New Users of Coxibs—Indications and Comorbidities

There were 117,662 new users of the 3 coxibs in 2002 and 2003. Of these new users, 37,140 (31.7%) started at one of the highest daily dose categories and 15,874 of these (42.7%) received a month's supply. Diagnoses associated with new use of high-dose coxibs that were prescribed for a month included osteoarthritis (24.1%) and musculoskeletal pain (50.6%). For these new users of high-dose coxibs, who were given a month's supply, diagnoses in the prior year indicating the presence of an inflammatory arthropathy were rare (5.8%). A large share of patients on high-dose coxibs given a month's supply refilled the prescription within 7 days of completion, 28.2% of celecoxib users, 23.1% of rofecoxib users, and 31.1% of valdecoxib users (Table 3).

Of the 15,874 patients who filled a new prescription for a month's supply of a high-dose coxib, 18.5% were aged 65 years or older, 17.2% had cardiovascular disease, 7.1% congestive heart failure or cardiomyopathy, 58.4% hypertension, 3.4% cerebrovascular disease, and 1.5% renal failure. There were no major differences in the proportion of patients with comorbidities between the individual coxibs.

DISCUSSION

Our results emphasize 3 main points. First, almost half of the NSAID prescriptions were for coxibs, and high-dose use was common. From 2002 to 2003, in the TennCare population, NSAID prevalence was 8.7%, with a 19.8% prevalence in those aged 65 to 74 years. Coxib prescriptions constituted half of these prescriptions and commonly exceeded the recommended dose. We found that 33.2% of celecoxib users received a daily dose of 400 mg, 14.9% of rofecoxib users were prescribed 50 mg/day, and 52.2% of valdecoxib users were prescribed

Table 3. Indications and Comorbidities Among New Users of Coxibs at Highest Dose and for 28+ Days in TennCare in 2002 and 2003, and the Proportion who Refilled Prescription within 7 Days of Completion (Chronic Users)

	Celecoxib 400 mg (300 to 700 mg) N=5,861	Rofecoxib 50 mg (>37.5 mg) N=3,986	Valdecoxib 20 to 40 mg (>15 mg) N=6,027	Total High-dose Coxibs N=15,874
Older age (%)				
65+	19.7	9.9	23.1	18.5
Indication (%)				
Inflammatory arthritis	6.2	4.4	6.3	5.8
Osteoarthritis	24.6	16.9	28.2	24.1
Musculoskeletal pain	49.5	55.1	48.8	50.6
All others	19.8	23.5	16.7	19.5
Comorbidities (%)				
Ischemic heart disease	17.8	12.7	19.6	17.2
Congestive heart failure/cardiomyopathy	8.0	4.6	7.9	7.1
Hypertension	61.0	47.8	62.8	58.4
Cerebrovascular disease	3.8	2.3	3.8	3.4
Renal failure	1.6	1.1	1.7	1.5
Refill within 7 d (%)	28.2	23.1	31.1	28.0

the highest daily dose. Dose escalation over time might account for some high-dose use; however, 31.7% of new coxib prescriptions were for the highest dose categories.

Second, a substantial portion of patients on high-dose coxibs received a month's supply. Over 80% of prevalent users and 42% of new users received a month's supply, the maximum prescription length. In addition, 28% of these new high-dose users and 62.5% of prevalent users refilled their prescriptions within 7 days of the end of the month's supply, suggesting chronic use.

Finally, high-dose coxibs were frequently prescribed for patients with cardiovascular disease and other risk factors, including older age. Approximately 17% of incident high-dose coxib users had cardiovascular disease, and 58% had hypertension. It is now accepted that persons at risk for cardiovascular disease should avoid these drugs. The 2- to 4-fold increase in cardiovascular risk associated with high-dose coxibs is equivalent to the risk incurred by a 20 mm Hg increase in systolic blood pressure or smoking.[7–9,19] Although some of these risks have been established only recently, there was no evidence at any time for the superior efficacy of higher doses. In February 2001, the FDA mandated that the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial cardiovascular findings be included on the rofecoxib label.[16] The labeling information change advised providers to exercise caution in prescribing rofecoxib to patients with ischemic heart disease and discouraged use of the 50 mg dose chronically. Our study demonstrates that despite FDA warnings, label changes, and studies highlighting risk, patients continued using coxibs at high doses and chronically.

Our study has limitations that should be noted. We described coxib utilization through analysis of prescription data collected through TennCare. There was no chart review or patient interviews to estimate whether a filled prescription actually represented drug use. Previous studies conducted in this population have verified the accuracy of this database for NSAID prescriptions.[20,21] Providers may choose to prescribe a month's supply but it may be used intermittently, as indicated on the label. However, 28% of high-dose incident coxib prescriptions were refilled within 7 days of the prescription end, suggesting daily use. The results demonstrating the high proportion of associated cardiovascular comorbidities might be specific to the TennCare population. Zhao et al.[22] described a similar prevalence of coxib use in an employer database claims population. He also reported index coxib prescriptions given to patients who were at an increased risk of cardiovascular events compared with patients prescribed nonspecific NSAIDs. We report a single state's drug utilization for a Medicaid population, and utilization may be different in other populations.

The lack of evidence-based prescribing of coxibs raises concerns about appropriate prescribing. At times, sufficient evidence may be available to endorse "off-label" use of therapeutics, such as spironolactone for congestive heart failure.[23] However, as recent evidence with estrogen replacement reminds us, caution is warranted in making therapeutic decisions without clinical trial data.[24,25] Although much of the evidence for coxib dose and duration-related adverse effects was not available in 2002 to 2003,[26,27] we suggest that using doses above recommended levels represents suboptimal prescribing, even in the absence of evidence for harm. The practice of escalating doses and duration is a well-recognized hazard of medications prescribed to treat symptoms.[10,28] The coxib experience may serve as a cautionary example that could help change this practice.

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