The Patient's Perspective on the Recall of Vioxx

GILLIAN A. HAWKER, JEFFREY N. KATZ, and DANIEL H. SOLOMON

ABSTRACT. ***Objective.*** Rofecoxib was recalled in September 2004 when studies identified increased cardiovascular risk compared with placebo among patients taking rofecoxib. We examined the reactions of people with arthritis to this recall.

Methods. Telephone interviews were conducted between December 2004 and February 2005 in a previously assembled community based cohort (n = 1085) with disabling hip/knee osteoarthritis (OA) residing in 2 regions of Ontario, Canada (one urban, one rural). Respondents' self-reported experience with cyclooxygenase (COX-2) selective nonsteroidal antiinflammatory drugs (NSAID; coxibs), issues around communication of the recall, attitudes about pain medications, and understanding of the rofecoxib-associated cardiovascular risks were assessed. Participants were also asked about contraindications for traditional NSAID use (specific clinical conditions, use of blood thinners and glucocorticoids, and history of gastrointestinal (GI) ulcer and/or bleeding).

Results. The response rate was 93.5%; 968 completed the survey. Half (53.0%) had used a coxib for arthritis; 277 (28.6%) had used rofecoxib. Only 3.8% of "ever" coxib users reported previous GI ulcer or hemorrhage. 94.8% of respondents had heard about the recall; most (94.7%) had heard via television. Among the 83 individuals taking rofecoxib at recall, 90.4% had been offered another pain medication, mainly another coxib. Most of the 968 participants (> 60%) were unfamiliar with rofecoxib-associated cardiovascular risks. Of those with an opinion, most overestimated the absolute risk associated with rofecoxib (55.7% cited a risk > 5 events/100 people/year).

Conclusion. In an elderly community cohort with OA, the prevalence of coxib use was high despite few major contraindications to NSAID. Many were unaware of or overestimated the absolute risks associated with rofecoxib use, highlighting the need for strategies by which physicians/pharmacists can provide their patients with timely and accurate drug safety information. (J Rheumatol 2006;33:1082–8)

Key Indexing Terms:
ROFECOXIB VIOXX PUBLIC OPINION SURVEY

The antiinflammatory drug rofecoxib (Vioxx®) was voluntarily withdrawn from the market on September 30, 2004, after studies showed that longterm use increased the risk of myocardial infarction and stroke[1-15]. In February 2005, after detailed review of the data that led to withdrawal, an advisory committee to the Food and Drug Administration in the United States recommended the reinstatement of rofecoxib, provided the package carries an appropriate warning label[16]. A similar recommendation was recently made in Canada by an independent panel that reviewed the safety of the coxibs for Health Canada[17]. To date, the drug remains off the market.

Rofecoxib was one of 3 cyclooxygenase (COX-2) selective nonsteroidal antiinflammatory drugs (NSAID; coxibs) available at the time of its recall. Similar to traditional NSAID, the coxibs inhibit the cyclooxygenase-2 enzyme responsible for stimulating prostaglandin production in the joint and hence the inflammatory response. However, in contrast to nonselective or traditional NSAID, the coxibs exert little inhibitory effect on the COX-1 enzyme responsible for stimulating prostaglandin production important in gastroprotection and hemostasis. As a result, the coxibs have similar therapeutic antiinflammatory response but with reduced risk of gastrointestinal (GI) toxicity[18,19]. Since the initial recall of rofecoxib, substantial media attention has been paid to the safety of the coxibs. The media and peer-reviewed publications have documented the reactions of researchers, health professionals, and health policymakers to the recall[1-15,20]. In comparison, little attention has been paid to the reaction of persons with arthritis. In a recent study from the US, over 50% of NSAID users

From the Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; Section of Clinical Sciences, Division of Rheumatology, Immunology and Allergy; and Department of Orthopaedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massuchusetts, USA.

Supported by a grant from the Canadian Institutes of Health Research. Dr. Hawker receives salary support as the F.M. Hill Chair in Academic Women's Medicine at Sunnybrook and Women's College Health Sciences Centre and the University of Toronto. Dr. Katz is supported by National Institutes of Health (NIH) grants K24 AR 021213 and P60 AR 47782, the Arthritis Foundation, the New England Baptist Hospital, and a research grant from Novartis. Dr. Solomon has received research support from Merck and Pfizer as well as the NIH (K23 AR48616, R01 DA15507), the Arthritis Foundation, and the Engalitcheff Arthritis Outcomes Initiative.

G.A. Hawker, MD, MSc, FRCPC, Department of Health Policy, Management and Evaluation, University of Toronto, Institute for Clinical Evaluative Sciences, and Division of Rheumatology, Department of Medicine, Sunnybrook and Women's College Health Sciences Centre and the University of Toronto; J.N. Katz, MD, MSc, Section of Clinical Sciences, Division of Rheumatology, Immunology and Allergy, Department of Orthopaedic Surgery, Brigham and Women's Hospital, Harvard Medical School; D.H. Solomon, MD, MPH, Section of Clinical Sciences, Division of Rheumatology, Immunology and Allergy, Division of Pharmacoepidemiology, Department of Orthopaedic Surgery, Brigham and Women's Hospital, Harvard Medical School.

Address reprint requests to Dr. G.A. Hawker, Sunnybrook and Women's College Health Sciences Centre, 76 Grenville Street, Room 815, Toronto, Ontario M5S 1B2. E-mail: gillian.hawker@sw.ca

Accepted for publication January 12, 2006.

were taking coxibs[21]. Thus, the recall of rofecoxib is expected to have significant effects at all levels of society. As a recall of this magnitude is uncommon, it provides an important opportunity to learn about patients' attitudes to such drug safety issues.

We surveyed a preexisting community cohort of individuals with disabling hip/knee OA to determine their response to the recall. We asked about their experience with the coxibs. We examined issues around the communication of the recall, including their reactions to the ban and how this may have influenced their attitudes toward their arthritis pain medications. Finally, we assessed their understanding of the cardiovascular risks associated with rofecoxib. We hypothesized that there would be a general lack of understanding, and likely overestimation, of the rofecoxib-associated cardiovascular risks, and that these perceptions would foster reluctance to use effective pain medications among the elderly living with OA.

MATERIALS AND METHODS

A population cohort of 2411 individuals aged 55 years and older with disabling hip/knee OA was established using a 2-phase sampling process between 1996 and 1998[22,23]. A brief mail/telephone screening questionnaire (Phase I) was administered to 100% of the population aged 55 years and older residing in 2 regions of Ontario, Canada, one rural, one urban. Ontarians have comprehensive, universal health insurance coverage, averting barriers to healthcare based on insurance status. The Phase I screener assessed participant demographics and the presence of symptomatic joints and functional disabilities. Respondents were selected for Phase II if they reported: (1) difficulty in the last 3 months with each of stair-climbing, arising from a chair, standing, and walking; and (2) swelling, pain, or stiffness in any joint lasting at least 6 weeks; and (3) that a hip and/or knee had been "troublesome." Response rates for all questionnaires and interviews was 72% or higher.

In 1999, Phase II participants were invited to participate in a 5-year followup study: 2103 of the original 2411 participants were alive and agreed to participate. Demographic information, collected annually, included age, sex, gross annual household income, highest level of education attained, living circumstances (nursing home/independent with others/independent alone), and comorbidity (number of health problems for which they were receiving treatment or had seen a physician in the past year). Arthritis symptoms and disability were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[24]. Response rates for annual surveys, adjusted for deaths and "unable to complete," were at least 78%.

Between December 2004 and the end of February 2005, 9 to 20 weeks after Merck Co. withdrew Vioxx, we surveyed the cohort about this recall. Of the 2103 who entered the prospective study, 477 were deceased, 35 lost to followup, 242 too ill to participate, and 264 had refused further participation, leaving 1085 individuals eligible to participate in the rofecoxib survey. Compared with the original Phase II cohort of 2411, those eligible for the rofecoxib survey were younger (mean age 75.9 vs 82.4 yrs), had higher income (percentage ≤ $20,000: 55.2% vs 69.2%; all dollars are Canadian, 2004) and education (percentage with post-secondary education 18.9% vs 13.0%), and were more likely to be female (76.4% vs 70.1%).

Prior coxib experience and indications for use. Participants were asked about their current and prior use of rofecoxib, celecoxib (Celebrex®), and valdecoxib (Bextra®). For each coxib, "ever" users were asked duration of use and the main reason for choice of the coxib over traditional NSAID, i.e., more effective, side effects, cost, safety, doctor recommendation, or "other." All respondents were assessed for coxib indications (relative indications — age, heart disease, renal disease, hypertension, diabetes; absolute indications — history of an ulcer or GI hemorrhage, use of blood thinners [prescribed blood thinners and low dose acetylsalicylic acid (ASA)], and use of systemic corticosteroids). Ever coxib users were additionally asked about side effects with traditional NSAID.

Communication of the recall. Participants were asked if they knew about the rofecoxib recall, and if so, from which sources. We asked their opinion regarding the best method to communicate such information. Ever rofecoxib users were asked if they were using rofecoxib currently and if not, when rofecoxib was discontinued and the reason(s) for discontinuation (recall from market, concern about heart attack risk, no longer available, lack of effect, side effects, cost, and other). They indicated whether they had been told to discontinue rofecoxib therapy, and if so, by whom — doctor, family member/friend/neighbor, pharmacist, other health professional, or other.

Effect of the recall. For those who had discontinued rofecoxib because of the recall, we asked if alternative treatments had been offered (none, other prescription pain medication, other nonprescription pain therapy, cannot recall), and how they rated their arthritis pain now compared with their pain while taking rofecoxib (5-point scale from "much better" to "much worse"). We asked them if, knowing what they know now, they would take rofecoxib again if it were available (yes/no). All participants were asked if the recall had "changed how they feel" about their arthritis pain medications, and if yes, how.

Perceptions of risk. Participants were asked to estimate the percentage of all available prescription medications in Canada with a potentially life-threatening side effect. They were then asked to provide their "best guess" of the cardiovascular risk associated with rofecoxib. First, we asked their opinion of the risk of heart attack over a one-year period relative to an individual taking a traditional NSAID (1.5, 2, 2.5, 3, > 3 times higher, or unsure). Next, we asked them to estimate the number of people out of 100 who take rofecoxib for a year, who would be expected to suffer a heart attack or stroke (< 1, 1–5, 6–10, 11–20, 21–30, > 30, or unsure).

Statistical analysis. Descriptive analyses were performed. We assessed for differences in responses by sex, age (< 75 vs ≥ 75 years), level of education (≤ high school vs postsecondary), income (≤ $20,000 vs > $20,000), race (Caucasian vs non-Caucasian), comorbidity (0, 1, and 2+ comorbidities), and prior rofecoxib experience (ever vs never) using chi-square and Fisher's exact tests. Statistical significance was considered at a 2-tailed level of 0.05. Analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA).

The Sunnybrook and Women's College Health Sciences Centre Ethics Review Board approved the study.

RESULTS

Study sample. The numbers of people eligible for the study and response rates are summarized in Table 1. Of the 1035 cohort members who were alive and eligible to participate in the survey, 968 (93.5%) completed the telephone interview. Respondents' mean age was 75.9 years; 76.4% were female and 94.1% were Caucasian (Table 2). A quarter lived alone (26.1%), 23.7% had less than high school education, and 55.2% had an annual income ≤ $20,000.

Table 1. Study sample and response rates.

Cohort Status	N (%)
Invited to participate in Vioxx survey (December 2004)	1085
Deceased	3 (0.3)
Lost to followup	8 (0.8)
Refused participation	14 (1.3)
Ineligible (cognitive impairment, hearing impairment, non-English speaking)	47 (4.3)
Unable to participate due to serious illness	10 (0.9)
Could not be contacted for interview	35 (3.2)
Completed interview	968 (89.2)
Response rate (adjusted for deceased and ineligible)	968/1035 (93.5)

Table 2. Cohort characteristics (n = 968*).

Mean age, yrs (SD)	75.9 (7.4)
Female, n (%)	740 (76.4)
Caucasian, n (%)	911 (94.1)
Living alone, independently, n (%)	248/950 (26.1)
Education < high school, n (%)	222/935 (23.7)
Annual household income ≤ $20,000 (%)	441/799 (55.2)
Mean WOMAC pain scale score, per 20* (SD) (min–max)	7.8 (3.8) (0–18)
Mean WOMAC physical function scale score, per 68* (SD) (min–max)	28.7 (11.5) (0–62)
Comorbidity, n/950 (%)	
No. comorbid conditions	
0	406 (42.7)
1	318 (33.5)
2+	236 (24.8)
Specific conditions treated in the past year (%)	
Hypertension	493 (51.9)
Heart disease	271 (28.5)
Kidney disease	7 (0.7)
Diabetes	166 (17.5)
Coxib use for arthritis, n (%)	
Any coxib	513 (53.0)
Rofecoxib	277 (28.6)
Celecoxib	407 (42.1)
Valdecoxib	14 (1.5)

* The denominator is given where less than 100% responded to the question.

Prior coxib experience and indications for use. Half the respondents (n = 513, 53.0%) had used one or more of the coxibs for arthritis — 277 had used rofecoxib (28.6%), 407 celecoxib (42.1%), and 14 valdecoxib (1.5%), and 178 had used ≥ 2 of these drugs (34.7%). Compared with "never" coxib users, ever users were younger (p = 0.002) and had higher income (p = 0.03) and education (p = 0.02). Since few had used valdecoxib, further analyses focused on rofecoxib and celecoxib. Mean length of use was 53.0 weeks for rofecoxib and 48.1 weeks for celecoxib. Among ever coxib users, "doctor recommended it" was most often reported as the main reason for choosing the agent (480/513, 93.5%); "side effects with conventional NSAID" were reported by only 1.2%. Most reported that their doctor had told them that coxibs work better than conventional NSAID to relieve their arthritis pain (94.6% of ever rofecoxib users and 91.7% of ever celecoxib users).

Frequency of reported contraindications to traditional NSAID. Never and ever coxib users were similarly likely to self-report any absolute or relative contraindication to traditional NSAID use (Table 3). Few ever coxib users (3.8%) reported a history of an ulcer (3.7% rofecoxib users and 3.5% celecoxib users) compared with 3.3% of never users (p = 0.74); only 1.4% of ever users and 0.9% of never users reported a prior GI hemorrhage. One-third (34.7%) of ever users and 32.2% of never users were taking low-dose ASA, while 12.5% and 12.1%, respectively, were taking prescription blood thinners at the time of the survey. Overall, 202 (39.4%) ever coxib users had any absolute contraindication to nonselective NSAID use (38.3% for ever rofecoxib users and 40.0% for ever celecoxib users) compared with 48.1% of never users (p = 0.54). Relative contraindications to traditional NSAID use were more common; approximately two-thirds of both ever and never users had one or more of hypertension, heart disease, renal disease, or diabetes (p = 0.51; Table 3), and all respondents were 65 years of age or older.

Communication of the recall. Of the 968 respondents, 918 (94.8%) had heard about the recall. Among these 918 individuals, most heard about the recall through television (94.7%; Table 4). Individuals who were taking rofecoxib at the time of the recall were significantly more likely than past users and never users to have also heard about the recall from their doctor (25.3% vs 4.2% and 1.1%; p < 0.0001) or pharmacist (10.8% vs 1.1% and 0.0%; p < 0.0001). When asked how best to get information to the public about drug side effects, most recommended using the media (57.6%), with no differences of opinion based on rofecoxib experience.

Effect of the recall. Eighty-three of the ever rofecoxib users (30.0%) were taking rofecoxib at the time of its recall; all but 2 had discontinued rofecoxib by the time of the survey. Of the 83, 47 (56.6%) discontinued rofecoxib on their own, 26 (31.3%) were instructed to do so by a physician, 4 (4.8%) by a pharmacist, and 6 (7.2%) by both a physician and a pharmacist. Ninety percent (90.4%) had been offered an alternative pain medication [alternative coxib: 22; nonselective NSAID: 40; narcotic analgesic (mainly acetaminophen with codeine): 13].

When asked to rate the severity of their arthritis pain now compared with that while taking rofecoxib, 61 (73.5%) reported that it was "worse" or "much worse." Fifteen of the 83 (18.1%) told us that they would take rofecoxib again if it were available. When asked why, all said that it had worked for them (5/15 said rofecoxib worked when nothing else had) and 3 indicated they were not concerned about the risks. Among those who would not use rofecoxib again, fear of side effects was most often cited as the reason (51/68, 75.0%).

Most respondents (695, 71.8%) reported that the recall of rofecoxib had not changed how they feel about their arthritis pain medications. For 418 (60.1%) of the 695, this was because they had either never taken rofecoxib, or only used it briefly. Other responses included a general dislike of medications already (67/695, 9.6%), lack of concern regarding drug safety (20/695, 2.9%) or acceptance of the fact that medications have side effects (8/695, 1.2%), trust in physician (46/695, 6.6%), and availability of effective alternatives to rofecoxib (97/695, 14.0%). Of the 273 who indicated a change in attitude, the most common response was that they were now more fearful or nervous about the use of pain medications (188/273, 68.9%). Overall, ever rofecoxib users (46.6%) and women (30.3%) were more likely than never users (20.7%; p = 0.0001) and men (21.05%; p = 0.007), respectively, to report a change in attitude, and to be more fearful now of using arthritis pain medications [30.2% ever users vs 15.15% never

Table 3. Coxib indications among ever and never users of a coxib (n = 968*).

	Never Used Coxib N = 455	Ever Used Coxib, N = 513	Vioxx, N = 277	Celebrex, N = 407
Absolute contraindications for traditional NSAID use				
Self-reported history of GI event, n (%)				
Any GI problems	15/450 (3.3)	19/499 (3.8)	10/270 (3.7)	14/397 (3.5)
Diagnosed on endoscopy or barium swallow	8/450 (1.8)	15/499 (3.0)	7/270 (2.6)	12/397 (3.0)
Bleeding ulcer confirmed on gastroscopy	4/450 (0.9)	7/499 (1.4)	3/270 (1.1)	5/397 (1.3)
Hospitalized for GI problems	1/450 (0.1)	5/499 (1.0)	2/270 (0.7)	3/397 (0.8)
Use of blood thinners, n (%)				
Prescription blood thinners (e.g., coumadin, heparin)	55 (12.1)	64 (12.5)	37 (13.4)	49 (12.0)
Acetylsalicylic acid (ASA)	147 (32.3)	178 (34.7)	91 (32.9)	144 (35.4)
Use of systemic corticosteroids	15 (3.3)	19 (3.7)	11 (4.0)	15 (3.7)
Self-report of any contraindication to nonselective NSAID† (GI ulcer or hemorrhage, use of ASA, anticoagulants, steroids)	219 (48.1)	202 (39.4)	106 (38.3)	163 (40.0)
Relative contraindications to traditional NSAID use				
Hypertension	229/451 (50.8)	264/499 (52.9)	136/270 (50.4)	213/398 (53.5)
Renal disease	4/451 (0.9)	3/499 (0.6)	1/270 (0.4)	2/398 (0.5)
Diabetes	80/451 (17.7)	86/499 (17.2)	46/270 (17.0)	66/398 (16.6)
Heart disease	121/451 (26.8)	150/499 (30.1)	80/270 (29.6)	112/398 (28.1)
Any of the above conditions†	293/451 (65.0)	340/499 (68.1)	173/270 (64.1)	273/398 (68.5)

* The denominator is given where less than 100% responded to the question. † P value for chi-square or Fisher exact test comparing the proportion of never coxib users versus ever users who had one or more absolute or one or more relative contraindications to nonselective or traditional NSAID use were non-significant (0.54 and 0.51, respectively).

Table 4. Communication of the Vioxx recall (n = 968*).

	Total N = 968 (%)	Never Vioxx Users, N = 691 (%)	Past Vioxx Users, N = 194 (%)	Vioxx Users at Recall, N = 83 (%)
Source of communication about Vioxx recall				
Had not heard about the recall	50 (5.2)	48 (6.9)	2/194 (1.0)	0/83 (0.0)
Heard about the recall via (n = 918)	918 (94.8)	643 (93.1)	192/194 (99.0)	83/83 (100.0)
Television	868/916 (94.7)	613/643 (95.3)	181/190 (95.3)	74 (89.2)
Newspapers	320/916 (34.9)	217/643 (33.7)	74/190 (38.9)	29 (34.9)
Magazines	17/916 (1.9)	14/643 (2.2)	1/190 (0.5)	2 (2.4)
Family/friends/neighbors/colleagues	228/916 (24.9)	153/643 (23.8)	53/190 (27.9)	22 (26.5)
Primary care doctor	36/916 (3.9)	7/643 (1.1)	8/190 (4.2)	21 (25.3)†
Pharmacist	11/916 (1.2)	0/643 (0)	2/190 (1.1)	9 (10.8)†
Best way to communicate drug safety issues to public (n = 968)**				
The media	556/966 (57.6)	401 (58.0)	112/192 (58.3)	43 (51.8)
Television	428/966 (44.3)	313 (45.3)	83/192 (43.2)	32 (38.6)
Newspaper	31/966 (3.2)	23 (3.3)	7/192 (3.7)	1 (1.2)
Internet	22/966 (2.3)	15 (2.2)	5/192 (2.6)	2 (2.4)
Radio	9/966 (0.9)	6 (0.9)	2/192 (1.0)	1 (1.2)
Magazines	5/966 (0.5)	4 (0.6)	1/192 (0.5)	0 (0.0)
Media, nonspecific	61/966 (6.3)	40 (5.8)	14/192 (7.3)	7 (8.4)
Pharmacist or pharmacies	157/966 (16.3)	110 (15.9)	31/192 (16.2)	16 (19.3)
Physicians	89/966 (9.2)	64 (9.3)	16/192 (8.3)	9 (10.8)
Should contact patients	15/966 (1.6)	8 (1.2)	4/192 (2.1)	3 (3.6)
Patient should contact doctor	47/966 (4.9)	35 (5.1)	8/192 (4.2)	4 (4.8)
Physicians should be better informed	20/966 (2.1)	16 (2.3)	3/192 (1.6)	1 (1.2)
Medical drug information books	7/966 (0.7)	5 (0.7)	1/192 (0.5)	1 (1.2)
Pharmaceutical companies	8/966 (0.8)	4 (0.6)	3/192 (1.6)	1 (1.2)
Other (includes word of mouth, flyers, and no ideas)	156/966 (16.1)	93 (13.5)	20/192 (10.4)	11 (13.3)

* The denominator is given when responses were less than 100%. ** Respondents were allowed to indicate more than one method of communication, thus the total percentage sums to more than 100%. † P value for comparison of proportions across subgroups is < 0.0001.

users ($p < 0.0001$); 21.5% women vs 12.7% men ($p = 0.003$)].

Perceptions of risk. Table 5 shows the risk perceptions of the cohort, stratified by rofecoxib experience (ever vs never users). Among the 968 respondents, 42.2% had "no idea" of the proportion of available medications with a potentially life-threatening side effect. Of those who voiced an opinion, most (63.7%) felt the proportion was between 1% and 25%. Only 2.1% reported that no medications carried such a risk.

When asked about the relative risk of heart attack among rofecoxib users versus nonusers, most respondents were unsure (60.9%); ever rofecoxib users were more likely than never users to hold an opinion (48.7% vs 35.3%; $p = 0.0001$). Among those with an opinion, the groups did not differ in their estimate of the relative risk. Two-thirds (66.8%) thought the relative risk was at or below 2 times the risk in nonusers. When asked to state the absolute risk of heart attack or stroke in 100 individuals taking rofecoxib for a year, similarly, most were unsure (52.6%). Of the remaining 459 respondents, 6.8% reported the risk to be < 1%, 37.5% between 1% and 5%, and the remainder perceived the absolute risk to be > 5%. Perceived absolute risk was higher for ever versus never rofecoxib users ($p = 0.006$; Table 5). No significant differences in risk perceptions were found by age, sex, race, education, or income.

DISCUSSION

To examine patients' reactions to the recall of rofecoxib, we asked participants in an ongoing prospective community based cohort study of hip and knee OA to give us their impressions. To our knowledge, this is the first report of the response of a large sample of arthritis patients to this recall.

Over half of our elderly cohort had used one or more of the coxibs, which were first listed on the Ontario Provincial Drug Benefit formulary in April 2000 as "limited-use" products. As limited-use products, the coxibs were covered as a benefit if the prescribing physician indicated on the prescription using a prespecified code that prior NSAID use had failed or was not tolerated by the patient, or that the patient had a documented history of clinically significant GI ulcer or hemorrhage. Patients who did not meet these criteria were still able to receive a prescription for these products, but would be required to pay for it.

Table 5. Perceptions of cardiovascular risk with Vioxx (n = 968).

	Overall N = 968 (%)	Prior Vioxx Experience: Ever Users, N = 277 (%)	Prior Vioxx Experience: Never Users, N = 691 (%)	p
What percentage of all available medications have an associated "life-threatening" side effect?, N (%)				
Don't know	408 (42.2)	102 (36.8)	306 (44.3)	0.03*
Opinion	560 (57.8)	175 (63.2)	385 (55.7)	
None	12/560 (2.1)	2/175 (1.1)	10/385 (2.6)	0.003†
1–25%	357/560 (63.7)	97/175 (55.5)	260/385 (67.5)	
26–50%	156/560 (27.9)	58/175 (33.1)	98/385 (25.5)	
51–75%	33/560 (5.9)	18/175 (10.3)	15/385 (3.9)	
76–100%	2/560 (0.4)	0/175 (0.0)	2/385 (0.5)	
Perceived relative risk of myocardial infarction in Vioxx users versus nonusers, n (%)				
Don't know	589 (60.9)	142 (51.3)	447 (64.7)	0.0001*
Opinion	379 (39.2)	135 (48.7)	244 (35.3)	
1.5	64/379 (16.9)	18/135 (13.3)	46/244 (18.8)	NS†
2.0	189/379 (49.9)	62/135 (45.9)	127/244 (52.1)	
2.5	27/379 (7.1)	10/135 (7.4)	17/244 (7.0)	
3.0	86/379 (22.7)	41/135 (30.4)	45/244 (18.4)	
> 3.0	13/379 (3.4)	4/135 (3.0)	9/244 (3.7)	
Perceived absolute risk of myocardial infarction or stroke in 100 Vioxx users at 1 year, n (%)				
Don't know	509 (52.6)	122 (44.0)	387 (56.0)	0.0008*
Opinion	459 (47.4)	155 (56.0)	304 (44.0)	
< 1 %	31/459 (6.8)	4/155 (2.6)	27/304 (8.9)	0.006†
1–5 %	172/459 (37.5)	53/155 (34.2)	119/304 (39.1)	
6–10 %	123/459 (26.8)	41/155 (26.5)	82/304 (27.0)	
11–20 %	81/459 (17.7)	32/155 (20.7)	49 /304 (16.1)	
21–30 %	40/459 (8.7)	22/155 (14.2)	18/304 (5.9)	
> 30 %	12/459 (2.6)	3/155 (1.9)	9/304 (3.0)	

* Chi-square test comparison of proportions who reported "don't know". † Chi-square or Fisher exact test comparison of distribution of responses for ever versus never users who gave an opinion.

Although the major theoretical clinical advantage of the coxib class of medications is their reduced risk for GI toxicity[18,19], fewer than 5% of participants reported intolerance to conventional NSAID or a history of a significant GI event, and we found no association between history of a prior GI event and coxib use. These findings are consistent with those of others[25-27]. Mamdani, *et al*[25], reported that among patients age 70+ years who received a COX-2 inhibitor prescription, only 28.9% had received an upper GI diagnostic examination, a proxy for occurrence of a significant GI event, in the previous 5 years. Assuming participants' self-reported responses regarding intolerance of traditional NSAID and GI adverse events are accurate, the majority of our ever coxib users appeared not to be appropriate candidates for receipt of a coxib under the limited-use criteria. This implies any one of the following: (1) they chose to pay for the medication (this is supported by the fact that ever coxib users had higher income than never users); and/or (2) physicians chose to apply the limited-use criteria more liberally, possibly to account for the high prevalence of comorbidities that might place an older individual at risk with use of a traditional NSAID; and/or (3) traditional NSAID were deemed ineffective.

Over 90% of ever coxib users reported their doctors had told them that the coxibs work better than conventional NSAID as arthritis pain relievers. In the absence of evidence to support this conviction, and assuming that participants are recalling what was said to them accurately, this is a concern and perhaps reflects the common perception that "newer must be better."

Among those who had personal experience using rofecoxib, some participants reported being more fearful now about using pain medications. Only 18% who were taking rofecoxib at the time of its recall were willing to consider using rofecoxib again should it become available. Studies suggest that there is already undermanagement of chronic pain in the elderly[28] — our findings raise concern that the rofecoxib recall may exacerbate this problem.

Perhaps as might be expected, most participants heard about the recall through the media. Physicians and other health professionals played a comparatively minor role in the dissemination of information about the recall to their patients. In general, participants recognized the media as the best way to communicate drug safety issues to patients. However, our findings do raise questions about the role of healthcare providers in such situations.

Merck recalled rofecoxib from the market on the basis of findings from the APPROVe trial, which randomized the 2586 patients with colon polyps at low risk for heart attack or stroke to receive rofecoxib or placebo. Among those randomized, 26 taking placebo compared with 46 taking rofecoxib suffered a cardiovascular event (relative risk 1.92, $p = 0.008$)[29]. Among those randomized to rofecoxib, the risk of an event was 1.5 events per 100 patient-years compared with 0.78 events per 100 patient-years in the placebo group. When asked their perceptions of the cardiovascular risk associated with rofecoxib use, most participants were unsure. Of those with an opinion, most correctly estimated the relative risk for heart attack, but tended to overestimate the absolute risk; 56% estimated the absolute risk of heart attack over a one-year period as 6 in every 100 rofecoxib users, well above the published risk. To our knowledge, no previous studies have explicitly examined patients' perceptions of risk associated with coxib use. However, Fraenkel, *et al*[30] used an adaptive conjoint analysis survey in arthritis patients to examine the relationship between preferences for coxib use and risk-benefit perceptions. Their findings suggest that patients' willingness to pay for coxibs may reflect misperceptions of the risk of toxicity associated with these medications. A number of other studies, however, have examined patients' perceptions regarding risk for developing a disease[31-35]. These studies consistently show that patients have difficulties understanding risk as portrayed by percentages and tend to overestimate their risk in general, but moreso their absolute risk than risk relative to others[31,32,34,35]. These studies furthermore indicate that the optimal method for communication of risk will vary according to the patients' level of education and age[31-33,36,37]. Similarly, some physicians may not fully understand or interpret study findings correctly when presented with relative versus absolute risk reduction information[38,39], and thus may not accurately communicate the risks to their patients. Our findings provide further support for the need for improved knowledge translation of key study results to the lay community in a format that is understandable and correct. This is particularly important in light of evidence to show that patients' risk perceptions influence their healthcare choices and adherence to physician recommendations[30,36,40].

The strengths of our study include the large cohort size, community setting, and the fact that over half had used rofecoxib at some point in the past for their arthritis, including 83 individuals who were taking it at the time of its recall. Our high participation rate among those eligible for the survey reflects the interest of our cohort in discussing the rofecoxib recall and how it has affected their lives. However, there are also some potential limitations. Study participants were individuals who have been enrolled in a longitudinal observational study of hip and knee OA in Ontario, Canada. Thus, the opinions expressed may not be reflective of the opinions of the general Canadian public, nor of individuals living with OA in Canada overall or in countries where the healthcare system is different. Finally, prior use of a coxib, indications for use, and coexistence of other medical problems were based on self-report and are therefore subject to recall bias.

In a community based cohort of elderly individuals with OA, consistent with previous studies, the prevalence of use of one or more of the coxibs for the management of arthritis pain was high, and was unexplained by the presence of absolute contraindications to use of traditional NSAID. The main source of information regarding the recall was the media,

although up to one-quarter of those taking rofecoxib at the time of the recall were also informed by a health professional. Many individuals were unaware of, or overestimated, the absolute risk of adverse events associated with rofecoxib use. These findings highlight the need for prompt and clear information on risks and benefits of therapies for consumers, and the need for a method whereby physicians/pharmacists can provide their patients with timely and accurate information on risks.

Dr. Hawker had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Couzin J. Drug safety. Withdrawal of Vioxx casts a shadow over COX-2 inhibitors. Science 2004;306:384-5.
2. DeMaria AN. The fallout from Vioxx. J Am Coll Cardiol 2004;44:2080-1.
3. Eisenberg RS. Learning the value of drugs — is rofecoxib a regulatory success story. N Engl J Med 2005;325:1285-7.
4. Finckh A, Aronson MD. Cardiovascular risks of cyclooxygenase-2 inhibitors: where we stand now. Ann Intern Med 2005;142:212-4.
5. Hampton T. Experts point to lessons learned from controversy over rofecoxib safety. JAMA 2005;293:413-4.
6. Horton R. Vioxx, the implosion of Merck, and aftershocks at the FDA. Lancet 2004;364:1995-6.
7. Hunt RH, Barkun AN, Baron D, et al. Recommendations for the appropriate use of anti-inflammatory drugs in the era of coxibs: defining the role of gastroprotective agents. Can J Gastroenterol 2002;16:231-40.
8. Kennedy D. Clinical trials and public trust [editorial]. Science 2004;306:1649.
9. Mansfield PR, Vitry AI, Wright JM. Withdraw all COX-2-selective drugs [letter]. Med J Aust 2005;182:197.
10. Marris E. Suppressed study raises spectre of flawed drug regulation in US. Nature 2004;432:537.
11. Okie S. Raising the safety bar — the FDA's coxib meeting. N Engl J Med 2005;352:1283-5.
12. Oritz E. Market withdrawal of Vioxx: is it time to rethink the use of COX-2 inhibitors? J Manag Care Pharm 2004;10:551-4.
13. Solomon DH, Avorn J. Coxibs, science, and the public trust. Arch Intern Med 2005;165:158-60.
14. Topol EJ. Failing the public health — rofecoxib, Merck and the FDA. N Engl J Med 2004;351:1707-9.
15. Vioxx: an unequal partnership between safety and efficacy. Lancet 2004;364:1287-8.
16. Report of the Joint Meeting of the FDA Advisory Committees on Arthritis Drugs and Drug Safety and Risk Management. Available from: http:/www.fda.gov/ohrms/dockets/ac/cder05.html#ArthritisDrugs. Accessed March 3, 2006.
17. Report of the Expert Advisory Panel on the Safety of Cox-2 Selective non-steroidal anti-inflammatory drugs (NSAIDs). Available from: http:/www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/sci-consult/cox2/sap_report_gcs_rapport_cox2_e.html. Accessed March 3, 2006.
18. 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;343:1520-8.
19. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib versus nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study; a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284:1247-55.
20. Abraham C. The painful battle over the 'wonder drug' Vioxx. The Globe and Mail 2005 Saturday Feb 19.
21. Schneeweiss S, Glynn RJ, Avorn J, Solomon DH. Diminishing influence of patient factors in prescribing of newly marketed COX-2 inhibitors. J Clin Epidemiol 2005;58:98-102.
22. Hawker GA, Wright JG, Coyte PC, et al. Determining the need for hip and knee arthroplasty: the role of clinical severity and patients' preferences. Med Care 2001;39:206-16.
23. Hawker GA, Wright JG, Coyte PC, et al. Differences between men and women in the rate of use of hip and knee arthroplasty. N Engl J Med 2000;342:1016-22.
24. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
25. Mamdani M, Rochon P, Laupacis A, Anderson G. Initial patterns of use of COX-2 inhibitors by elderly patients in Ontario: findings and implications. CMAJ 2002;167:1125-6.
26. Solomon DH, Schneeweiss S, Glynn RJ, Levin R, Avorn J. Determinants of selective cyclooxygenase-2 inhibitor prescribing: are patient or physician characteristics more important? Am J Med 2003;115:715-20.
27. Patino FG, Allison J, Olivieri J, et al. The effects of physician specialty and patient comorbidities on the use and discontinuation of coxibs. Arthritis Rheum 2003;49:293-9.
28. Hanlon JT, Fillenbaum GG, Studenski SA, Ziqubu-Page T, Wall WE Jr. Factors associated with suboptimal analgesic use in community-dwelling elderly. Ann Pharmacother 1996;30:739-44.
29. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092-102.
30. Fraenkel L, Wittink DR, Concato J, Fried T. Are preferences for cyclooxygenase-2 inhibitors influenced by the certainty effect? J Rheumatol 2004;31:591-3.
31. Christian AH, Mochiari HY, Mosca LJ. Coronary heart disease in ethnically diverse women: risk perception and communication. Mayo Clin Proc 2005;80:1593-9.
32. Haomiao J, Santana A, Lubetkin EI. Measuring risk perception among low-income minority primary care patients. J Ambul Care Manage 2004;27:314-27.
33. Schapira MM, Davids SL, McAuliffe TL, Nattinger AB. Agreement between scales in the measurement of breast cancer risk perceptions. Risk Anal 2004;24:665-73.
34. Weinstein ND, Atwood K, Puleo E, Fletcher R, Colditz G, Emmons KM. Colon cancer: risk perceptions and risk communication. J Health Commun 2004;9:53-65.
35. Frijling BD, Lobo CM, Keus IM, et al. Perceptions of cardiovascular risk among patients with hypertension or diabetes. Patient Educ Couns 2004;52:47-53.
36. Lipkus IM, Lyna PR, Rimer BK. Colorectal cancer risk perceptions and screening intentions in a minority population. J Natl Med Assoc 2000;92:492-500.
37. Lipkus IM, Hollands JG. The visual communication of risk. J Natl Cancer Inst Monogr 1999;25:149-63.
38. Bucher HC, Weinbacher M, Gyr K. Influence of method of reporting study results on decision of physicians to prescribe drugs to lower cholesterol concentration. BMJ 1994;309:761-4.
39. Bucher HC, Morabia A. Teaching physicians about different measures of risk reduction may alter their treatment preference. Soz Praventivmed 1998;43:67-72.
40. Murphy DJ, Gahm GJ, Santilli S, North P, Oliver SC, Sharpiro H. Seniors' preferences for cancer screening and medication use based on absolute risk reduction. J Gerontol A Biol Sci Med Sci 2002;57:M100-5.