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ORIGINAL ARTICLE

Prescribing Pattern of Drugs in the Treatment of Osteoarthritis in Italian General Practice: The Effect of Rofecoxib Withdrawal

MARIANNA ALACQUA,[1] GIANLUCA TRIFIRÒ,[2] LORENZO CAVAGNA,[3] ROBERTO CAPORALI,[3] CARLO MAURIZIO MONTECUCCO,[3] SALVATORE MORETTI,[4] DOMENICO UGO TARI,[4] MARIELLA GALDO,[4] ACHILLE P. CAPUTI,[2] AND VINCENZO ARCORACI[1]

Objective. **In October 2004, rofecoxib was removed from the world market because of an increased risk of myocardial infarction. The aim of the present study was to compare the trend of nonsteroidal antiinflammatory drug (NSAID) use and other analgesics in osteoarthritis (OA) treatment before and after rofecoxib withdrawal in Italian general practice.**

Methods. **From the Caserta-1 Local Health Service database, 97 general practitioners were recruited. Prevalence and incidence of use of any study drug were calculated within 1 year before and after rofecoxib withdrawal.**

Results. **One-year prevalence of nonselective and preferential NSAID use did not change after rofecoxib withdrawal, whereas coxib use fell from 4.4% (95% confidence interval [95% CI] 4.2–4.5%) in the period before rofecoxib withdrawal (period I) to 1.6% (95% CI 1.5–1.7%) in the period after withdrawal (period II). Weak opioids were used in no more than 0.4% (95% CI 0.3–0.5%) in period II, after their introduction to reimbursement in December 2004. Also, 1-year incidence of coxib decreased from 31.3 per 1,000 (95% CI 30.2–32.4%) in period I to 8.7 per 1,000 (95% CI 8.1–9.2%) in period II. The disappearance of rofecoxib was associated with replacement drugs such as newly marketed dexibuprofen and aceclofenac, whereas nimesulide use coincidentally decreased.**

Conclusion. **Rofecoxib withdrawal has markedly changed the prescribing pattern of drugs that are used in OA-related pain treatment, with a striking decrease of coxib use in Italian general practice. Education strategies addressed to health professionals should be planned to improve the management of pain treatment, particularly in degenerative joint diseases.**

INTRODUCTION

Osteoarthritis (OA) is widely known as the most frequent musculoskeletal disorder, mainly occurring in the elderly (1,2), with a radiographic prevalence of nearly 70% in persons over age 65 (1). Disease burden is related to pain occurrence, frequently leading to functional disability ranging from slight limitation of movements to severe impairment of normal daily living activities (3,4). Therefore, pain relief plays an important role in the treatment of OA. Although acetaminophen is indicated as first-line therapy for controlling pain in persons with OA (5–7), nonsteroidal antiinflammatory drugs (NSAIDs) are the most effective medications (8,9). In the late 1980s, the increasing evidence of serious gastrointestinal (GI) adverse events (e.g., GI perforation, ulceration, and bleeding) led to a progressive decline in NSAID use for OA treatment, especially among elderly patients, while acetaminophen use did not increase as expected (10). Starting in 1998 (11), the marketing of a new class of NSAIDs with a low GI toxicity risk, the selective cyclooxygenase 2 (COX-2) inhibitors (coxibs), mainly celecoxib and rofecoxib (12–14), changed the prescribing pattern of painkillers in OA. Indeed, coxibs were suggested as first-line therapy in the treatment of OA-related pain in patients at high risk of GI bleeding (15,16). In October 2004, however, rofecoxib was withdrawn from the market because of evidence of an increased risk of myocardial infarction (17). In light of these events, the goal of our study was to compare the trend in

[1]Marianna Alacqua, MD, Vincenzo Arcoraci, MD: University of Messina, Messina, Italy; [2]Gianluca Trifirò, MD, Achille P. Caputi, MD: University of Messina and IRCCS Centro Neurolesi "Bonino-Pulejo," Messina, Italy; [3]Lorenzo Cavagna, MD, Roberto Caporali, MD, Carlo Maurizio Montecucco, MD: University of Pavia, IRCCS S. Matteo Foundation, Pavia, Italy; [4]Salvatore Moretti, MD, Domenico Ugo Tari, MD, Mariella Galdo, MD: Caserta 1 Local Health Service, Caserta, Italy.

Address correspondence to Marianna Alacqua, MD, Department of Clinical and Experimental Medicine and Pharmacology, Pharmacology Unit, University of Messina, Via Consolare Valeria-Gazzi, 98125 Messina, Italy. E-mail: alacqua@unime.it.

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use of different NSAIDs and other analgesic drugs for the treatment of OA-related pain before and after rofecoxib withdrawal in a general practice in southern Italy.

Because NSAIDs are a major cause of serious adverse drug reactions and of regulatory interventions, and taking into account the high prevalence of OA, we think that our report may be important to obtain information about the pattern of prescribing painkillers by general practitioners (GPs) after a sudden and unexpected withdrawal of a drug from the market.

PATIENTS AND METHODS

Data source. Data were extracted from the Arianna database during the period September 30, 2003 to September 30, 2005. This database, set up by the Health Service Agency of Caserta city in the year 2000, currently contains information about a population of almost 300,000 individuals living in the catchment area of Caserta who are registered with 225 (73.7%) of 305 GPs practicing in the same area. Participating GPs record data during their daily clinical practice using dedicated software and send monthly complete and anonymous data concerning their patients to the Arianna database. Information collected includes patient demographics and drug prescriptions coded according to the Anatomical Therapeutic Chemical (ATC) classification system and linked to medical diagnoses coded by the International Classification of Diseases, Ninth Revision (ICD-9).

All participating GPs received extensive training in data collection techniques. Routine quality checks included analysis of several parameters such as missing patient codes, number of daily filled prescriptions, proportion of prescriptions correctly linked to medical diagnoses, and monthly continuity of data submission. Any variation within defined ranges was investigated and back submitted to each participating GP in order to receive immediate feedback about data quality and completeness. GPs failing to meet these standard quality criteria were not retained within the project, according to basic standards in the conduct of pharmacoepidemiologic studies (18). So far, the Arianna database has been shown to provide accurate and reliable information about drug utilization in general practice (19–21).

Educational intervention for GPs. Starting in 2001, GPs enrolled in the study were well trained concerning the guidelines for OA diagnosis (22,23) and treatment (5–7), thanks to a continuous medical educational program of interactive teaching intervention and decisional algorithms presentation (24–27) by 2 well-experienced rheumatologists (RC and LC).

Study population. Overall, 97 GPs who continuously sent data to the Arianna database during the period September 30, 2003 to September 30, 2005 were selected for this investigation. Among 142,346 individuals age ≥25 years who were registered with these GPs, patients who received at least 1 prescription for the treatment of OA-related pain (ICD-9 code 715) during the observation years were identified. Patients were included in the study irrespective of whether pharmacologic treatment was initiated by GPs or by specialists working in the public or private sector. Indeed, in Italy, outpatients being treated by specialists receive medicines free of charge only if prescribed by a GP.

The following drug cohorts were identified: 1) NSAIDs, divided (based on affinity to cox enzyme isoforms) into COX-2 preferential (nabumetone [ATC code M01AX01], meloxicam [ATC code M01AC06], and nimesulide [ATC code M01AX17]), coxib (celecoxib [ATC code M01AH01], rofecoxib [ATC code M01AH02], valdecoxib [ATC code M01AH03], and etoricoxib [ATC code M01AH05]), and nonselective (NS) NSAIDs (all M01A, except for coxib and COX-2 preferential), and 2) weak opioids (ATC codes N02AE, N02AX) that are reimbursed by the Italian National Health System (NHS) since December 2004. Acetylsalicylic acid is not reimbursed when prescribed as an analgesic drug, and parecoxib was never marketed in Italy; therefore, these medications were not included in the analysis. Acetaminophen is also not reimbursed by the Italian NHS. At the end of the study, however, all GPs enrolled in this investigation completed a questionnaire that asked them to indicate whether acetaminophen utilization for OA-related pain was increased or decreased after rofecoxib withdrawal. After identification of users of study drugs, information about patient demographics and drug prescriptions recorded during the study period was retrieved using the Arianna database. Furthermore, utilization of different study drugs was evaluated before and after rofecoxib withdrawal, according to presence of concurrent GI diseases (ICD-9 codes 530–537, 578) and coronary heart disease (ICD-9 codes 410–414).

Prevalence and incidence of use. For each 1-year period, the prevalence of the study drugs was calculated as the number of study drug users divided by the number of patients alive and registered in the GPs' lists. Within each 1-year period, we defined a new user as a patient receiving a first prescription for OA-related pain treatment without any prescription in the previous year. Before and after rofecoxib withdrawal, the cumulative incidence rate was measured as the number of new users divided by the number of patients free from study drug use in the previous year. Regarding opioid prescriptions, our data were limited to the period subsequent to rofecoxib withdrawal, because these drugs were not previously reimbursed and therefore were not registered in the database. Both prevalence and incidence were expressed as rates per 100 or per 1,000 inhabitants, together with 95% confidence intervals (95% CIs).

Statistical analysis. Chi-square test for categorical variables and Student's *t*-test for continuous variables, with a significance level of $P < 0.05$, were used for assessing the differences among users of various study drug types within 2 years of observation. Statistical analyses were performed using STATA 6.0 (StataCorp, College Station, TX).

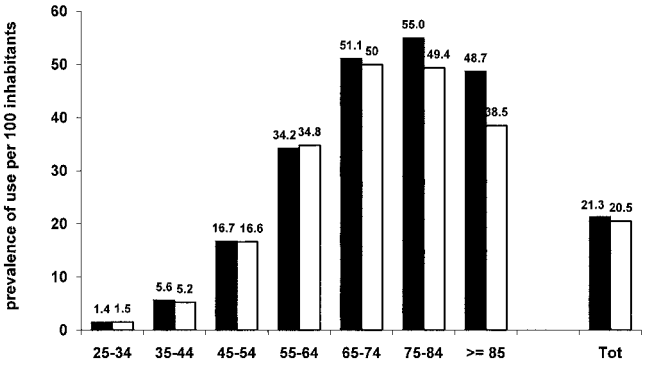

Figure 1. Prevalence of use, per 100 inhabitants, of drugs for osteoarthritis-related pain, stratified by age groups and study periods. Period I (solid bars) = before rofecoxib withdrawal (from October 1, 2003 to September 30, 2004); period II (open bars) = after rofecoxib withdrawal (from October 1, 2004 to September 30, 2005). Tot = total.

RESULTS

Prevalence of study drug use before and after rofecoxib withdrawal. Overall, there was a minor but significant ($P < 0.05$) decrease in the prescribing of OA symptomatic drugs from 21.3 (95% CI 20.9–21.5) to 20.5 (95% CI 20.2–20.8) per 100 inhabitants in the period before (period I) and after (period II) rofecoxib withdrawal, respectively (Figure 1). In particular, such a decrease was more clearly shown ($P < 0.05$) in patients age >65 years (period I: 52.3%, 95% CI 51.3–53.2; period II: 48.6%, 95% CI 47.6–49.4).

Regarding different study drugs, NS NSAID use resulted in a slight increase in prevalence after rofecoxib withdrawal from 12.1% (95% CI 11.8–12.2) in period I to 12.7% (95% CI 12.4–12.8) in period II (Figure 2). In contrast, the prevalence of COX-2 preferential use remained rather stable between the study years (period I: 11.8%, 95% CI 11.5–11.9; period II: 11.5%, 95% CI 11.2–11.6). The prevalence of coxib use fell from 4.4% (95% CI 4.2–4.5) in period I to 1.6% (95% CI 1.5–1.7) in period II. Weak

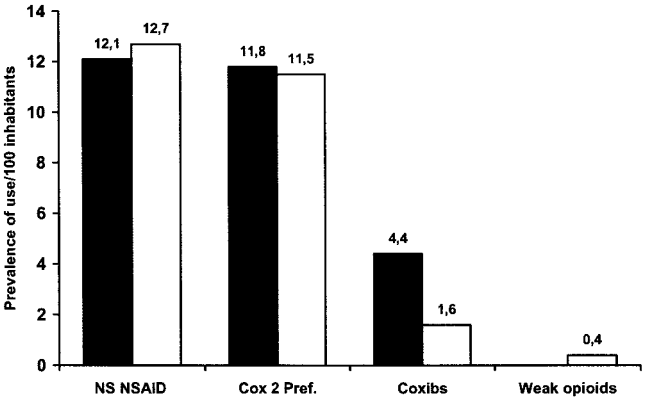

Figure 2. Prevalence of use, per 100 inhabitants, of different study drug types, stratified by study periods. Period I (solid bars) = before rofecoxib withdrawal (from October 1, 2003 to September 30, 2004); period II (open bars) = after rofecoxib withdrawal (from October 1, 2004 to September 30, 2005). NS NSAID = nonselective nonsteroidal antiinflammatory drug; pref. = preferential.

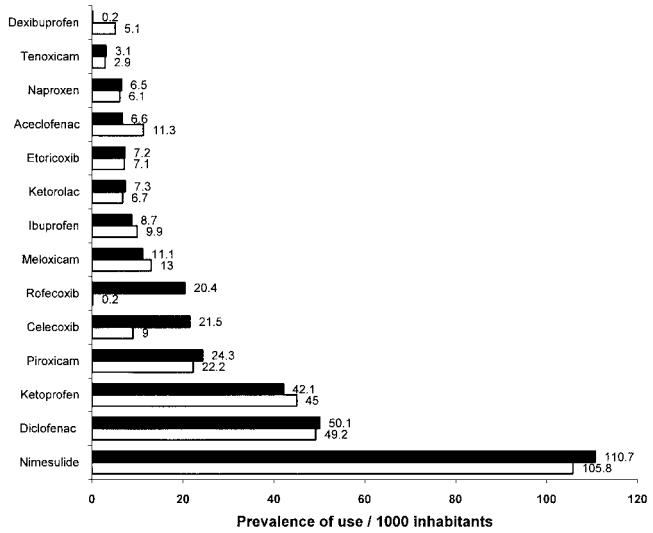

Figure 3. Prevalence of use, per 1,000 inhabitants, of individual medications stratified by study periods. Medications accounting for >90% of total drug prescriptions for osteoarthritis-related pain treatment have been included in the analysis. Period I (solid bars) = before rofecoxib withdrawal (from October 1, 2003 to September 30, 2004); period II (open bars) = after rofecoxib withdrawal (from October 1, 2004 to September 30, 2005).

opioids, reimbursed by the Italian NHS since December 2004, were used in 0.4% (95% CI 0.3–0.5%) of patients with OA after rofecoxib withdrawal.

Looking specifically at coxibs, the prevalence of use per 1,000 inhabitants decreased for both rofecoxib (period I: 20.4, 95% CI 19.5–21.2; period II: 0.2, 95% CI 0.1–0.3) and celecoxib (period I: 21.5, 95% CI 20.5–22.4; period II: 9.0, 95% CI 8.3–9.5) (data not shown). Only use of etoricoxib did not change during the 2 observation years (period I: 7.2, 95% CI 6.6–7.7; period II: 7.1, 95% CI 6.5–7.6). Valdecoxib, marketed in June 2004 and withdrawn in April 2005, was poorly used during the study period compared with other coxibs (0.9, 95% CI 0.7–1.0).

Figure 3 shows the prevalence of use, per 1,000 inhabitants, of medications accounting for 90% of total painkiller prescriptions in patients with OA. Almost 50% of patients treated for OA-related pain received at least 1 prescription of nimesulide during the study period. Prevalence of nimesulide use was 2 times higher than that of diclofenac (the second most used medication) in both years, although its prevalence of use slightly decreased after the rofecoxib withdrawal. The disappearance of rofecoxib induced significant changes in the prescribing of different drug classes. Concerning coxibs, a more than 50% reduction in celecoxib use was reported, whereas no changes in the prescribing of etoricoxib were shown. Regarding COX-2 preferential and NS NSAID use, aceclofenac use was 2 times higher in period II (11.3 per 1,000) compared with period I (6.6 per 1,000), whereas use of dexibuprofen, marketed in May 2004 in Italy, increased from 0.2 per 1,000 to 5.1 per 1,000 after rofecoxib removal.

One-year incident use of NSAIDs before and after rofecoxib withdrawal. The cumulative incidence of treatment with NS NSAIDs was 73.6 (95% CI 71.9–75.3) per 1,000

Table 1. Demographic and clinical characteristics of NSAID users due to osteoarthritis before and after rofecoxib withdrawal*

	Coxib		Nonselective NSAID		Selective NSAID	
	Before (n = 4,320)	After (n = 1,630)	Before (n = 11,762)	After (n = 12,693)	Before (n = 11,462)	After (n = 11,500)
Age, mean ± SD years	67.5 ± 11.5	68.3 ± 11.3	63.7 ± 13.3	63.8 ± 12.9	66.0 ± 12.0	66.0 ± 11.5
<65	1,568 (36.3)	542 (33.2)	5,657 (48.1)	6,154 (48.5)	4,832 (42.2)	4,917 (42.7)
>65	2,752 (63.7)	1,088 (66.8)	6,105 (51.9)	6,539 (51.5)	6,630 (57.8)	6,583 (57.3)
Sex						
Male	1,335 (30.9)	445 (27.3)	4,388 (38.3)	4,661 (36.7)	4,321 (37.7)	4,310 (37.5)
Female	2,985 (69.1)	1,185 (72.7)	7,374 (62.7)	8,032 (63.3)	7,141 (62.3)	7,190 (62.5)
Concurrent disease						
GI diseases†	711 (16.4)	309 (18.9)	1,653 (14.0)	1,857 (14.6)	1,461 (12.7)	1,578 (13.7)
CHD‡	210 (4.8)	74 (4.5)	504 (4.3)	488 (3.8)	571 (5.0)	547 (4.7)
Concomitant drugs						
Antiplatelet agents	976 (22.5)	363 (22.3)	2,147 (18.2)	2,432 (19.2)	2,304 (20.1)	2,403 (20.9)
Anticoagulants	53 (1.2)	10 (0.6)	106 (0.9)	118 (0.9)	113 (1.0)	111 (1.0)
PPI due to						
Gastroprotection	200 (4.6)	84 (5.1)	428 (3.6)	350 (2.7)	331 (2.9)	270 (2.3)
Other GI diseases	838 (19.3)	280 (17.2)	1,787 (15.2)	1,679 (13.2)	1,513 (13.2)	1,378 (12.0)

* Values are the number (percentage) unless otherwise indicated. NSAID = nonsteroidal antiinflammatory drug; GI = gastrointestinal; CHD = coronary heart disease; PPI = proton-pump inhibitor.
† Diseases of the esophagus, gastric and duodenal ulcer, gastritis and duodenitis, functional disorders of the stomach and duodenum, and GI bleeding.
‡ Myocardial infarction, angina pectoris, and other coronary heart disease. Both concomitant diseases and medications were evaluated at the first prescription of drugs for osteoarthritis within each study year.

inhabitants and 78.7 (95% CI 76.9–80.4) before and after rofecoxib withdrawal, respectively. Incident use of COX-2 preferentials was unmodified during the study period: 54.9 per 1,000 inhabitants (95% CI 53.4–56.5). In contrast, incident use of coxibs strongly decreased from 31.3 per 1,000 (95% CI 30.2–32.4) in period I to 8.7 (95% CI 8.1–9.2) in period II.

Clinical characteristics of study drug users. Clinical characteristics of study drug users are described in Table 1. Coxib users were mostly women and were older than other NSAID users. Moreover, the proportion of coxib users age >65 years was higher after rofecoxib withdrawal (66.8%, 95% CI 62.8–70.8) compared with before (63.7%, 95% CI 61.3–66.1).

The proportion of coxib users who were affected by GI diseases or used antiplatelet agents or proton-pump inhibitors (when used as gastroprotective agents) was higher than users of other NSAIDs, particularly after rofecoxib withdrawal. In contrast, the proportion of patients with coronary heart disease was rather similar among users of all NSAID subgroups, with a slight reduction (not statistically significant) after rofecoxib withdrawal.

DISCUSSION

In the late 1980s, awareness of NSAID-related GI adverse events led to a decreased use of these medications in older patients with OA (10). By itself, this fact is not surprising because elderly persons are at a high risk of NSAID-related GI toxicity (28–30). When coxibs were introduced into the drug market, these health issues seemed to be partially solved (12–14) and NSAID use in the elderly increased >40%, entirely due to COX-2 inhibitors (14). Coxibs, however, are not completely safe and their marketing surprisingly led to an increased hospitalization rate due to upper GI hemorrhage in patients age >65 years (14). In contrast, cardiovascular risks were also reported for rofecoxib (13). As a consequence, on September 30, 2004, rofecoxib was withdrawn from the market due to the results of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study (17), showing that long-term rofecoxib use was related to higher risk of myocardial infarction compared with placebo.

Although the initial impact of coxibs on the pharmacologic treatment of patients with OA is well known (31), we were unaware of the consequences of the withdrawal of rofecoxib on pain treatment in OA. Indeed, previous drug utilization studies demonstrated that rofecoxib withdrawal reduced the prescription of celecoxib (32), also with a delayed effect (33), and reduced the prescription of all coxibs (31), whereas an increase in the use of classic NSAIDs, such as diclofenac, ibuprofen, meloxicam, and etodolac, has been reported (32). In these articles, however, despite the amount of data available, no information was given about the real motivation of coxib and NSAID prescriptions, and thus it was not possible to specifically evaluate the burden of rofecoxib withdrawal on OA treatment.

In our analysis, overall use of painkillers in patients with OA decreased slightly but significantly after rofecoxib withdrawal. This decrease occurred particularly in patients age >65 years and was mainly due to a reduction in coxib utilization, whereas COX-2 preferential and NS NSAID use did not significantly change.

Because acetaminophen is not reimbursed by the Italian NHS, our data source did not make it possible to analyze utilization of acetaminophen. For this reason, at the end of the study, we administered a specific and simple questionnaire to GPs about acetaminophen utilization in patients

with OA. GPs indicated, in general, a low use of such an analgesic in patients with OA, without any variation after rofecoxib withdrawal. In line with a previous survey enrolling a large number of Italian GPs (34), our study also suggests an underutilization of acetaminophen in OA-related pain treatment after rofecoxib withdrawal. This finding might be partly explained by the fact that acetaminophen is in charge of citizens.

Furthermore, the high prevalence of NSAID use can be related to the analgesic and antiphlogistic properties of NSAIDs; in fact, inflammation is one of the main determinants of pain and disease progression in OA (31,33). Thus, a class of drugs with analgesic power that act on inflammation may have a very important place in this setting, and this is in line with OA patients' preference for NSAIDs (8,9).

The interpretation of pain treatment in patients with OA is not univocal. First, pain may now be considered less by GPs than before rofecoxib withdrawal, as previously described by Ausiello and Stafford for traditional NSAIDs. Second, it is possible to speculate an overtreatment of OA-related pain by GPs before rofecoxib withdrawal, according to the well-established GI safety of coxibs (12–14).

In contrast with previous studies (35,36), in patients age >65 years, we found a lower utilization of coxibs compared with COX-2 preferential and NS NSAIDs both before and after rofecoxib withdrawal. The strong reduction in coxib prescriptions after rofecoxib removal, particularly in older patients, suggests that cardiotoxicity plays a primary role in changing the prescribing behavior of GPs.

Moreover, prevalence of celecoxib use decreased to less than half, suggesting that a class effect of coxibs is considered by GPs. Although data about rofecoxib are undisputable, as outlined by the re-analysis of the APPROVe study (37), celecoxib does not seem to increase the risk of cardiovascular events at the commonly used dose (38–40), probably as a result of lower selectivity for COX-2 compared with other coxibs. In contrast, growing evidence underlines the cardiovascular risk of traditional NSAIDs such as diclofenac (40,41), naproxen (42), ibuprofen (41), and other NSAIDs such as nabumetone, meloxicam, etodolac, and nimesulide (43). Nevertheless, according to the study findings, fewer patients affected by coronary heart disease were treated in all NSAID groups in period II.

Interestingly, celecoxib use decreased more than 50% after rofecoxib withdrawal, whereas the use of etoricoxib (marketed in Italy since March 2004) remained unmodified. The extensive marketing campaign launched by drug manufacturers to promote new drugs might partly explain such a peculiar finding (44).

Concerning coprescription of gastroprotective agents, our results show a low rate of proton-pump inhibitor treatment in users of traditional NSAIDs (45). In contrast, the rate of gastroprotection with proton-pump inhibitors in coxib users was higher than in other NSAID users. This trend has been previously described for both traditional NSAIDs (46,47) and coxibs (47). This finding might be explained by the channeling effect of coxibs that are more likely to be prescribed in patients with higher GI risks compared with other NSAIDs (48).

Finally, we observed a low rate of utilization of weak opioids, despite their well-defined role in published guidelines (5–7) and the fact that they became fully reimbursed in Italy after December 2004. This evidence might be related to the concerns about tolerability of weak opioids, which are associated with a high frequency of side effects such as dry mouth, nausea, and constipation (49,50).

Overall, our investigation highlights that the adherence of GPs to published guidelines (5–7) was not satisfactory and this should be analyzed despite accurate and regular training.

To our knowledge, this is the first drug utilization study performed in Italy with the aim of evaluating the effect of rofecoxib withdrawal on pain treatment in patients with OA in a general practice setting. However, several limitations of the study should be considered. First, diagnoses were made only by GPs and were not confirmed by a rheumatologist/orthopedic specialist when drug prescription was directly decided by a GP. Second, data on pain severity requiring drug prescriptions were missing. Another limitation was the lack of data on acetaminophen utilization directly measured in the study population during the observation years. However, as previously mentioned, we tried to estimate such a utilization through a questionnaire that was administered to GPs at the end of the study. Furthermore, we missed information on self-treatment and over-the-counter drugs because we used an outpatient prescription database. Nevertheless, the goal of the study was to look at the medications that are actually prescribed by GPs. Finally, data on weak opioid use before December 2004 were missing because these medications did not become fully reimbursable until this date and our data source contained only data on drug prescriptions that are reimbursed by the NHS. Given that our study reported a low utilization of weak opioids after rofecoxib withdrawal, we might speculate that the use of these medications in the previous period was similar or even lower.

In conclusion, rofecoxib withdrawal led to a reduction of coxib use in patients with OA despite the fact that utilization of COX-2 preferentials, NS NSAIDs, and analgesic opioids remained stable. Even though an educational program was performed during the study period, our findings suggest that GPs tend not to be adherent to recommendations of treatment guidelines for OA-related pain, or recommendations regarding gastroprotection in classic NSAID and coxib users.

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AUTHOR CONTRIBUTIONS

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

Study design. Alacqua, Trifirò, Caputi.
Acquisition of data. Galdo, Caputi, Arcoraci.
Analysis and interpretation of data. Alacqua, Trifirò, Cavagna, Caporali, Montecucco, Moretti, Galdo, Arcoraci.
Manuscript preparation. Alacqua, Trifirò, Cavagna, Caporali, Montecucco, Moretti, Tari.
Statistical analysis. Tari, Arcoraci.

REFERENCES

1. Altman RD. The syndrome of osteoarthritis. J Rheumatol 1997;24:766–7.
2. Loeser RF, Shakoor N. Aging or osteoarthritis: which is the problem? Rheum Dis Clin North Am 2003;29:653–73.
3. Maurer K. Basic data on arthritis knee, hip and sacroiliac joints in adult ages 25-74 years. Vital Health Stat 11 1979;213: 1–31.
4. World Health Organisation and the Bone and Joint Decade. 2001. URL: http://www.boneandjointdecade.org/.
5. Pendleton A, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JW, et al. EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2000;59: 936–44.
6. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. Arthritis Rheum 2000;43:1905–15.
7. Zhang W, Doherty M, Arden N, Bannwarth B, Bijlsma J, Gunther KP, et al, and the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2005;64: 669–81.
8. Pincus T, Swearingen C, Cummins P, Callahan LF. Preference for nonsteroidal antiinflammatory drugs versus acetaminophen and concomitant use of both types of drugs in patients with osteoarthritis. J Rheumatol 2000;27:1020–7.
9. Towheed TE, Judd MJ, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2003;2: CD004257.
10. Ausiello JC, Stafford RS. Trends in medication use for osteoarthritis treatment. J Rheumatol 2002;29:999–1005.
11. Mamdani M, Juurlink DN, Kopp A, Naglie G, Austin PC, Laupacis A. Gastrointestinal bleeding after the introduction of COX 2 inhibitors: ecological study. BMJ 2004;328:1415–6.
12. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs 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.
13. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al, and the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343: 1520–8.
14. Mamdani M, Rochon PA, Juurlink DN, Kopp A, Anderson GM, Naglie G, et al. Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclooxygenase-2 inhibitors or conventional non-steroidal antiinflammatory drugs. BMJ 2002;325:624–9.
15. Langman MJ, Jensen DM, Watson DJ, Harper SE, Zhao PL, Quan H, et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999;282:1929–33.
16. Goldstein JL, Silverstein FE, Agrawal NM, Hubbard RC, Kaiser J, Maurath CJ, et al. Reduced risk of upper gastrointestinal ulcer complications with celecoxib, a novel COX-2 inhibitor. Am J Gastroenterol 2000;95:1681–90.
17. Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, et al, and the Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial [published erratum appears in N Engl J Med 2006;355:221]. N Engl J Med 2005;352:1092–102.
18. Lawrenson R, Williams T, Farmer R. Clinical information for research: the use of general practice databases. J Public Health Med 1999;21:299–304.
19. Piacentini N, Trifiro G, Tari M, Moretti S, Arcoraci V, and the UVEC group. Statin-macrolide interaction risk: a population-based study throughout a general practice database. Eur J Clin Pharmacol 2005;61:615–20.
20. Trifiro G, Corrao S, Alacqua M, Moretti S, Tari M, Caputi AP, et al. Interaction risk with proton pump inhibitors in general practice: significant disagreement between different drug-related information sources. Br J Clin Pharmacol 2006;62:582–90.
21. Trifiro G, Barbui C, Spina E, Moretti S, Tari M, Alacqua M, et al. Antidepressant drugs: prevalence, incidence and indication of use in general practice of Southern Italy during the years 2003-2004. Pharmacoepidemiol Drug Saf 2007;16: 552–9.
22. Altman R, Alarcon G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601–10.
23. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
24. Davis D, O'Brien MA, Freemantle N, Wolf FM, Mazmanian P, Taylor-Vaisey A. Impact of formal continuing medical education: do conferences, workshops, rounds, and other traditional continuing education activities change physician behavior or health care outcomes? JAMA 1999;282:867–74.

25. Mazmanian PE, Davis DA. Continuing medical education and the physician as a learner: guide to the evidence. JAMA 2002; 288:1057–60.
26. Hayward RS, Guyatt GH, Moore KA, McKibbon A, Carter AO. Canadian physicians' attitudes about and preferences regarding clinical practice guidelines. CMAJ 1997;156:1715–23.
27. Rahme E, Choquette D, Beaulieu M, Bessette L, Joseph L, Toubouti Y, et al. Impact of a general practitioner educational intervention on osteoarthritis treatment in an elderly population. Am J Med 2005;118:1262–70.
28. Buchanan WW. Implications of NSAID therapy in elderly patients. J Rheumatol 1990;20:29–32.
29. Weinblatt ME. Nonsteroidal anti-inflammatory drug toxicity: increased risk in the elderly. Scand J Rheumatol Suppl 1991; 91:9–17.
30. Willett LR, Carson JL, Strom BL. Epidemiology of gastrointestinal damage associated with nonsteroidal anti-inflammatory drugs. Drug Saf 1994;10:170–81.
31. Thiebaud P, Patel BV, Nichol MB. Impact of rofecoxib withdrawal on cyclooxygenase-2 utilization among patients with and without cardiovascular risk. Value Health 2006;9:361–8.
32. Usher C, Bennett K, Teeling M, Feely J. Characterizing new users of NSAIDs before and after rofecoxib withdrawal. Br J Clin Pharmacol 2007;63:494–7.
33. Williams D, Singh M, Hind C. The effect of the withdrawal of rofecoxib on prescribing patterns of COX-2 inhibitors in Scotland. Br J Clin Pharmacol 2006;62:366–8.
34. Scarpa R, Sarzi-Puttini P, Cimmino MA, Caporali R, Parazzini F, Zaninelli A, et al. Analysis of pharmacologic and non pharmacologic prescription patterns of general practitioners and specialists in the AMICA study. Semin Arthritis Rheum 2005;35(1 Suppl 1):24–30.
35. Price-Forbes AN, Callaghan R, Allen ME, Rowe IF, on behalf of the West Midlands Rheumatology Services and Training Committee. A regional audit of the use of COX-2 selective non-steroidal anti-inflammatory drugs (NSAIDs) in rheumatology clinics in the West Midlands, in relation to NICE guidelines. Rheumatology (Oxford) 2005;44:921–44.
36. Sarzi-Puttini P, Cimmino M, Scarpa R, Caporali R, Parazzini F, Zaninelli A, et al. Do physicians treat symptomatic osteoarthritis patients properly? Results of the AMICA experience. Semin Arthritis Rheum 2005;35(1 Suppl 1):38–42.
37. Lagako SW. Time-to-event analyses for long-term treatments: the APPROVe trial. N Engl J Med 2006;355:113–7.
38. Arber N, Eagle CJ, Spicak J, Racz I, Dite P, Hajer J, et al. Celecoxib for the prevention of colorectal adenomatous polyps. N Engl J Med 2006;355:885–95.
39. White WB, West CR, Borer JS, Gorelik PB, Lavange L, Pan SX, et al. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. Am J Cardiol 2007;99:91–8.
40. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase: a systematic review of the observational studies of selective and non-selective inhibitors of cyclooxygenase 2. JAMA 2006;296:1633–44.
41. Hippisley-Cox J, Coupland C. Risk of myocardial infarction in patients taking cyclo-oxygenase inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005;330:1366–72.
42. ADAPT Research Group. Cardiovascular and cerebrovascular events in the randomized, controlled Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). PLoS Clin Trials 2006;1:e33.
43. Helin-Salmivaara A, Virtanen A, Vesalainen R, Gronroos JM, Klaukka T, Idanpaan-Heikkila JE, et al. NSAID use and the risk of hospitalization for first myocardial infarction in the general population: a nationwide case-control study from Finland. Eur Heart J 2006;27:1657–63.
44. Kozyrskyj A, Raymond C, Racher A. Characterizing early prescribers of newly marketed drugs in Canada: a population-based study. Eur J Clin Pharmacol 2007;63:597–604.
45. Smalley W, Stein CM, Arbogast PG, Eisen G, Ray WA, Griffin M. Underutilization of gastroprotective measures in patients receiving nonsteroidal antiinflammatory drugs. Arthritis Rheum 2002;46:2195–200.
46. Micklewright R, Lane S, Linley W, McQuade C, Thompson F, Maskrey N. Review article: NSAIDs, gastroprotection and cyclo-oxygenase-II-selective inhibitors. Aliment Pharmacol Ther 2003;17:321–32.
47. Caporali R, Cimmino MA, Sarzi-Puttini P, Scarpa R, Parazzini F, Zaninelli A, et al. Comorbid conditions in the AMICA study patients: effects on the quality of life and drug prescriptions by general practitioners and specialists. Semin Arthritis Rheum 2005;35:31–7.
48. Mosis G, Stijnen T, Castellsague J, Dieleman JP, van der Lei J, Stricker BH, et al. Channeling and prevalence of cardiovascular contraindications in users of cyclooxygenase 2 selective nonsteroidal antiinflammatory drugs. Arthritis Rheum 2006; 55:537–42.
49. Large RG, Schug SA. Opioids for chronic pain of non-malignant origin: caring or crippling? Health Care Anal 1995;3:5–11.
50. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Res Ther 2005;7:R1046–51.