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Prescribing of COX-2 inhibitors in Germany after safety warnings and market withdrawals

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Received May 3, 2006, accepted May 24, 2006

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Pharmazie 61: 878–886 (2006)

The emergence of safety concerns associated with the use of selective cyclooxygenase-2 (COX-2) inhibitors (coxibs) led to market withdrawals of rofecoxib in September 2004 and valdecoxib in April 2005. These events were accompanied by safety alerts from drug authorities and recommendations from professional medical associations. This study analysed the temporal influence of these measures on drug use in Germany, with the objective to assess overall appropriateness of prescribing and to evaluate the potential for pharmaceutical interventions. Drug prescriptions for patients within the statutory health insurance system (GKV) were analysed based on the total amount of DDDs of single drug substances dispensed every month in German pharmacies. The market withdrawal of rofecoxib in September 2004 resulted initially in increased prescribing of other coxibs. New safety warnings on coxibs later in 2004 and the withdrawal of valdecoxib in April 2005 led to pronounced reductions in coxib prescribing. Comparing the third quarter of 2005 with 2004, coxib prescriptions dropped from 47.5 to 10.4 million DDDs. Conversely, in the same time frame, NSAID prescriptions increased by 19.0 million DDDs. This is mostly due to increased prescribing of ibuprofen, diclofenac and, to a lesser degree, meloxicam, acemetacin, piroxicam, and naproxen. However, total prescribing of inhibitors of cyclooxygenases decreased by about 8.4%, indicating a relative reluctance to prescribe these drugs after cardiovascular safety warnings have been issued by drug authorities. Unexpectedly, also prescribing of metamizol (dipyrone) increased by 2.8 million DDDs (20%), despite recommendations to limit its use by medical associations. Furthermore, increased prescribing of proton pump inhibitors of 12.6 million DDDs could be observed. NSAIDs and coxibs are to a larger extent prescribed by a broad range of medical specialist groups including orthopaedists and surgeons, whereas drugs used in gastrointestinal or cardiovascular disorders are mainly prescribed by general practitioners and internal specialists, respectively. Therefore, the individual physician may not always be aware of the risk profiles of their patients. Pharmacists can close this gap by providing comprehensive medication records and information on self medication used by the patient to prescribing practitioners, thereby contributing to improved patient safety.

Abbreviations:

ABDA	ABDA-Bundesvereinigung Deutscher Apothekerverbände
ATC code	Anatomical Therapeutic Chemical code/classification
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
COX	Cyclooxygenase
DDD	defined daily dose
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
EMA	European Agency for the Evaluation of Medicinal Products
FDA	Food and Drug Administration
GKV	gesetzliche Krankenversicherung
NSAID	non-steroidal antiinflammatory drug
SSRI	selective serotonin reuptake inhibitor
WHO	World Health Organization
WiDO	Wissenschaftliches Institut der Ortskrankenkassen

1. Introduction

Gastrointestinal side effects (bleeding, ulcer, perforation) associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) represent the most prevalent category of adverse drug reactions (Singh and Triadafilopoulos 1999) and account for a large number of hospitalisations and deaths (Singh 1998). Nevertheless, NSAIDs represent a mainstay of pharmacotherapy for both acute and chronic diseases associated with pain and inflammation like rheumatoid arthritis and osteoarthritis worldwide. This is also highlighted in current German guidelines (Arzneimittelkommission der Deutschen Ärzteschaft 2001; Schneider et al. 2004). The high prevalence of these diseases prompted researchers to identify drugs inhibiting specifically the enzyme cyclooxygenase 2 (COX-2) with the objective to reduce gastrointestinal side effects. Pivotal studies provided evidence that use of inhibitors of cyclooxy-

genase 2 (coxibs) such as rofecoxib and celecoxib display similar efficacy, but are associated with fewer gastrointestinal adverse events compared to classical NSAIDs such as naproxen or diclofenac (Bombardier et al. 2000; Silverstein et al. 2000) – at least within several months of use. This led to the advancement of coxibs as an important drug class for treating pain associated with inflammatory diseases.

However, more pronounced inhibition of COX-2 may lead to an increased risk for cardiovascular events. The most likely mechanism is an imbalance in products from different types of cyclooxygenases: suppression of production of vasodilatory and antiaggregatory prostacyclin by COX-2 from the endothelium, while production of aggregatory thromboxane A₂ by COX-1 from platelets remains unaffected, may lead to increased risk of thrombotic events (McAdam et al. 1999; Mukherjee et al. 2001). These concerns were confirmed by further evidence analysing the APPROVE and APC trials (Bresalier et al. 2005; Solomon et al. 2005). Both, rofecoxib and celecoxib were shown to increase the risk of cardiovascular events compared to placebo, especially after longer duration of therapy (>18 months of drug use). The results from the APPROVE trial prompted Merck & Co. Inc. to voluntarily withdraw rofecoxib from the markets worldwide. In the following months, further evaluation of available data prompted drug authorities to issue additional recommendations on the use of coxibs, but also the safety of classical NSAIDs was questioned. It can be expected that these regulatory measures did not leave prescribing of physicians unaffected.

In 2004, rofecoxib, celecoxib and valdecoxib were marketed in Germany with the indication of symptomatic therapy of pain in patients with rheumatoid arthritis or osteoarthritis. Etoricoxib was introduced into the German market in September 2004 with the additional approval for treatment of pain and inflammation during acute gouty arthritis. While efficacy of these drugs was comparable to classical NSAIDs, the coxibs show a more favourable risk profile for gastrointestinal complications. According to guidelines valid in 2004, coxibs were therefore an option for patients at risk for gastrointestinal side effects under therapy with classical NSAIDs (Arzneimittelkommission der Deutschen Ärzteschaft 2001; Schneider et al. 2004). Alternative recommended treatments were classical NSAIDs in combination with proton pump inhibitors or misoprostol, whereas high-dose histamine-H₂-receptor antagonists were less frequently recommended. If NSAIDs cannot be given due to contraindications, paracetamol (acetaminophen) or opioid analgesics should be considered. It must be noticed, however, that the efficacy of paracetamol for these indications proved to be relatively modest in more recent studies (Battisti et al. 2004; Bourreau et al. 2004; Schnitzer et al. 2005). Moreover, drugs containing paracetamol are in general not reimbursed for most indications since January 2004 (Gemeinsamer Bundesausschuss 2005). In addition, metamizol (dipyrone) is marketed in Germany for treatment of acute and chronic pain, although there is no explicit indication for its use in degenerative arthritic disorders (Arzneimittelkommission der Deutschen Ärzteschaft 2001).

The present study aimed at analysing changes in prescribing of the above-mentioned drugs before and after safety warnings have been issued for coxibs. This should allow to evaluate how quickly doctors react to new evidence of risks and which drugs are prescribed instead. Overall appropriateness of drug prescribing could be evaluated. In

addition, changes in drug expenditure after withdrawal of new, innovative and more expensive drugs were calculated. Finally, prescribing of relevant drug classes by different medical specialist groups was analysed in order to assess the potential for pharmaceutical interventions. Thus, pharmacists may improve patient safety when different prescribers are not fully aware of individual patients' gastrointestinal or cardiovascular risk profiles.

2. Investigations, results and discussion

2.1. Changes in coxib prescribing

In the third quarter of 2004, just before the market withdrawal of rofecoxib, 71.5 million DDDs of prescriptions of inhibitors of cyclooxygenases were, on average, filled every month in Germany sufficient to provide approximately two million patients with these drugs (data do not include private health insurance and use of over-the-counter products). Coxibs accounted for 15.8 million DDDs dispensed monthly, representing a share of 28.4%. The remaining 71.6% were largely covered by diclofenac (32.4 million DDDs monthly, representing 45.4%) and ibuprofen (14.3 million DDDs monthly, representing 20.0%). Metamizol was being prescribed much less frequently with an average of 4.72 million DDDs monthly, whereas prescribing of paracetamol was less relevant (0.32 million DDDs monthly).

New evidence for an increased cardiovascular risk of rofecoxib at the end of September 2004 resulted in the voluntary marked withdrawal by the manufacturer Merck & Co., Inc. Further results from clinical trials and epidemiological studies as well as spontaneous reporting of side effects of coxibs within routine clinical use prompted drug authorities to issue a range of notifications regarding the cardiovascular safety profiles of coxibs but also classical NSAIDs (Table 1).

Following the market withdrawals of rofecoxib in September 2004 and valdecoxib in April 2005 as well as safety warnings from authorities, pronounced changes in coxib prescribing could be observed (Fig. 1). Initially, prescribing of celecoxib as well as valdecoxib rose in October 2004, followed by a decrease in the next months. At the end of December 2004, new evidence accumulated that cardiovascular risks may be a class effect of all COX inhibitors (see communications from BfArM on December 20th and 22nd 2004, Table 1). The latest event affecting coxib prescribing is represented by the market withdrawal of valdecoxib in April 2005 after spontaneous reporting of cardiovascular as well as severe cutaneous reactions caused by the drug.

Since May 2005, coxib prescribing remains on a low level. In summary, prescribing of coxibs is quite limited with only 10.4 million DDDs in the third quarter of 2005, corresponding to approximately 100,000 treated patients. Interestingly, the currently available drugs celecoxib and etoricoxib are prescribed to a similar extent. Etoricoxib may be favourable for patients with regard to once daily versus twice daily dosing compared to celecoxib. Moreover, etoricoxib is not only approved for use in rheumatoid arthritis and osteoarthritis, but also in acute gouty arthritis. Nevertheless, the rationale behind this is not obvious, as etoricoxib does not offer a pharmacological advantage over celecoxib in terms of the cardiovascular risk profile. Etoricoxib inhibits COX-2 with very high selectivity, while that of celecoxib is much lower (Jones 2005). Furthermore, it has a longer half-life of 22 h versus

Table 1: Important warnings/press releases issued by drug authorities regarding coxibs and NSAIDs during 2004 and 2005 (BfArM 2004, BfArM 2005, EMEA 2005, FDA 2004)

Date	Authority	Content
30.09.2004	FDA	Worldwide market withdrawal of Vioxx [®] by Merck & Co. Inc. (MSD)
15.10.2004	BfArM	EMA commences evaluation of cardiovascular risks during long-term use of coxibs
20.12.2004	BfArM	Limitation of the use of celecoxib in patients at high risk for cardiovascular events
22.12.2004	BfArM	New evidence for cardiovascular risks associated with naproxen
21.02.2005	BfArM	Introduction of new contraindications and warnings for coxibs relating to cardiovascular comorbidity
08.04.2005	BfArM	Pfizer suspends marketing of Bextra [®] after spontaneous reporting of cardiovascular events and hypersensitivity reactions
10.06.2005	BfArM	New study results published in British Medical Journal – cyclooxygenase inhibitors should be utilized only as recommended
04.07.2005	BfArM	EMA concludes action on coxibs; new contraindications and warnings for coxibs regarding cardiovascular risk and hypersensitivity reactions
10.08.2005	BfArM	EMA accomplishes review of safety of non-selective NSAIDs: no further changes of advice to patients and prescribers; use of the lowest effective dose for the shortest possible duration recommended
17.10.2005	EMA	Update of risk assessment of NSAIDs: no new safety concerns; already existing contraindications have to be considered

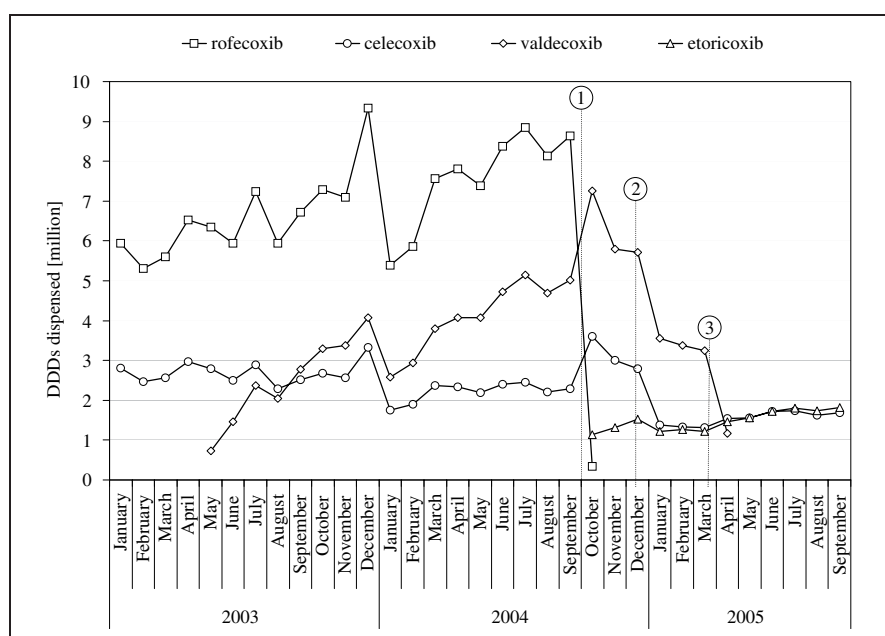


Fig. 1: Dispensing of coxibs from January 2003 to September 2005. Pronounced changes can be observed after market withdrawal of rofecoxib in September 2004 (1), after safety warnings for coxibs in December 2004 (2) and after market withdrawal of valdecoxib in April 2005 (3)

8–12 h for celecoxib. Both high selectivity for COX-2 and a long half-life are hypothetically considered to increase the risk for adverse cardiovascular events (Jones 2005; Konstantinopoulos and Lehmann 2005). The currently available randomized controlled clinical trials for etoricoxib have been conducted over too short periods of time and in too few patients to allow for valid comparisons with celecoxib. However, also etoricoxib seems to increase the risk for cardiovascular adverse events, especially myocardial infarction (Aldington et al. 2005). Moreover, its use is explicitly contraindicated in patients with uncontrolled high blood pressure. Due to safety concerns, the drug was not granted approval from the FDA so far.

It is difficult to predict the overall significance of coxibs in future prescribing. To this end, further randomized clinical trials evaluating the cardiovascular risks of classical NSAIDs as well as the benefit of a coxib plus a proton pump inhibitor in patients at very high risk of gastrointestinal events are required. In addition, it is currently not known if and when lumiracoxib will be approved and marketed in Germany. Lumiracoxib has a very short plasma half-life of approximately 6 h (Scott et al. 2004), which may be of advantage with regard to cardiovascular

adverse events. Moreover, the chemical structure, very similar to diclofenac, is an aryl acetic acid – unlike the sulfonyl structure of other coxibs. Therefore, preferred accumulation in inflamed tissues is being discussed. In total, the potential for unwanted side effects could be decreased. The results of the TARGET trial, conducted in more than 18,000 patients for one year, are promising. Cardiovascular events under therapy with lumiracoxib were not significantly different compared to naproxen or ibuprofen (Farkouh et al. 2004; Schnitzer et al. 2004).

2.2. Changes in prescribing of NSAIDs and other analgesics

The collapse of coxib prescribing can be expected to result in profound changes in utilization of other NSAIDs and related drugs. In the following analysis, these changes are quantified by comparing the third quarter of 2005 with the third quarter of 2004. Thus, the 3-months period from July to September 2004 before the initial market withdrawal of rofecoxib is being used as reference period and compared to the same period in 2005, after the last pronounced changes in coxib prescribing could be observed.

Use of classical NSAIDs increased from 167.2 million DDDs in the third quarter of 2004 to 186.2 million DDDs in 2005, representing a rise of 19.0 million DDDs (11.4%). This increase does not fully counterbalance the decline of 37.0 million DDDs of coxibs. Nevertheless, this indicates that probably most of the patients who formerly received coxibs were switched to other NSAIDs. Obviously, most patients with chronic arthritic conditions cannot abandon anti-inflammatory and analgesic medication. The largest increase in prescribing could be observed for the unselective (and cheap) COX inhibitor ibuprofen with an increase of 8.1 million DDDs (19.0%), followed by diclofenac with 7.6 million DDDs additionally prescribed (7.8%) (Fig. 2). Other drugs such as meloxicam or acemetacin, which show some selectivity for inhibition of COX-2, and, to a lesser degree, piroxicam and naproxen were also increasingly prescribed (Kato et al. 2001; Mitchell et al. 1993; Tavares and Bennett 1993). Furthermore, prescribing of fixed combinations of diclofenac with misoprostol as gastroprotective agent increased. In contrast, the unselective drug indomethacin lost 0.17 million DDDs (-3.6%). Especially in the elderly, the use of indomethacin is not recommended because of a higher incidence of side effects (Fick et al. 2003). All other NSAIDs combined amounted to less than 4% of total DDDs of NSAIDs dispensed during the third quarter 2005 and are therefore not mentioned in detail.

Overall prescribing of inhibitors of cyclooxygenases (coxibs and NSAIDs combined) decreased slightly from 215 to 197 million DDDs in the third quarter of 2005, which is 8.4% less compared to the year before. Thus, a relative reluctance to prescribe COX inhibitors may be anticipated. This is in accordance with the current recommendations from authorities and professional organisations that these drugs should be used at the lowest effective dose for the shortest possible period of time. However, an overall decrease of 8.4% is relatively modest, indicating that in clinical practice most patients cannot omit their analgesic and antiinflammatory therapy.

Apart from these NSAIDs, also metamizol was additionally prescribed with an increase of 2.8 million DDDs

(20.0%) (Fig. 2). This was relatively unexpected as professional medical associations frequently appeal to restrict prescribing due to unwanted side effects (Arzneimittelkommission der Deutschen Ärzteschaft 2006; Schoenhofer et al. 2003; The International Agranulocytosis and Aplastic Anemia Study Group 1986). Moreover, according to guidelines, metamizol is explicitly not to be used in chronic inflammatory diseases of the joints (Arzneimittelkommission der Deutschen Ärzteschaft 2001), which represents the main indication for coxibs. It is noteworthy that prescribing of metamizol with 17.0 million DDDs in the third quarter of 2005 has outweighed coxib prescriptions with 10.4 million DDDs by far.

Prescribing of paracetamol remained largely unchanged, despite of its mention in the guideline (Arzneimittelkommission der Deutschen Ärzteschaft 2001). This may be due to lack of reimbursement from health insurance companies (Gemeinsamer Bundesausschuss 2005), or alternatively due to relatively limited efficacy compared to COX inhibitors for treatment of pain and inflammation in arthritic diseases (Boureau et al. 2004; Lee et al. 2004; Schnitzer et al. 2005). Also, prescribing of low potency opioids such as tramadol, tilidine or dihydrocodeine did not change in response to coxibs withdrawals (data not shown), although these drugs may, with exceptions, be used in the treatment of arthritic pain (Arzneimittelkommission der Deutschen Ärzteschaft 2001; Schneider et al. 2004). Obviously, most prescribers do not consider these drugs a suitable alternative to coxibs.

2.3. Changes in prescribing of gastroprotective agents

As coxibs were mainly indicated for patients with gastrointestinal risk factors, also prescribing of gastroprotective agents was analysed. Proton pump inhibitors have been increasingly dispensed in recent years, and this trend proceeded also in the year 2004 (Fig. 3). An analysis of linear trends from January 2003 until September 2004 compared to the period from October 2004 until September 2005 yielded trend lines with similar slopes. This suggests the occurrence of a parallel translation towards a higher

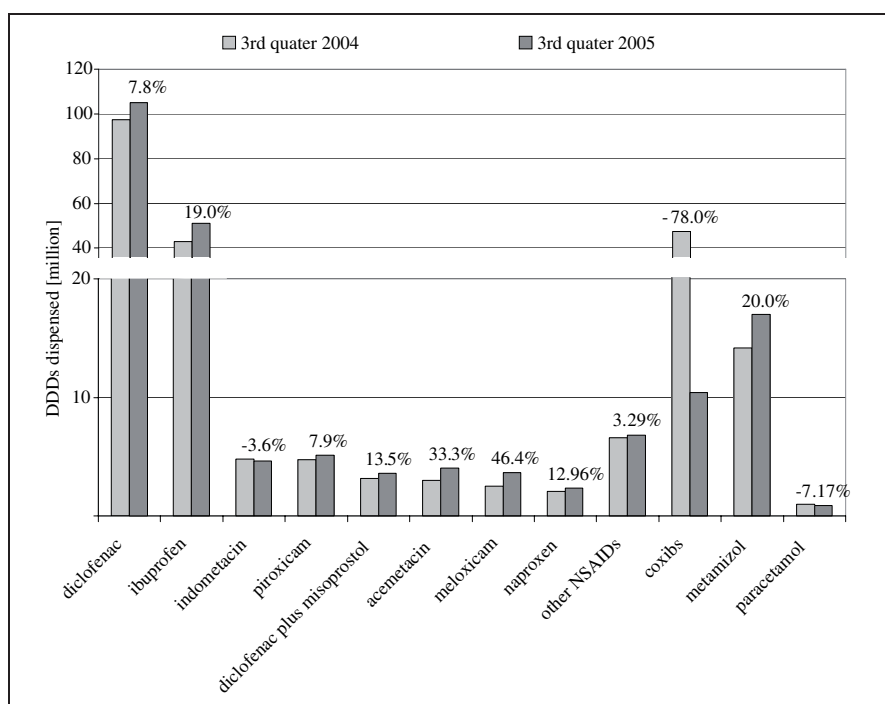


Fig. 2: Dispensed quantities (DDD) of NSAIDs, coxibs, metamizol, and paracetamol during the 3rd quarter of 2004 and the 3rd quarter of 2005. Percentages indicate the relative change in the 3rd quarter 2005 compared to the year before

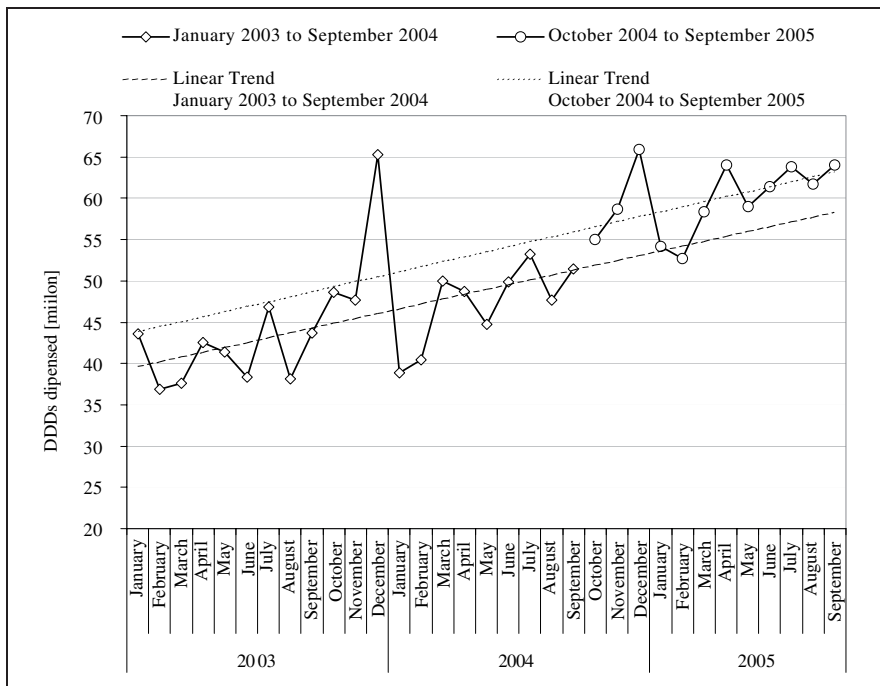


Fig. 3: Prescribing of proton pump inhibitors from January 2003 to September 2005. Trend line from January 2003 to September 2004: slope = 584,016; Y-intercept = 39,072,819; $R^2 = 0.291$; two-tailed test of significance $p = 0.012$ (ANOVA). Trend line from October 2004 to September 2005: slope = 604,933; Y-intercept = 43,273,775; $R^2 = 0.255$; two-tailed test of significance $p = 0.094$ (ANOVA)

level after the market withdrawal of rofecoxib and reductions in coxib prescribing. Although these data have to be interpreted with caution, one may estimate that 4.2 million DDDs per month corresponding to 12.6 million DDDs per quarter of proton pump inhibitors have been additionally prescribed as a result of reduced coxib prescribing. In contrast, neither prescribing of histamine- H_2 -receptor antagonists nor of misoprostol in monotherapy increased (data not shown).

2.4. Overall drug utilization and potential for pharmaceutical interventions

Analysing our data, the prescribed DDDs can be used to estimate drug utilization in the population that is covered by the statutory health insurance system in Germany. Under the assumption that the DDD is a close approximation for drug use by one individual patient per day in routine clinical practice, the prescribing figures for DDDs allow for quantitative conclusions on drug utilization. The main outcomes of this analysis show that coxib prescribing decreased by 37.0 million DDDs in the third quarter of 2005 compared to the year before, whereas prescribing of classical NSAIDs increased by 19.0 million DDDs. Thus, it can be assumed that approximately only half of the patients that were formerly treated with coxibs are continued on NSAIDs. This corresponds closely to figures based on a patient-individualised analysis of data from one German health insurance company, where 52.5% of patients formerly treated with coxibs were changed to NSAID therapy (Grossmann and Kampmann 2005). Furthermore, while 19.0 million DDDs of NSAIDs have been additionally prescribed after the coxib collapse, supplementary prescribing of proton pump inhibitors increased by approximately 12.6 million DDDs in the third quarter 2005 compared to the year before. It may, therefore, be estimated that probably only two thirds of former coxib patients switched to NSAIDs are also receiving proton pump inhibitors as gastroprotective comedication. Alternatively, coxibs may have been previously prescribed to patients who did not have gastrointestinal risk factors. Stu-

dies from the Netherlands have reported that only 60 to 70% of patients treated with NSAIDs and being at high risk for gastrointestinal events are adequately provided with gastroprotective medication (Bouvy et al. 2005; Hering and Goettsch 2004). Similarly, cardiovascular risk factors may not be sufficiently considered when coxibs or NSAIDs are being prescribed (Bouvy and Cheung 2005; Grossmann and Kampmann 2005). Moreover, a large part of NSAID prescriptions are issued for patients older than 65 years (Sebaldt et al. 2004), where both cardiovascular as well as gastrointestinal risk factors are often present simultaneously (Bouvy et al. 2005).

The fact that risk factors are not adequately considered when NSAIDs or coxibs are being prescribed, may be explained by a lack of relevant information available to the prescribing physician. As a large proportion of risk factors such as age or comedication indicating gastrointestinal or cardiovascular diseases can be detected and monitored in pharmacies, pharmacists can close this information gap and contribute to patient safety by providing doctors with the necessary information on individual patients' risk factors. This is especially important as drugs that increase the risk for gastrointestinal events or that indicate the presence of cardiovascular risk factors are often to a large extent prescribed by different types of medical specialists, which may be unaware of comedication prescribed by other doctors (Table 2). For example, comedication with glucocorticoids, anticoagulants or selective serotonin reuptake inhibitors (SSRI) can increase the risk for adverse gastrointestinal events under therapy with NSAIDs (Bjorkman 1999; de Abajo et al. 1999; de Jong et al. 2003). While NSAIDs (included in ATC code M02) and systemic glucocorticoids (ATC code H02) are often prescribed by orthopaedists and surgeons, these groups rarely prescribe gastroprotective (ATC code A02) or cardiovascular drugs (lipid lowering drugs ATC code C10; antihypertensive drugs ATC codes C02, C03, C07, C08, C09). Similarly, prescribing of SSRIs (included in ATC code N06), which can increase the risk of gastrointestinal bleeding, is to a large part conducted by psychiatrists/neurologists, whereas this group hardly prescribes NSAIDs or gastroprotective comedica-

Table 2: Share of drug packages (%) in different ATC codes prescribed by different groups of medical specialists in the year 2005

ATC code 2nd level		Specialist group				
		General practitioners	Internal specialists	Psychiatrists/neurologists	Orthopaedists	Surgeons
<i>Antiinflammatory and antirheumatic products</i>	M01	55.8	14.0	0.6	13.2	5.0
<i>Drugs for acid related disorders</i>	A02	67.4	27.7	0.2	0.4	0.6
<i>Antithrombotic agents</i>	B01	61.9	27.9	0.8	2.0	3.9
<i>Corticosteroids for systemic use</i>	H02	42.1	22.5	1.6	10.5	2.0
<i>Psychoanaleptics</i>	N06	44.5	12.4	32.1	0.2	0.1
<i>Lipid modifying agents</i>	C10	68.0	30.6	0.0	0.0	0.0
<i>Antihypertensive therapeutics</i>	C02, C03, C07, C08, C09	70.5	28.0	0.1	0.0	0.0

tion. Therefore, prescribers may be unaware of the individual risk profile of a patient. As most of the relevant information such as the age of the patient and comedication can be gathered in pharmacies, pharmacists can contribute to patient safety by providing doctors with necessary information on patients' risk factors. This is especially feasible if patient medication records are kept in the pharmacy and if also additional information as to the use of over-the-counter drugs is known to the pharmacist – for example information on drugs such as NSAIDs taken additionally to prescribed drugs or antacids and H₂-blockers which could indicate symptomatic gastrointestinal problems. In collaboration with doctors and patients, the benefit-risk-assessment for individual patients can be estimated and medication can be adjusted accordingly.

Finally, it must be noted that despite uncertainty as to the definite risks associated with different COX inhibitors, coxibs nevertheless represent a pharmacotherapeutic alternative to classical NSAIDs in some cases. Apart from a better gastrointestinal safety profile, further clinical conditions of an individual patient may be considered before a decision on the optimal drug is reached. For example, in patients with intolerance to NSAIDs due to asthmatic reactions, angioedema or urticaria, coxibs may represent a valuable alternative treatment that can be safely administered in most cases (Gyllfors et al. 2003; Sanchez-Borges et al. 2005a, 2005b; Szczeklik et al. 2001). Moreover, also the classical NSAIDs cannot be considered as free of any cardiovascular risks (Herdegen and Fauler 2006; Hippisley-Cox and Coupland 2005; Mamdani et al. 2004). In addition, uncertainty prevails as to possible benefits of com-

binations of coxibs plus proton pump inhibitors in patients at very high risk for gastrointestinal complications, as this combination has not been tested in clinical trials so far. Therefore, in clinical practice, assessment of risks and benefits of coxib versus NSAID therapy can only be undertaken for individual patients comprising all the relevant information available.

2.5. Changes in drug expenditure

From a pharmacoeconomic perspective, one might expect that reduced prescribing of coxibs as a new, innovative class of drugs would lead to substantial savings in drug expenditure. However, total drug expenditure on NSAIDs, coxibs, metamizol and proton pump inhibitors combined showed only a slight decrease. A total of 437.1 million euros were spent by health insurance companies and patients on these drugs in the period from July to September 2005, which is 19.1 million euros less compared to the year before (−4.4%). These cost savings are largely due to reductions in coxib prescribing, which are on average almost twice as expensive as other NSAIDs per DDD (Table 3). Therefore, overall cost savings are higher than the expenditure due to increased prescribing of additional proton pump inhibitors. This was additionally supported by the introduction of a reference price for proton pump inhibitors in January 2005, which resulted in pronounced average price reductions per DDD for this drug class (Table 3).

In contrast to overall drug expenditures, the costs paid by the statutory health insurance system have increased by

Table 3: Total drug expenditure and expenditure of statutory health insurance companies in the 3rd quarters of 2004 and 2005: average costs per DDD and expenditure

		Average costs per DDD (euros)		Expenditure (million euros)			difference (million euros)	[%]
		3rd quarter 2004	3rd quarter 2005	3rd quarter 2004	3rd quarter 2005			
Total	NSAIDs	0.66	0.63	110.2	117.5	+7.3	+6.6	
	Coxibs	1.36	1.26	64.5	13.1	−51.3	−79.5	
	Metamizol	1.60	1.56	22.7	26.6	+3.9	+17.2	
	Proton pump inhibitors	1.57	1.37	239.7	260.7	+21.0	+8.8	
	Sum	—	—	437.1	418.0	−19.1	−4.4	
Health insurance companies	NSAIDs	0.38	0.39	63.5	72.7	+9.1	+14.3	
	Coxibs	1.05	1.07	49.7	11.2	−38.6	−77.7	
	Metamizol	0.96	1.00	13.6	17.0	+3.4	+25.0	
	Proton pump inhibitors	1.24	1.24	189.4	235.3	+45.9	+24.2	
	Sum	—	—	316.3	336.2	+19.8	+6.3	

19.8 million to 316.3 million euros in the third quarter of 2005 (+6.3%; Table 3). In this case, the savings for coxibs are outweighed by high additional costs for proton pump inhibitors. The introduction of reference pricing is linked to a simultaneous abatement of rebates, which manufacturers have to grant to the statutory health insurance companies. As the manufacturers' rebates were lost with the introduction of reference prices, drug costs for health insurance companies increased, and this was even more pronounced as the amount of proton pump inhibitors being prescribed increased. In conclusion, from a pharmacoeconomic perspective the introduction of reference pricing can lead to overall reductions in drug expenditure, but may be associated with an immediate increase in additional costs for health insurance companies. This is mainly due to the abrogation of manufacturers' rebates, and this is especially pronounced when the amount of prescriptions increases simultaneously – as it was the case with proton pump inhibitors after reduced prescribing of coxibs.

2.6. Conclusions

In conclusion, the results from this analysis show that physicians modify their prescribing regimens promptly in reaction to safety warnings issued by drug authorities. However, reduced prescribing of coxibs led to a simultaneous increase in NSAID prescribing, and especially of those NSAIDs with a relative preference for COX-2, which may however be associated with similar safety risks as coxibs. Overall utilization of inhibitors of cyclooxygenases in total decreased by only 8.4% of prescribed DDDs indicating that patients rarely can abstain from anti-inflammatory and analgesic therapy. Therefore, the general safety warnings from authorities to use COX inhibitors at the shortest possible dose for the shortest possible duration can, to a large part, not be realized in clinical practice. The result that metamizol was also increasingly prescribed warrants further research into the underlying reasons, as metamizol is not explicitly indicated for arthritic conditions and limitation of its use is generally recommended by professional associations. Quantification of additional prescribing of proton pump inhibitors indicates that patients may be undersupplied with gastroprotective medication. Moreover, an analysis of the prescription patterns of different groups of medical specialists shows that drugs increasing the risk for gastrointestinal adverse events under therapy with NSAIDs or drugs indicating the presence of cardiovascular risk factors are largely prescribed by different medical specialists. Therefore, doctors prescribing NSAIDs or coxibs may not be fully aware of gastrointestinal or cardiovascular risk profiles of their patients. Pharmacists could assist in providing the necessary information on possible comedication prescribed by other doctors as well as on over-the-counter drug use. Such collaboration between health care professionals may essentially increase patient safety.

3. Experimental

Data were analysed based on claims data of drugs dispensed to patients within the statutory health insurance system (Gesetzliche Krankenversicherung GKV). Data were collected by five electronic data processing centres, which cover more than 83% of community pharmacies in Germany. Data handling was performed within the scope of routine reimbursement procedures between pharmacies and health insurance companies. A copy of these data was supplied to the GIDE after anonymization of patient-individualised data fields in accordance with German legal requirements in § 300 (2) of the social security code (Sozialgesetzbuch SGB V 2005).

The monthly data on drugs dispensed in more than 83% of German pharmacies spread over all regions within Germany were included in the original data. This represents a sufficiently large sample size to extrapolate data to 100%. Thus, all results displayed in this publication are projected to reflect the nationwide figures for patients within the statutory health insurance system in Germany, representing 70.3 to 70.4 million insured patients during the years 2003 to 2005 (Bundesministerium für Gesundheit 2006; Bundesministerium für Gesundheit und Soziale Sicherung 2005).

The GIDE data include the product code as well as the quantity in numbers of packages, the month of dispensing and the type of medical specialist who issued the prescription. The product codes were linked to information extracted from the ABDA database resources (ABDATA 2003–2005). Information used in this study included the World Health Organisation Anatomical Therapeutic Chemical classification (ATC code), the type and amount of active ingredient as well as pricing information valid at the 15th of the month of dispensing.

The total amount of DDDs dispensed was calculated on a per package basis. To this end, the DDD per package was established and multiplied with the sum of packages sold. ATC and DDD definitions were based on the methodology of the WHO (WHO Collaborating Centre for Drug Statistics Methodology 2006) or, if not available, the official German ATC/DDD classification for 2006 (WiDO Wissenschaftliches Institut der Ortskrankenkassen and DIMDI Deutsches Institut für medizinische Dokumentation und Informatik 2006).

Only drugs dispensed in community pharmacies to individual patients were included in the analysis. Other sources such as supplies to doctors for direct application in their surgeries were excluded. Furthermore, drugs dispensed to patients within hospitals or drugs distributed via mail-order from foreign pharmacies are not available within the GIDE database.

The amount of packages as well as the expenditure were available for all drugs separately based on the ATC code level. For reasons of efficient data processing, the DDDs were calculated only for the 10,000 products sold most frequently or accounting for the highest expenditure. This procedure covers 94% of total packages and 95% of total sales of prescribed medicines in Germany. If not all products of a single drug were included in the analysis, the total amount of DDDs dispensed was calculated from the average DDD per package multiplied with the total amount of packages sold based on the ATC code level.

As the coxibs available on the German market were not registered for use in children, only products with indications for adults were analysed. Thus, products where a low dosage or a special formulation such as syrup indicate use in children were excluded from the analysis. This was relevant for products containing paracetamol and ibuprofen.

The parenterally administered drug parecoxib is of minor importance for ambulatory health care in Germany with a share of less than 0.5% of packages and sales within the group of coxibs. It was, therefore, not included in the analysis.

In the analysis of proton pump inhibitor prescribing, specific products containing fixed drug combinations for eradication of *Helicobacter pylori* (proton pump inhibitor plus antibiotic) were excluded.

For analysis of trends in proton pump inhibitor prescribing, linear trend lines were calculated with Microsoft Excel[®] 2000. Significance of linear regression was calculated by ANOVA using SPSS[®] version 12.01. P-values of $p < 0.05$ were considered significant.

Acknowledgements: This work was supported by the assistance of the pharmacy students Michael Barsch and Klaus Uhlenhut in cooperation with the Institute for Pharmacology (director: Prof. Dr. Walter E. Mueller), Biocenter, Johann Wolfgang Goethe-University, Frankfurt am Main, Germany.

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