NEW DRUGS IN GENERAL PRACTICE

PRESCRIBING PATTERNS AND EXTERNAL INFLUENCES

Stefan R. Florentinus

Cover design: Claudine Florentinus-Stokkel
Cover photo: Prof. Andrew Davidhazy. Please visit: www.rit.edu/~andpph

CIP-gegevens Koninklijke Bibliotheek, Den Haag

Florentinus, Stefan Remco

New drugs in general practice / Prescribing patterns and external influences /
Stefan R. Florentinus
Thesis Utrecht - with ref. - with summary in Dutch
ISBN-10: 90-393-4261-x
ISBN-13: 978-90-393-4261-9

NEW DRUGS IN GENERAL PRACTICE: PRESCRIBING PATTERNS AND EXTERNAL INFLUENCES

Nieuwe geneesmiddelen in de huisartsenpraktijk:
Voorschrijfpatronen en externe invloeden
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus prof. dr. W.H. Gispen,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

donderdag 18 mei 2006 des middags te 2:30 uur

door

Stefan Remco Florentinus
geboren op 22 januari 1977 te Amstelveen, Nederland

Promotores

Prof. dr. H.G.M. Leufkens
Prof. dr. P.P. Groenewegen

Copromotores

Dr. E.R. Heerdink
Dr. ir. L. van Dijk

This thesis was part of the UNICA (Utrecht University and NIVEL primary CAre) project; a collaboration between the Division of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences (UIPS) and NIVEL (Netherlands Institute for Health Services Research).

This thesis was supported by an unrestricted grant from the Royal Dutch Pharmaceutical Society (KNMP), The Hague, The Netherlands. The study presented in Chapter 4.1 was funded by an unrestricted grant from the Dutch Health Care Inspectorate (IGZ).

Be not the first by whom the new are tried,
Nor yet the last to lay the old aside.
Alexander Pope

Voor mijn familie

CONTENTS

Chapter 1

INTRODUCTION

Introduction

Fuelled by chemistry and increasingly guided by molecular biology, drug discoveries are an important pillar of present day medical practice [1,2]. The discoveries of, for example, penicillin, cortisone, streptomycin, and chlorpromazine, are just a few definitive moments that revolutionised modern medicine [3]. Without the discovery of new drugs, today's medical practice would probably still be in the pre World War II era characterised by a high mortality rate due to absence of effective antibiotics, vaccines, and many other drugs [3,4]. However, despite all positive contributions brought about, every new drug represents a delicate compromise between the promise of healing, the risk of possible side effects, and the price [5].

In response to the drug tragedies with thalidomide and diethylstilbestrol in the 1960s-1970s [6,7], extensive efforts have been made to establish and optimise drug regulation to ensure the safety, efficacy, and quality of the new drugs reaching market approval [8,9]. Nowadays, new drugs are subjected to extensive clinical testing in randomized clinical trials to ensure relative efficacy of the new drug entering the market. As important progress has been made both on the development and safety aspects of new drugs, today's pharmaceutical market place is faced with new challenges, namely a declining rate by which new and innovative drugs become available, increasing (development) costs of the new drugs, and to ensure safe and proper use of new drug in the post-marketing phase [10-15].

As most Western countries face an aging population with a high prevalence of morbidity, there is a growing need for safe and effective new drugs [14]. The increasing demand for effective and safe new drugs is matched, however, by a declining number of new drugs being introduced on the market every year [14,15]. Not only is the overall number falling, so is the number of new drugs that are truly innovative. Most of the drugs that leave the clinical testing phase and enter the pharmaceutical market place are gradual innovations of existing compounds or therapies.

The declining output of the pharmaceutical pipeline is paralleled with increasing costs for developing new drugs [16,17]. The high costs of new drugs are partly a reflection of the high-risk investments preceding drug development and the economic pressure on pharmaceutical companies to produce blockbuster drugs (drugs with an annual worldwide sale of $1 billion plus) with the accompanying marketing efforts to ensure sufficient market share [18]. In 2002, the worldwide sales of prescription drugs exceeded $430 billion, of which 85 percent was spend in North America, Europe, and Japan [19]. The high development costs of new drugs give rise to concerns about the budget impact of new drugs on the consistently rising national health expenditures [14,15,17,20,21]. As the price of new drugs is in general higher than that of similar compound belonging to the same drug class, new drugs place pressure on the sustainability of our welfare state, but also on free market healthcare systems such as in the US [21].

Despite the enormous improvements in drug regulations, there is still a high degree of uncertainty at the moment of market introduction about the new agent's surplus value in daily clinical practice [22,23]. This uncertainty not only applies to the new drug's effectiveness, but also to its safety profile when used in large populations [24-26]. Although new drugs are nowadays relatively safe when they receive market authorisation several new drugs such as among others tolcapone (withdrawn in 1998) [27], mibefradil (1998) [28], cerivastatin (2001) [29], and rofecoxib (2004) [30] were withdrawn after being on the market for only a few years.

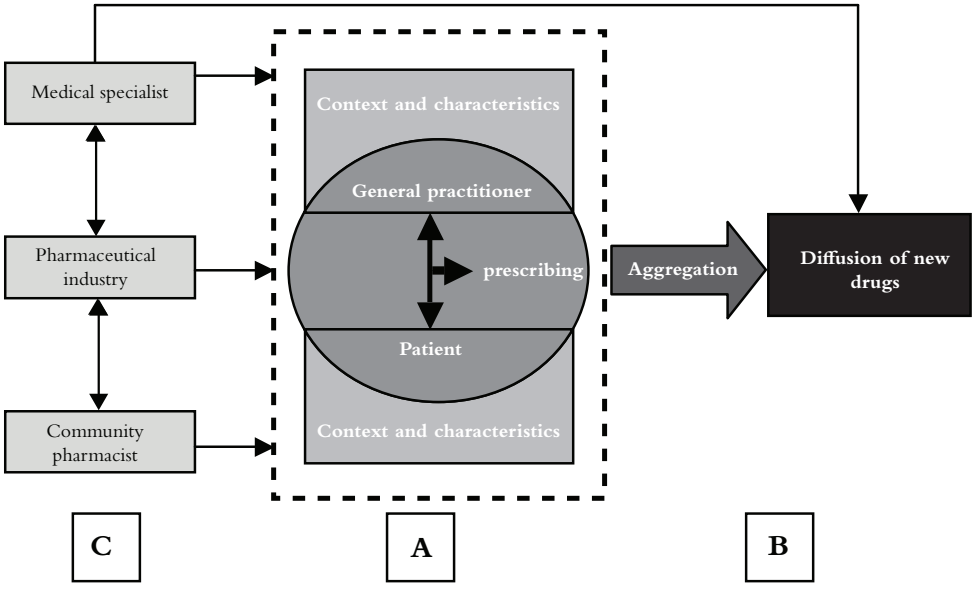
When new drugs show erratic market uptake, there may be valid concern about uncertain risk-benefit for patients, suboptimal allocation of financial resources in health care, and possible market withdrawal of new drugs that could have been prevented [25,26,31,32]. To understand the dynamics of new drug prescribing, insight in the reasons of general practitioners (GPs) to adopt new drugs, and the underlying mechanisms, is important. GPs play a major role in (long term) drug prescribing and in many countries GPs are the cornerstone of primary healthcare, especially in the UK and The Netherlands where they function as gatekeepers for hospital care. In addition, compared to medical specialists who are often regarded as the early prescribers of new drugs, GPs treat a large and diverse patient population that may contribute to a wide range of patients being treated for an array of different indications. The phenomenon of new drug prescribing is composed of a micro-level component, i.e. the decisions of individual GPs in a specific doctor-patient encounter, and a macro-level component, that is the aggregation of these micro-level decisions into a pattern of diffusion of new drugs. Numerous factors, on both micro- and macro-level, influence the probability that a GP adopts a new drug, making the topic very complex.

Previous studies on prescribing of new drugs by GPs.

The following section will provide an overview of the literature on prescribing of new drugs by GPs. To organise the literature we use a theoretical model in which the encounters between individual GPs and patients during their private consultations are the basis of the model (Figure 1), as is illustrated by the central part (A) of the model. Notwithstanding the possibility that a group of GPs has collectively decided to use a new drug, the actual decision to prescribe is taken in a specific GP patient encounter. The aggregation of these decisions builds the diffusion patterns of new drugs in general practice. This is the outcome of the model and represented by right part (B) of the model. Ideally, the decision to prescribe a new drug is the outcome of a shared decision making process, based on the scientific evidence and the medical need of the patient. However, in daily medical practice the context of these encounters and the characteristics of both the patient and the GP are important determinants of the decision whether a drug will be prescribed and if so, which specific drug it will be.

The diffusion of new drugs is not solely the summation of the outcomes of the GP-patient encounters. External influences of, among others medical specialists, community pharmacists, or pharmaceutical companies, shape the contexts within wich the decisions are made. Besides, medical specialists also have a direct influence through their own prescribing and subsequent repeat prescribing by GPs. The external influences are illustrated in the left part (C) of Figure 1.

Figure 1: *Theoretical model used to organise the literature on GP prescribing of new drugs.*



The decision making process resulting in prescribing of new drugs – part A

Insight in the decision-making process is fundamental to understand new drug prescribing. Extensive research has been dedicated to elucidate the decision-making processes of physicians when deciding to initiate drug therapy [33-35]. Unfortunately, it is unknown whether or to what extent these models also apply to situations in which new drugs are prescribed. When making a decision to prescribe, GPs tend to work with only a restricted number of drugs [36-38]. This personal head-held formulary, or so-called 'evoked set', is unique to every GP and consists of an idiosyncratic personal list of drugs [33]. Changes in their personal repertoire seem to be limited. Taylor and Bond analysed initial prescriptions of 189 British GPs over a period of 12 months to describe the types of drugs GPs prescribe and the additions

and deletions from their repertoire [39]. They noted that most GPs have a personal set of about 100-200 drugs (mean=144 drugs) to cover the wide range of illnesses seen in general practice. Newly adopted drugs accounted for only 5.4% of all non-repeat prescriptions, which in turn were 62.3% of all prescriptions. Of all newly adopted drugs, only 42% served as a substitute for another drug. 'Newly adopted' was, however, defined as a drug added to the GP's personal repertory during the previous 12 months and therefore not necessarily a newly marketed drug. This means that newly marketed drugs accounted for less than 5.4% of all non-repeat prescriptions. Apart from the obvious limitations to human information processing, the reason for GPs to work with a limited set of drugs to treat a wide range of diseases is to gain clinical experiences with the drugs and thereby reduce the uncertainty associated with prescribing [38].

Attitudes towards the prescribing of new drugs

Qualitative research has shed light on the factors that GPs report as being important in their decision-making process leading to prescribing of new drugs. Prescribing of new drugs, especially during the early post-marketing period, always holds of some degree of uncertainty. GPs have to substitute the tried and proven, albeit imperfect, old drug by a new, which carries within it uncertainties about effectiveness and safety. Some consider new drug prescribing even as an act of faith rather than a rational decision [40].

Most GPs regard themselves as conservative when it comes to new drugs, but important differences do exist between GPs with respect to their attitudes towards new drugs, their risk management, and the information sources they consult before prescribing. Prosser and Walley explored in a qualitative study differences in approach and attitudes towards new drugs between heavy and low prescribers in a group of 30 British GPs [41]. They noted that low prescribers displayed a more conservative approach by adopting 'a wait and see' policy until safety and effectiveness is proven. Moreover, low prescribers gradually accumulated information from several sources, especially medical specialists. Heavy prescribers also relied on specialist prescribing, but expressed less reservation about commercial sources. They acknowledged the possible risks of new drugs, but laid more emphasis on their potential benefits. In addition, heavy prescribers often developed a special interest in a particular clinical or therapeutic area in which they were willing and felt comfortable to experiment. The trialability of a new drug and subsequent outcomes of the testing phase, plays for both groups an important role in the decision to adopt [42]. However, Dybdahl et al. found no consistent association between the GP's level of drug prescribing in a specific therapeutic group and their adoption of a new drug belonging to that group [43].

Jacoby et al. identified a wide range of factors by using in-depth semi-structured interviews to explore influences on decisions of 56 GPs to prescribe eight new drugs [44]. Important

internal factors were the GP's own clinical experience, the level of confidence in their role as a doctor, their level of expertise in a specific clinical area, and their attitudes towards cost-conscious prescribing. Important external factors were peers, pharmaceutical representatives, and scientific literature. An interesting finding was that low prescribers conformed more to group norms, such as practice formularies. They laid more emphasis on similarities between prescribing habits of colleagues as a result of more intense, both formal and informal, communication. The causal pathway here is, however, unclear.

Characteristics of the innovative GP

In attempts to understand the phenomenon of new drug prescribing, several studies tried to profile the innovators or early prescribers [37,45,46,47-52]. The studies identified various predisposing characteristics, but these were not always consistently associated with rapid or extensive prescribing of new drugs. In a study by Inman and Pearce, male GPs prescribed more new drugs than female GPs. In the group that prescribed most heavily, women accounted for only 9% [48]. Tamblyn et al. noted that male GPs were more likely than women to prescribe any new drug (RR=1.20; 95% CI 1.04-1.39), but male GPs did not have a higher utilisation rate[52]. The authors give some explanations for the higher representation of men among early prescribers. For example, the fact that women more often work part-time [48] or that men are more confident in prescribing new drugs than female GPs [52]. In general, psychological literature shows men to be more inclined to take risks than women.

The type of practice is another characteristic that seems to be positively correlated with new drug prescribing. Although recently Dybdahl et al. found no differences in time to adoption between single-handed and group practices when correcting for practise size [53], other studies did find that GPs working in group practices display a shorter time to their first prescription for a new drug than GPs practising single-handed [37,46,49]. Williamson found that in a group of 140 GPs, 45% of the single-handed compared to 60% of the group practising GPs adopted a new drug in a period of 20 to 40 weeks [37]. Explanations for this finding may lie in the fact that GPs working in the same partnership show more resemblance in attitudes and behaviour than GPs working in different partnerships [46,54]. Within group practices, GPs can exchange information about new drugs more freely due to their close intra-group colleague contact and that may lower the threshold to initiate new drug prescribing. Coleman et al. noted that the decision to adopt was a function of the GP's integration in a social network of friendship, discussion, and professional advice [46]. GPs that were socially integrated and regarded by colleagues as opinion leaders prescribed new drugs faster than GPs who were less often mentioned by colleagues as a discussion partner.

Various other GP characteristics have been positively associated the prescribing of new drugs, namely an older age or more years since graduation [48], a higher practice volume [47,52],

fund holding [51], medical school [52], and the country of first medical degree [48,52]. Although several correlations between GP characteristics and prescribing of new drugs have been found, the characteristics explain only a fraction of the variance in prescribing. Besides, not all characteristics of GPs show the same consistent correlation in term of direction in the different studies. For example, some studies found that older GPs tend to prescribe more new drugs [48], or that young or middle aged GPs tend to do so [46], whereas other studies found no correlation [49,52]. The same accounts for a greater list size [49,52]. Studies have shown that the variation in new drug prescribing depends on personal beliefs of GPs. Both heavy and low prescribers regard themselves as conservative towards prescribing of new drugs, but clear differences do exist between the two groups [41,55]. So it seems that a combination of attitudes makes some GPs more receptive to new drugs. Most GPs will hold a mixture of conflicting attitudes and beliefs about new drugs that on the one hand supports cautiousness whilst on the other hand the wish to treat patients more successfully [44].

Influences of patients

GPs state that patients are an important factor in the decision to prescribe a new drug. Patients may exert their influence during a consultation in different ways [56,57]. It is important to distinguish between decisions that are primarily based on the patient's medical needs and those that arise from conceding to patient requests. New drugs are mostly not a GP's first choice, but are used to fit the drug treatment to the patient context. Suboptimal effectiveness of previous treatment and optimising compliance may legitimate prescribing of new drugs [55]. Prescribing of new drugs to patients poorly managed on older medication, may however result in new drugs being selectively prescribed to more severely ill patients. Therefore, new drugs may be channelled into patient populations consisting of more severely ill patients who are more susceptible to side effects. Conceding to a patient's request is also stated by GPs as an important reason to prescribe new drugs and leads to uncomfortable situations [38,55,56,58]. Patient pressure may particularly be powerful for drugs intended to treat a problem that falls in the grey zone of the medical and social definitions of health; or so-called lifestyle drugs, such as sildenafil and orlistat [55]. Trying to maintain a good doctor-patient relation, time constraints, poor management with current therapy, acknowledgement of the patient's right to be involved in decision making process, and avoiding conflicts are important motives to concede to patient requests [58].

Aggregation of new drug prescribing to patterns of diffusion – part B

As described above there is a wide variability between GPs attitudes towards new drugs and the subsequent prescribing of these drugs. The decision to prescribe is hard to predict on basis of a small number of characteristics of GPs. However, all individual decisions made by GPs to incorporate a new drug in their evoked-set, are translated into diffusion patterns of the new drug in general practice. Rogers defined 'diffusion' as the process by

which an innovation is communicated through certain channels over time among members of a social network [42]. Based on their time to adopt an innovation, people are classified as belonging to one of the five adopter categories, namely innovators, early adopters, early majority, late majority and laggards. Plotting the cumulative number of adopters over time results in a typical S-shape adoption curve. When it comes to understanding the safety and economical aspects associated with rapid prescribing of new drugs, much attention has been paid to profile the innovators and early adaptors. Several studies focussed on the magnitude of new drug prescribing and quantified new drug prescribing by GPs [37,48,49,51,52,59]. An interesting finding of these studies is that a minority of the physicians is heavily engaged in rapid prescribing of new drugs and account for a disproportionate share of all early prescriptions [48,52]. This is in concordance with Roger's classification of adopters.

Inman and Pearce studied among 28,402 British GPs the prescribing pattern of 27 newly marketed drugs six months after market introduction, between September 1984 and June 1991 [48]. In total, 543,788 prescriptions were analysed. The main outcome variable was the number of new drugs prescribed by a GP during the study period. They noted that 10% of the GPs that prescribed most heavily accounted for 42% of the total prescribing, while 1% of very high prescribers accounted for 10%. A study by Tamblyn et al. reported similar results [52]. Tamblyn et al. conducted a study among 1,842 Canadian GPs and medical specialists to estimate the initial utilisation rate of 20 new drugs and to find associations between characteristics of the physicians and prescribing of new drugs. All drugs were introduced between 1989 and 1994 and the follow-up was limited to first six months after introduction. The main outcome variable was the prescribing rate per physician, which was defined as the number of patients receiving a new drug out of the total number of patients receiving a drug from the same therapeutic drug class. The study noted that the 20 new drugs were prescribed by 1.3%-22.3% of the physicians. There was an eight to 17-fold difference in utilisation rates between the prescribers. Jones et al. analysed prescribing data for proton pump inhibitors (PPIs) of 53 British GPs over the period January 1995 to December 1997 [51]. The aim of the study was to compare the prescribing of different PPIs among GPs and to explore how their PPI use changed after the introduction of a cheaper compound. They observed an 87-fold difference in prescribing between the heaviest and lowest prescriber of the new PPI.

Although the studies identify a select group that is heavily inclined to prescribe new drugs, the labelling of a GP as an innovator is very much drug dependent [49,53]. Steffensen et al. studied the diffusion of five new drugs in Danish general practice over the period 1993 to 1996 by analysing prescribing data of 95 single-handed GPs [49]. The main outcome variable was the time to adoption, which was defined as the period from reimbursement to the GP's

third prescription. The third prescription was used to reduce the risk of misclassification by including repeat prescribing of specialist-initiated prescriptions. The adoption time was asymmetrically distributed among the GPs and dependent on the new drug. The adoption curve of sumatriptan, a drug used for the treatment of migraine, showed a steep initial phase with 80% of the GPs prescribing the new drug within 21 weeks after its release. However, the adoption time for the antibiotic clarithromycin differed from that of sumatriptan. Only about 20% of the GPs prescribed clarithromycin after 32 weeks following market introduction. A study by Jones et al. showed similar results. The study used prescribing data, combined with questionnaires, of 56 British GPs to estimate the uptake of eight new drugs that were launched between May 1994 and January 1996. The results showed that GPs were inconsistent in their uptake. GPs who were early and heavy prescribers of one drug could be low prescribers of another drug [50]. This means that early adopters of one drug were not by definition early adopters of another drug. Instead, it was found that being a late adopter is a more consistent characteristic than being an early adopter and therefore adoption is both GP and drug dependent. The study also showed that the classical S-shaped adoption curve, which is often found for innovations, did not apply to prescribing of new drugs. This may indicate that a GP is not easily categorised as an innovator, early prescriber, early majority, late majority, or laggard based solely on the analysis of their prescribing behaviour and, in addition, that the decision to adopt is heavily dependent on the new drug in question.

External factors influencing the decision to prescribe new drugs – part C

Although in theory numerous factors influence the GP's decision to adopt new drugs, the following section is limited to only three important factors, namely medical specialists, the pharmaceutical industry (in particular pharmaceutical representatives), and community pharmacists.

Influences of medical specialists

The interface between general practice and specialist care is important in the adoption of new drugs by GPs [60-66]. Several mechanisms are involved through which the influences of medical specialists reach GPs. The most direct manner is the specialist's own prescribing of new drugs that may be repeated by GPs and creates a 'learning by demonstration' effect. Besides the direct influence, medical specialists also serve as an important information source and provide a legitimation function for the uptake of new drugs.

When it comes to information sources used by GPs three domains have been reported to be important: (1) the information, i.e. what is disseminated (2) the source credibility, i.e. who is the communicator and (3) the clinical experience of the recipient [55]. The information conveyed by medical specialists is limited and follows a trickle down model mainly through discharge

letters. Active discussions or information exchange about new drugs seems to be limited [50,55]. This may partly be explained by the fact that discharge letters form a passive information source that reaches the GP without requiring any action of the recipient [60,67-69]. The credibility of medical specialists as an information source is rated high by GPs. The influence of medical specialists is mostly visible in the second phase of the adoption process, during which GPs decide to start prescribing [69]. Compared to pharmaceutical representatives, who often fulfill an alerting function, medical specialists are mainly used as legitimation for prescribing new drugs. Prosser et al. interviewed 107 British GPs to identify factors influencing the GP's decision to prescribe new drugs [55]. They noted that for 10% of the GPs, medical specialists were their first source of information about the new drug, mainly by discharge letters, but for 33% of the GPs pharmaceutical representatives fulfilled this role.

Another important mechanism by which medical specialists influence drug uptake by GPs is the referral of patients to specialist care and the subsequent repeat prescribing of medication initiated by specialists. The perception of the influence of specialists on their prescribing varies among GPs, but the actual influence may be greater than GPs are aware of [63,65]. Furthermore, the influence of medical specialists on their prescribing behaviour is not always appreciated by all GPs. The high costs associated with new drugs are partly credited to repeating prescriptions that are specialist initiated. Avery et al. showed that of 162 British GP practices those with high cost growth prescribed significantly more expensive and specialist initiated drugs than practices with low cost growth [70]. Robertson et al. interviewed 35 Australian GPs about their perceived influence of medical specialists on their prescribing habits. They noted that medical specialists influence GP prescribing in several ways but the influence is not uniform across all areas. The influence was greater in less common diseases, for conditions that required specialist intervention, and in difficult to manage patients [63,65]. Interventions by specialists resulted in changes in the selection of drugs used within a therapeutic group, uptake of new drugs, and sometimes modification of established prescribing habits. There are distinct differences between low and heavy prescribers in the way they evaluate the prescribing of medical specialists. Low prescribers often use medical specialists as a prescribing guide, whereas the specialist endorsement is not a requisite for heavy prescribers to develop a favourable risk-benefit assessment [41].

Several studies have looked at the specialist's direct influence on GP prescribing, mainly by analysing repeat prescribing. Studies focussing in particular on the effect of new drug prescribing are limited. Two studies looked to some extent at the influence of specialist on new drug prescribing by GPs [63,71]. Other studies focussed on particular drug classes or patient groups [61,62,68,72,73,74]. In general, the influence of specialist prescribing on the GP's prescribing behaviour is considerable, both in volume and in costs. Consequently, the prescribing behaviour of GPs can be regarded as a derivative of the prescribing behaviour of

medical specialists. Two studies found that around 66% of all prescriptions signed by GPs were hospital initiated [61,73].

Robertson et al. studied the influence of specialists by analysing prescribing data of 88 Australian GPs [63]. The aim was to estimate the effect and whether specialists had a greater impact on prescribing of new drugs. In total, 4,362 prescriptions were analysed. The influence of medical specialists was drug class dependent. Eighty-five percent of the proton pump inhibitors was initiated by medical specialists, whereas this was only the case in 8% of the prescriptions for diuretics. However, this difference was not observed for newly introduced drugs compared to established drugs. The more recently introduced angiotensin II antagonists and atorvastatin were not more likely to have been specialist initiated than prescriptions for established ACE-inhibitors and statins. This seems to be in line with findings of a study by Tamblyn et al. who found no associations between the referral rates of GPs to specialists and the number of new drugs prescribed or the likelihood to prescribe any new drug [52].

Influences of the pharmaceutical industry

One of the earliest studies on new drug prescribing by GPs is the study by Coleman et al. from 1966 on the diffusion of the new antibiotic tetracycline in a population of American GPs [46]. Coleman et al. concluded that the GP's social integration in a network of friendship, advice and discussion played an important role in the adoption of the new drug. However, the study lacked to include marketing efforts in the model. A later study by Winick failed to repeat similar findings [45] and a recent reanalysis of Coleman's data, but with the inclusion marketing efforts, showed that the GP's time to adoption could as well have been the result of exposure to pharmaceutical marketing [75].

The literature pertaining to the prescribing of new drugs by GPs undoubtedly identifies pharmaceutical representatives as one of the key influences on their decision to adopt new drugs. Qualitative research has elucidated many reasons of GPs to accept visits by pharmaceutical representatives and the mechanism by which they are influenced. The GP's decision to accept visits is shaped by a mixture of reasons that are imbedded in their personal beliefs and social norms. The reason mostly mentioned by GPs to see pharmaceutical representative is the wish to stay up to date with new products and medical innovation [55,69,76,77,78,79]. The success of pharmaceutical representatives is dependent on several factors. Firstly, the increasing workload and the wealth of information available limit GPs to independently gather relevant information. Secondly, inaccessibility or tardiness of independent information sources contributes to the popularity of pharmaceutical representatives [78]. Other reasons often mentioned by GPs are an escape from the daily routine of seeing patients, or out of courtesy, or habit. However, not all GPs see pharmaceutical

representatives. Their decision not to do so mainly lies in a strong belief that pharmaceutical representatives provide commercially biased information. These beliefs are also expressed by GPs that do receive visits, but for them other reasons may still be in favour of receiving pharmaceutical representatives [78]. Another reason often mentioned for not seeing representatives is the social norm within practices.

The GP's perception of the information provided by pharmaceutical representatives varies but is often contradictory to their action. In general, GPs acknowledge that the information provided to them is biased and influences their prescribing, but they regard themselves capable of 'separating the wheat from the chaff'. Pharmaceutical representatives exert their influence in the awareness stage of the adoption process. Professional sources, such as medical specialists and scientific journals, are mentioned more often when the decision to prescribe is actually being considered [67,69,76,80]. GPs value professional sources higher than commercial sources, but this opinion is not always reflected in practice [81]. A study by Prosser and Wally identified a difference between heavy and low prescribers of new drugs in their use of pharmaceutical representatives [41]. Not only did heavy prescribers mention pharmaceutical representatives in 46% of the decisions to initiate new drug prescribing as important, compared to only 10% of the low prescribers, they also failed to gather additional information. Peay and Peay showed that a small group of physicians is heavily influenced by commercial sources. They identified a subgroup of about 15% of the doctors that relied exclusively on commercially based information sources for new drugs [69]. In a later article in which the adoption of temazepam was analysed, they concluded that the adoption was related to commercial sources rather than to a doctor's professional involvement [76]. This is in line with findings of a study by Jones et al. that looked at influences on new drug prescribing by GPs and medical specialists. The study concluded that drug company material was often the only information source used by GPs before prescribing [50].

Besides ensuring that the content of the information connects to the information needs of GPs, pharmaceutical representatives also put a lot of effort in the format of the information by building and maintaining personal relationships with GPs. Face-to-face contact ensures that GPs remember information about new drugs better than when offered to them in writing. By investing in personal relationships, pharmaceutical representatives hope to position themselves as professional information sources rather than sales people [77].

The former studies on the influence of pharmaceutical representatives identified factors on the micro-level on which the individual decisions to prescribe new drugs are made. Other studies measured the influence of pharmaceutical representatives or medical advertising on the macro-level [82]. Jones et al. monitored the advertisements of nine new drugs during a period of 30 months in 12 British journals to relate the level of advertising to prescribing

data of 50 GPs [82]. The study showed a seasonal variation in advertising with its peak between May and October and an overall complex but no constant pattern. Furthermore, no relation was found between the advertising intensity and prescribing of new drugs by GPs. This lack of association between advertising and increased prescribing of new drugs was iterated in a study by Tamblyn et al. [52]. The number of detail minutes and number of advertising pages, obtained by IMS Health, was used to assess the marketing intensity of new drugs. The number of detail minutes and advertisement pages varied considerable between the new drugs, but no apparent association was found between the marketing intensity and new drug prescribing by GPs.

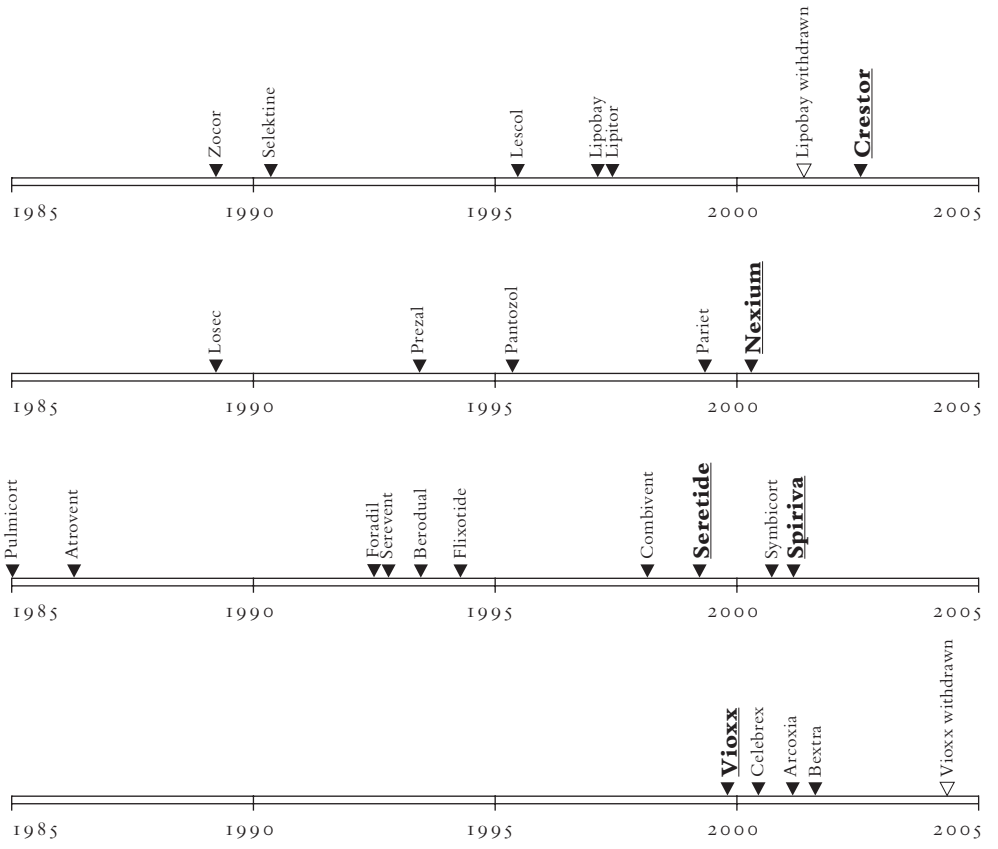
Influences of community pharmacists

The role of community pharmacists has changed from a traditional drug orientated role to a more patient orientated [83-88]. While still maintaining their role of dispensing medicines to patients, pharmacists are engaging more in management of prescribed medication, long-term and common ailments and advice and support to other health professionals [89-91]. As the pharmacist's role is changing to providing pharmaceutical care, so must their ability to influence drug prescribing by GPs [83]. Carroll reviewed the literature on the influences of American community pharmacists on prescribing of GPs [92]. He concludes that pharmacists routinely intervene to improve clinical problems and to provide a more affordable therapy for patients. In the majority of the interventions, physicians accept the suggestions. This is in line with studies from other countries where pharmacists have shown to contribute to optimisation of GP prescribing behaviour [89,93]. However, none of these studies report on any influences on new drug prescribing. From qualitative studies on reasons of GPs to initiate new drug prescribing, pharmacists are only scarcely mentioned as a source of information about drugs [55]. In a study among 17 British GPs on costs and variation in their prescribing, the role of community pharmacists was both valued and dismissed by GPs. One important condition for appreciation of the pharmacist's role is the development of professional partnerships. GPs acknowledged the expertise of community pharmacists in detecting prescribing errors, but the pharmacist's potential was rarely exploited [38]. Given the evidence that pharmacists do influence GP prescribing behaviour, it is likely that this influence is also aimed at new drugs.

Objective of this thesis

The main objective of this thesis is to detect and elucidate patterns by which new drugs are prescribed by GPs and to profile GPs inclined to adopt new drugs rapidly. In addition, the studies in this thesis focus on the external influences, in particular medical specialists, community pharmacists, and the pharmaceutical industry, shaping the GP's decision to prescribe new drugs. To understand the dynamics of new drug prescribing, we choose five drugs that were introduced on the Dutch market in the years 1999 untill 2003 as study case drugs. Figure 1 shows the Dutch registration dates of these new drugs in comparison to the drugs from the same therapeutic drug class.

Figure 1: *Dutch market introductions of the new drugs Crestor®, Nexium®, Seretide®, Spiriva®, and Vioxx®.*



The rationale for choosing these five drugs as study cases is that they form a representation of drugs on the scales of innovativeness and known safety profile at introduction (Figure 2). In addition, all five drugs showed rapid market penetration and were therefore in sufficient numbers prescribed in general practice. In The Netherlands, SFK (Foundation for Pharmaceutical Statistics) reported in 2002 that the drugs that were introduced during the preceding three years contributed to 5% of the total national drug expenditure, but more interestingly, over two third was credited to only ten new drugs [94,95]. In 2002, the top 3 drugs with the highest expenditure on all drugs was occupied by Seretide® (salmeterol/fluticasone), Vioxx® (rofecoxib), and Nexium® (esomeprozole) [94]. In 2004, the list was lead by Spiriva® (tiotropium) with Crestor® (rosuvastatin) in third place [95].

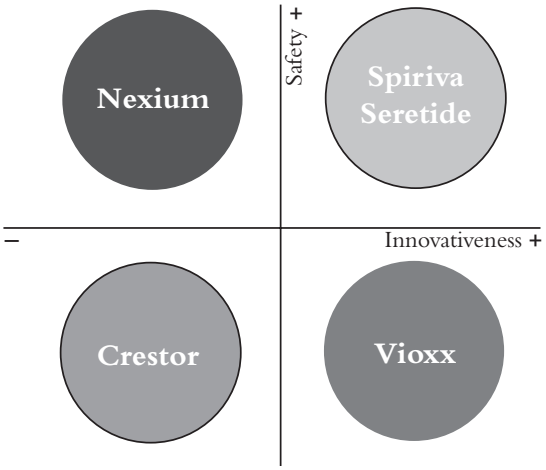
The study case drugs

Esomeprazole was the latest representative of the proton pump inhibitors, an effective group of drugs for the treatment of gastro-oesophageal reflux disease. Being its chemically pure form, esomeprazole became omeprazole's successor. Omeprazole (Losec®/Prilosec®) with annual sales of $6 billion was once the top-selling drug in the world, but was scheduled to go off patent in 2002. With its minimal clinical surplus value over the existing products, we used esomeprazole as an example of a me-too product [96,97]. Me-too drugs are drugs that are chemically very similar to existing drugs and largely exert the same pharmacological action, but are in general more expensive than the original compounds in the same therapeutic drug class.

Rosuvastatin is the sixth and latest representative of the HMG-CoA reductase inhibitors, also known as statins, which are effective drugs in the treatment of hypercholesterolemia. In 2002, one of the statins, namely cerivastatin (Lipobay®), was withdrawn from the market due to concerns about its hepatic toxicity [29]. Even before rosuvastatin was granted market approval, concerns were already raised about the new agent's safety profile [98-103].

Rofecoxib was the first representative of the new cyclo-oxygenase-2 (COX-2) inhibitors. COX-2 inhibitors are pharmacological selective versions of the long-existing and widely used nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diclofenac, and naproxen, which long-term use is often limited due to their gastro-intestinal side effects [104]. With their improved gastrointestinal safety profile COX-2 inhibitors were considered as an innovation in the treatment of pain and inflammation [104,105]. However, soon after rofecoxib market introduction concerns about its cardiovascular safety profile arose that eventually led to the worldwide withdrawal of rofecoxib in October 2004 [30,106,107,108,109].

Figure 2: *The innovativeness and safety profile at market introduction of the five study case drugs.*



Nexium®=esomeprazole, Seretide®=salmeterol/fluticasone, Vioxx®=rofecoxib, Crestor®=rosuvastine, Spiriva®=tiotropium.

Seretide® was not a new chemical entity but was the first product combining two existing drugs for the treatment of asthma and chronic obstructive pulmonary disease (COPD), namely salmeterol and fluticasone, in one single dosage form. In that sense, Seretide® can be regarded as an innovation in the treatment of asthma and COPD, since it implies simpler dose frequencies. Tiotropium was the successor of ipratropium (Atrovent®), a drug for the treatment of asthma and COPD, but belonging to another drug class than Seretide®. Since the recommended dose frequency was reduced from four times daily for ipratropium to once daily in the case of tiotropium, the new drug made a valuable contribution to the treatment of asthma/COPD. Both Seretide® and Spiriva® are examples of stepwise innovation leading to better versions of existing products [110].

Outline of the thesis

This thesis presents eight studies on the dynamiscs of new drug prescribing in general practice. Two studies describe the prescribing and dispensing data that form the basis of the subsequent studies on new drug prescribing. The studies featured in this thesis are the results of the UNICA-project (Utrecht University and NIVEL primary CAre), a novel and fruitful collaboration between the Utrecht University and NIVEL (Netherlands Institute for Health Services Research).

The thesis starts with **Chapter 2** covering the data platform that is used in the studies on GP prescribing of new drugs of Chapter 3 and 4. Chapter 2.1 determines the success rate of linking records from the dispensing database of SFK (Foundation for Pharmaceutical Statistics) to the prescribing database of the second Dutch national survey of general practice conducted by NIVEL in 2001. In Chapter 2.2, we assessed whether GP prescribing records provide accurate data on patients' actual drug exposure.

Chapter 3 consists of four studies on new drug prescribing. Chapter 3.1 aims to profile the early prescribers of new drugs. The other three studies in Chapter 3 examine two important external influences, namely medical specialists and community pharmacists. The central questions addressed in this chapter are: 1) Is early new drug prescribing concentrated in GPs with distinct characteristics? 2) Is new drug prescribing a trait of GPs? Or in other words, is there a universal early adopter? 3) To what extent is new drug prescribing influenced by medical specialists? 4) Do community pharmacists, through their participating in pharmacotherapy audit meetings (in Dutch known as FTO) with GPs, influence new drug prescribing? **Chapter 4** contains four case studies on prescribing of two new drugs, namely rofecoxib and rosuvastatin. These case studies provide clear examples of how new drugs are prescribed in general practice and illustrate how risk assessment plays a role while prescribing new drugs. Finally, in **Chapter 5** the results and conclusions of all studies are integrally discussed.

Chapter 2

DATA USED IN THE UNICA PROJECT

Chapter 2.1

Linking pharmacy dispensing data to prescribing data of general practitioners

Stefan R. Florentinus [1], Patrick C. Souverein [1], A.M.G. Fabiënne Griens [4], Peter P. Groenewegen [2,3], Hubert G.M. Leufkens [1], Eibert R. Heerdink [1]

[1] Utrecht University,
Division of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht, The Netherlands.

[2] NIVEL (Netherlands Institute for Health Services Research),
Utrecht, The Netherlands.

[3] Utrecht University,
Department of Sociology and Department of Human Geography,
Utrecht, The Netherlands.

[4] SFK (Foundation for Pharmaceutical Statistics),
The Hague, The Netherlands.

BMC Med Inform Decis Mak. (in press)

Abstract

Background: Databases are frequently used for pharmacoepidemiological research. However, most of these databases consist either of prescribing, dispensing or administrative data and therefore lack insight in the interaction between the several health professionals around the patient.

Objective: To determine the succes rate of linking pharmacy dispensing records to GP prescribing data.

Methods: To determine the success rate of linking records from the dispensing database of SFK (Foundation for Pharmaceutical Statistics) to the prescribing database of the second Dutch national survey of general practice, conducted by NIVEL (Netherlands Institute for Health Services Research), a deterministic record linkage approach was used with patient and prescription characteristics as matching variables between the two databases.

Results: The catchment area included 123 community pharmacies, 90 GP practices and 170,000 unique patients. Overall, 110,102 (64.8%) unique patients were linked using the matching variables patient's gender, year of birth, the 4-digit part of the postal code, date of dispensing/prescribing and ATC-code. The final database contained of the 110,102 patients both the prescribing data from 83 GP practices and the dispensing data of 112 community pharmacies.

Conclusions: This study shows that linkage of dispensing to prescribing data is feasible with a combination of patient characteristics, such as gender, year of birth and postal code, and prescription characteristics like prescription date and ATC-code. We obtained a linkage proportion of 64.8% resulting in complete prescribing and dispensing history of 110,102 patients. This offers an opportunity to gain insight in the mechanisms and factors influencing drug utilisation in general practice.

Introduction

To enhance the quality and efficiency of observational research in daily clinical practice, linkage of different databases is often desirable to gain more insight in the underlying mechanisms by which medicines are utilised in large populations. Linkage of dispensing data from community pharmacies to hospital admission data, for example, has proven to be beneficial in detecting serious drug-induced side effects [1,2]. Although important findings have been published, most of the databases used so far consist of either prescribing data of general practitioners (GPs), pharmacy records or administrative data from health insurance companies [3,4]. The origin of the databases defines the vantage point of the researcher and may therefore limit the usability the data. For example, prescribing data of GPs alone are not sufficient to compile a clear overview of all drugs prescribed in general practice. Prescriptions of hospital specialists are usually not archived in GP prescribing databases and, unless repeated by GPs, result in blind spots. Furthermore, community pharmacists also have an influence on the drugs prescribed, resulting in differences between prescribing and dispensing [5].

In The Netherlands, several organisations are involved in routine collection of medical records, such as prescribing data of GPs [6,7] and dispensing data from community pharmacies [8]. In 2000, NIVEL (Netherlands Institute for Health Services Research) launched the second Dutch national survey of general practice (DNSGP-2) to obtain up-to-date and national representative data on the Dutch general practice. The rationale and design of the DNSGP-2 is presented in detail elsewhere [9,10]. The DNSGP-2 resulted among other things in a dataset comprising over two million prescriptions, prescribed by 101 GP practices to 262,817 patients in the period October 2000 to January 2002. For each prescription information was available on the prescription date, quantity prescribed, duration of use, product code, ATC-code [11], and ICPC -coded diagnose [12]. GPs were asked to fill in a thorough questionnaire on several topics, including their attitude towards new drugs, the number of visits by pharmaceutical representatives, the use of information sources on pharmacotherapy, and use of guidelines. Patients provided information about ten socio-demographic characteristics, including among other things age, gender, type of insurance, self-perceived health, and highest level of education. The DNSGP-2 provided a unique opportunity to link detailed information on both GPs and patients to dispensing data from community pharmacies to obtain a complete overview of the Dutch primary care.

Pharmacy dispensing data are collected in The Netherlands by SFK (Foundation for Pharmaceutical Statistics) [8]. Since 1990, SFK has been collecting dispensing data from a growing number of community pharmacies. In 2004, the catchment area consisted of 1,540 community pharmacies that represent 90% of the total number of Dutch pharmacies. The panel of pharmacies serves 13.5 million people and together dispense medicines, medical aid

and bandages about 130 million times per year [8]. Both the DNSGP-2 and the SFK database display important –and partly overlapping– parts of Dutch primary care.

As in most other healthcare systems, information is increasingly stored in electronic form and made available for scientific research. Combining the different databases makes it possible to eliminate shortcomings of individual databases and could result in opportunities greater than those presently thought of. Primary non-compliance, generic substitution, and interventions by pharmacists are just a few topics that could be addressed [13-15]. Therefore, the objective of this study was to determine the success rate of linking patient records from the SFK dispensing database to the prescribing database of the DNSGP-2. Combining the information from both data sources offers an opportunity to gain more insight into the factors influencing drug exposure in patients.

Methods

Data collection

All GPs who participated in the DNSGP-2 listed the pharmacies where most of their patients filled their prescriptions. All pharmacists from the identified pharmacies were invited by letter to participate and followed-up with a telephone call 1-2 weeks later. To maximise the likelihood of tracing all patients, we also contacted the pharmacies in the adjoining postal code areas. From the pharmacies that agreed to participate, the dispensing data were collected from SFK. The collected dispensing data covered the period January 1999 untill December 2003, whereas the prescribing data were mainly from the year 2001. Since not all patient of the same GP visit the same pharmacy and not all pharmacies agreed to participate, we estimated the total number of eligible patients to be 170,000. The estimation was based on the GP practice size, number of participating pharmacies and calculated by using estimations made by pharmacists of the proportion of a particular GP practice population that fills prescriptions at their pharmacy.

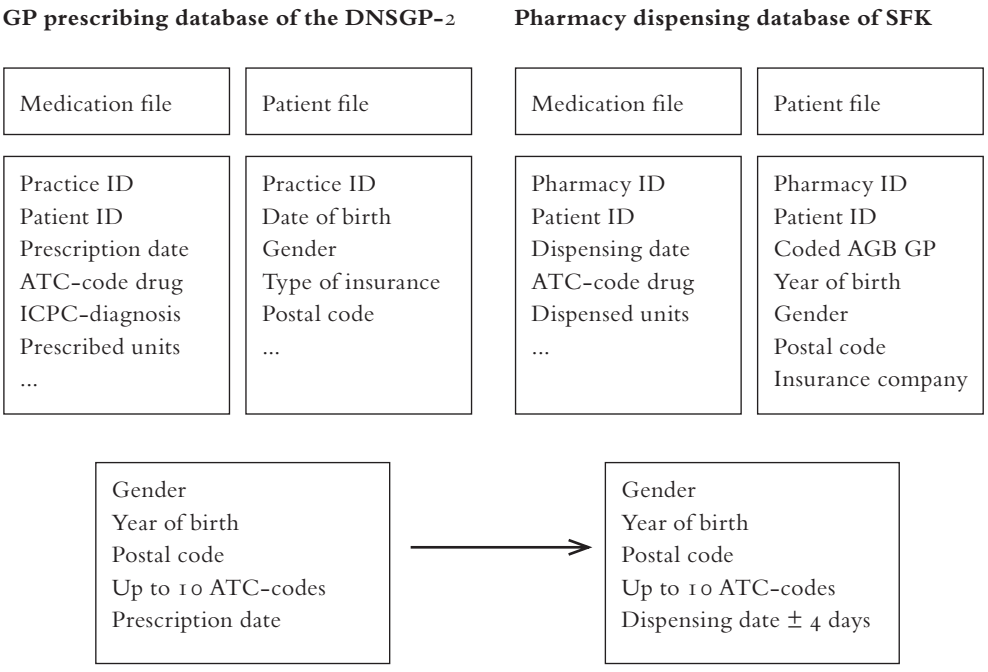
Matching procedure

We used a deterministic linkage method to match patient records from both data sources by using patient identifiers year of birth, gender and 4-digit postal code. The combination of these three characteristics, however, is not unique enough to identify patients within a GP practice of approximately 2,300 patients, let alone in a Dutch pharmacy listing on average 9,000 patients [8]. Therefore, we used prescriptions characteristics as identifiers, namely the Anatomical Therapeutic Classification code (ATC-code) [16] and prescribing date. The identifiers are listed in Figure 1. The records from the prescription database of the DNSGP-2 were defined as enquiry records (i.e. those from which is searched), whereas the pharmacy records were defined as the file records (i.e. those that have to be retrieved). For

each enquiry record, all file records were compared with respect to characteristics that are present in or logically related to both types of records.

The linkage procedure consisted of several subsequent steps. Firstly, patients were blocked on a combination of gender, year of birth and the 4-digit numbers of their postal code. Subsequently, the prescriptions of the patients recorded in both databases were compared within the blocks. Prescriptions were matched on date, ATC-code, and specificity of ATC-code. Up to 10 prescriptions per patient were used for matching. A successful match of patients' records was defined as a positive match on gender, year of birth, postal code and a minimum of 50% of enquiry prescriptions found.

Figure 1: *Structure of the matching process.*



By using prescriptions as patient identifiers, several aspects have to be taken into account. Firstly, medication is not always filled on the same day it is prescribed. Certainly nowadays, patients frequently request a refill prescription by phone and pick it up at the pharmacy the next day [17]. This results in a lag period of a few days between prescribing and dispensing. We defined a lag-time of four days as realistic. This means that patients' records could still be linked when there was a four day difference between the prescribing and dispensing date.

Secondly, the ATC-code of the dispensed drug does not have to be identical to the seven characters to the prescribed drug. Differences in ATC-code may be caused by interventions of community pharmacists to optimise pharmacotherapy or prevent possible adverse drug reactions [18,14]. To allow interventions of pharmacists, matching occurred in two stages. Patients were first matched using the complete ATC-code. When successfully linked, the patients' records were deleted from the enquiry and file database. The remaining patient records were matched using the first three characters of the ATC-code.

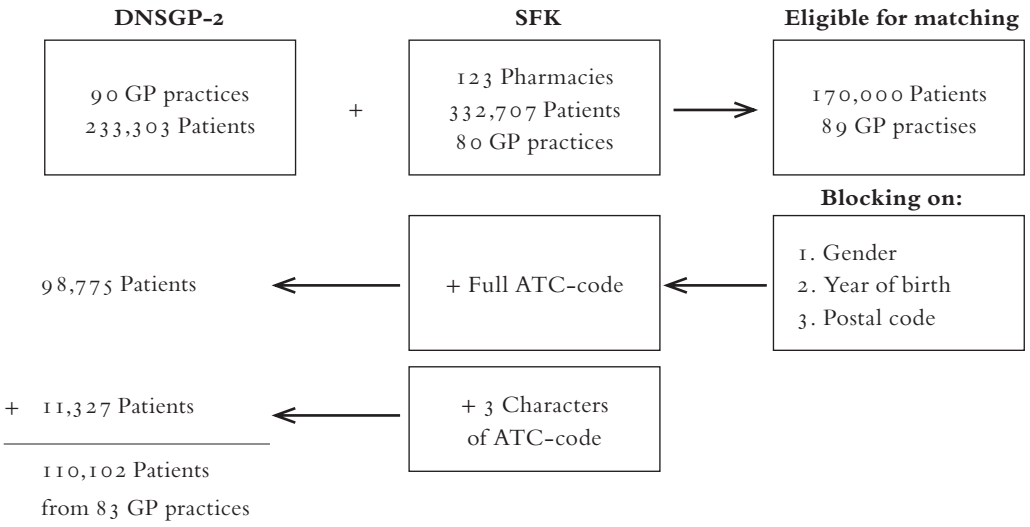
Thirdly, some drugs are prescribed more often than others. To benefit from this frequency of prescribing we categorised drugs in the enquiry database in three groups, namely drugs that were prescribed less than 5,000 times, between 5,000 and 10,000 times, and more than 10,000 times. Patient records were first matched by using drugs that were prescribed the least, followed by drugs that are more common. To safeguard patient privacy the study was conducted under strict privacy regulation of the DNSGP-2 [10].

Results

Among the 101 GP practices in the DNSGP-2, 11 were dispensing practices and were excluded. The analysis was based on 233,303 patients who received 1,841,271 prescriptions and were listed in 90 GP practices. Of the 203 community pharmacies approached, 123 (60.6%) pharmacies dispensed medication to patients of the particular GP and agreed to participate in the study. Of the 80 pharmacies that decided not to participate, 71 pharmacies responded never to dispense medication to patients of the DNSGP-2 GPs and nine pharmacies refused to participate in our study. This resulted in 89 GP practices of which both prescribing and dispensing data were available for matching. Taking into account the number of patients per GP practice, coverage of GP practices by pharmacies, and the registration period of both databases, we estimated that 170,000 patients could in theory be traced in the pharmacy records. Figure 2 shows the sampling procedure and subsequent outcome of the different steps in the matching procedure.

Blocking patients on gender, year of birth, and postal code, matching on full 7-character ATC-code resulted in 98,775 (58.1%) uniquely identified patients. The remaining 71,225 patients not linked initially, were matched using the 3-character ATC-code of the medicines prescribed. Subsequently, 11,327 (6.7%) more patients were matched. In total, medical records of 110,102 (64.8%) patients from 83 GP practices were linked. Of these patients, virtually complete prescribing and dispensing histories were available. The prescribing data encompassed for most of the patients the year 2001, whereas the dispensing data covered the years 1999-2003.

Figure 2: *Sampling procedure and outcome of matching.*



The 110,102 linked patients filled 4,816,247 prescriptions of both GPs and medical specialists during the period 1999-2003, with an average of 43.7 (SD=68.6) prescriptions per patient. Of these patients, 58.0% were female, 68.5% publicly insured, and the mean age was 42.2 (SD=21.8) years. Table 1 displays the characteristics of the DNSGP-2, SFK, and linked database. In the three databases, women were equally represented, ranging from 57.4% in the DNSGP-2 to 55.8% in SFK data. The average age of the patients in the linked-database was 42.2 years and higher than the average age in the DNSGP-2 database (39.1 years) and the SFK-database (38.4 years). The number of prescriptions per patient in the SFK and linked database was higher than in the DNSGP-2 due to the longer registration period of the first two databases. After correction for the registration period, the number of prescriptions per patient per month was 0.68 for the DNSGP-2, 0.63 for the SFK, and 0.91 for the linked database. The higher number of prescriptions per patient in the linked database is the sum of prescriptions of GPs and medical specialists, whereas the DNSGP-2 only collected prescriptions of GPs. Furthermore, the higher number of prescriptions per patient was also the result of the fact that only patients with prescriptions could be linked. The characteristics of included GP practices in the linked-database were also comparable to the original sample of the DNSGP-2 with respect to type of office, situated in deprived areas, and degree of urbanisation.

Table 1: *Characteristics of patients and GP practices in the enquiry, file, and final database.*

Database	DNSGP-2	SFK		
Type	Enquiry records	File records	Linked dataset	
Time period	Oct 2000 – Jun 2002	Jan 1999 – Dec 2003	Jan 1999 – Dec 2003	
% Female	57.8%	55.8%	58.0%	p=0.01
% Publicly insured	67.5%	- ★	68.5%	p<0.01
Mean age (SD)	39.1 years (22.7)	38.4 years (22.7)	42.2 years (21.8)	p<0.01
Mean number of Rx/patient (SD)	7.9 (11.9)	28.9 (59.6)	43.7 (68.6)	p<0.01
Nr. of Rx/patients/month	0.68	0.63	0.91	
Nr. of patients	233,303	332,707	110,102	
Nr. of Rx	1,841,271	10,049,944	4,816,247	
Pharmacies	- ¶	123	112	
GP practice	N=90 §	N=89	N=83	
Solo	49 (54.4%)	46 (53.5%)	43 (51.8%)	p=0.10
Duo	18 (20.0%)	17 (19.8%)	17 (20.5%)	
Group	14 (15.6%)	14 (16.3%)	14 (16.9%)	
Healthcare centre	9 (10.0%)	9 (10.5%)	9 (10.8%)	
Deprived area	8 (8.9%)	8 (8.3%)	8 (9.6%)	
Degree of urbanisation				
Not urbanised	9 (10.0%)	9 (10.5%)	9 (12.0%)	p=0.21
Hardly urbanised	17 (18.9%)	16 (18.6%)	14 (16.9%)	
Averaged urbanised	19 (21.1%)	19 (22.1%)	19 (22.9%)	
Strongly urbanised	24 (26.7%)	22 (25.6%)	21 (24.1%)	
Extremely urbanised	21 (23.3%)	20 (23.3%)	20 (24.1%)	

★ Not used in the linkage process.

¶ Not available in the DNSGP-2.

§ Only non-dispensing GP practices included. In total 101 GP-practices collected prescribing data during the DNSGP-2.

Discussion

The primary objective of this study was to determine the success rate of linking dispensing data of community pharmacies to prescribing data of general practitioners. The completeness, quality and validity of patient characteristics play a vital role in record linkage processes [19,20]. If patient characteristics are not valid, or change over time, this could negatively influence the matching. Although gender and year of birth do not change over time, they are still susceptible to registration errors [21]. However, we assumed that pharmacies and GPs register the patient's date of birth accurately because it is often used to retrieve the patient's history from the computer systems. With respect to the completeness of the dispensing data, Herings defined five scenarios leading to incompleteness, namely: (1) patients are not a member of the catchment area, but incidentally fill a prescription in the catchment area

(non-residents); (2) a patient number is not uniquely assigned to one patient (non-unique assignment); (3) a patient has more than one patient number in the register (internal multi-unique assignment); (4) a patient is registered in more than one pharmacy register (external multi-unique assignment); (5) a patient living in the catchment area fills a prescription outside the catchment area (non-eligible) [3].

In the linkage method we used, linkage of non-residents was unlikely. Although these patients filled a prescription in the catchment area, they most likely did not receive a prescription from a GP working in the catchment area. Non-unique assignment is also very unlikely in Dutch pharmacy and GP computer systems, as no system allows multiple assignment of a patient ID. Internal multiple assignment of a patient to more than one number due to entry errors of e.g. date of birth, gender or postal code, is limited. Herings found in a sample of 2,000 patients that 1.4% of the patients were multiple coded in a pharmacy. Finally, dispensing data can also be incomplete when patients fill prescriptions outside the catchment area and thereby become non-eligible. Herings et al. estimated the completeness of drug dispensing histories in Dutch pharmacies [3]. They noted that more than 99% of all patients had complete drug dispensing histories in cities where pharmacists maintained one central patient register.

The factor that had the most negative influence on the number of patients that could be matched were the different registration periods of the pharmacies. Most of the GP practices registered during 12 month (mean=12; SD=1.6) over the period October 2000 untill January 2002 while participating in the DNSGP-2, but not all pharmacies registered the same complete 12 months. Missing months may be an important reason why patient records could not be linked. If a drug was prescribed during a period in which no pharmacy data were available, this would lower the probability of linking. Another important factor that negatively influenced our matching process, are the pharmacies that refused to participate in the study. It is often difficult to trace patients back to a pharmacy, especially in larger cities where patients of a GP may visit different pharmacies. Part of the patients may go to one pharmacy, while the other part goes to another pharmacy. This means that if one pharmacy does not participate in the study a part of the patient records cannot be linked. In a sensitivity analysis, we noted that in isolated villages the proportion of linked patients was higher. However, the lack of coverage of the GP practice by community pharmacies probably resulted only in a reduction of the number of patients that could be linked. We do not think this negatively affected the completeness of dispensing histories, because the majority of patients normally visit only one pharmacy in The Netherlands.

The final linkage percentage of 64.8% is dependent on several factors. One of the most important is the estimation of the catchment population. We estimated the total number of

eligible patients to be 170,000, based on the number of patients per GP practice, coverage of the GP practice polulations by pharmacies, and the registration period of both databases. The coverage of GP practices by pharmacies was calculated by using estimates made by pharmacists of the proportion of a particular GP practice population that fills prescriptions at their pharmacy. These estimates show considerable variations and thereby may affect the estimation of the catchment populations. However, we think that the estimation of a catchment population of 170,000 patients to be realistic. Furthermore, the final linkage proportion is also directly influenced by the definition of a successful match. We defined a successful match when gender, year of birth, postal code, and a minimum of 50% of enquiry prescriptions were positively matched. This cut-off value is, of course, arbitrary and lowering this requirement positively influences the proportion of patients being matched, but increases the number of false positives. Choosing 50% as a cut-off point, however, allows matching of records of patients who only received two prescriptions. Increasing the cut-off point to, for example 75%, excludes all patients who received up to four prescriptions of which one or more were changed.

Limitations of the linking process lie mainly in the available linkage keys. To ensure the privacy of patients, SFK collects only the year of birth and not the complete date of birth. The combination of date of birth and gender is almost unique in a population of 2,000 individuals. Since the average Dutch GP practice consists of approximately 2,300 patients, the combination of gender and date of birth would almost be sufficient to identify patients within a GP practice. However, the specificity dramatically decreases for the combination of year of birth and gender. We decided not to use type of insurance as a matching variable, because differentiating between private and public insurance was difficult as some pharmacies register both private and publicly insured patients of one insurance company using a single code. Finally, we did not validate our linkage procedure by contacting individual patients. This is under the privacy statements of the DNSGP-2 and SFK prohibited. Several problems need further elaboration when linkage of both systems will be done on a continuous basis in the future.

Conclusions

This study shows that linkage of dispensing and prescribing data is feasible with a combination of patient characteristics, such as gender, year of birth and postal code, and prescription characteristics, like prescription date and ATC-code. The final database contains both dispensing and prescribing data of medical specialists and GPs completed with detailed information on not only the patients, but also on community pharmacists and GPs. It offers an opportunity to gain insight into the magnitude and direction of forces directing drug utilisation in general practice.

Chapter 2.2

Discrepancies between prescribing and dispensing of medicines in general practice

Stefan R. Florentinus [1], Patrick C. Souverein [1], Liset van Dijk [2], A.M.G. Fabiënne Griens [4], Eibert R. Heerdink [1], Peter P. Groenewegen [2,3], Hubert G.M. Leufkens[1]

[1] Utrecht University,
Division of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht, The Netherlands.

[2] NIVEL (Netherlands Institute for Health Services Research),
Utrecht, The Netherlands.

[3] Utrecht University,
Department of Sociology and Department of Human Geography,
Utrecht, The Netherlands.

[4] SFK (Foundation for Pharmaceutical Statistics),
The Hague, The Netherlands.

Submitted

Abstract

Background: GP prescribing data have proven to be powerful research tools for pharmaco-epidemiological studies. However, if patients fail to claim all of their prescriptions or receive prescriptions from other prescribers, valid concern exists about the coverage of the patient's actual drug exposure.

Objective: To determine whether GP prescribing data provide reliable coverage of actual drug exposure in patients.

Methods: Estimation of concordance between GP prescribing and pharmacy dispensing data over a 12 months period in a cohort of 110,102 patients registered at 83 GP practices and 112 community pharmacies. The primary outcome measure was primary drug defaulting of patients defined as the proportion of prescriptions patients failed to claim at the pharmacy out of the total number of prescriptions received from their GP. In addition, we calculated the proportion of prescriptions from other prescribers than their GP out the total number of prescriptions patients filled.

Results: Primary drug defaulting was present in 7.6% of the total number of prescriptions written by GPs. Of all prescriptions patients filled in a pharmacy, the GP prescribing data failed to cover 20.0% due to patients receiving prescriptions from other prescribers, mainly medical specialists. Primary drug defaulting was twice as high in patients with four or more chronic diseases compared to patients without any chronic diseases. In addition, patients with more chronic diseases had a lower coverage of their drug exposure in the GP data, due to patients receiving prescriptions from other prescribers.

Conclusions: The validity of GP prescribing data to estimate actual drug exposure in patients may be compromised by primary drug defaulting and by patients receiving prescriptions from other prescribers. This is especially the case in patients with multiple chronic diseases. Combining GP and pharmacy records makes it possible to eliminate the shortcomings of individual databases and provide a complete medication history.

Introduction

The availability of accurate data on drug exposure is of great importance for pharmacoepidemiology as misclassification of exposure may lead to biased risk estimates [1,2]. In most healthcare systems, information is increasingly stored in electronic form and made available for scientific research. This development has lead to the widespread use of prescribing records of general practitioner (GPs) and pharmacy dispensing records in pharmacoepidemiological studies.

Both GP and pharmacy records have proven to be powerful research tools for pharmacoepidemiological studies, but there are important differences between the data sources with implications for scientific research. Systems that originated out of a general practice setting, such as the British General Practice Research Database (GPRD) [3,4] and the Dutch Integrated Primary Care Information (ICPC) database [5,6], provide rich data on medication prescribed by GPs, including diagnoses and other relevant clinical information, but may be flawed in two ways. Firstly, they contain data on prescriptions, but generally no information on whether prescriptions are filled at pharmacies, thereby lacking data on primary drug defaulting. Secondly, they fail to cover all prescriptions when patients are treated by several physicians, especially medical specialists. Pharmacy dispensing records are a valuable data source used by systems such as the Scottish Medicine Monitoring Unit (MEMO) [7] and the Dutch PHARMO RLS database [8]. Pharmacy dispensing records cover prescriptions from both GP and medical specialist, but lack information on diagnoses or other medical information.

In pharmacoepidemiology, it is important to have an accurate exposure assessment, both in incidence and prevalence estimations and in studies on exposure-outcome relationships. GP data may give an overestimation of drug exposure because information on primary drug defaulting is missing, and on the other hand may miss drug use because of lack of information on prescriptions by other prescribers. In this study, we aim to determine to what extent GP data on drug prescribing offers complete coverage of actual drug exposure in patients. Furthermore, we consider whether this coverage is associated with chronic morbidity of the patients in order to estimate possible bias in exposure assessment.

Methods

Study setting

The prescribing and dispensing data used in this study were derived from two electronic sources. The prescribing data were obtained from the second Dutch national survey of general practice (DNSGP-2), conducted by NIVEL (Netherlands Institute for Health Services Research) in 2001 [9,10]. The DNSGP-2 resulted, among other variables, in a dataset comprising over two million prescriptions prescribed by 101 GP practices to 262,817 patients during a 12 month registration period. We obtained the DNSGP-2 patient dispensing data from SFK (Foundation for Pharmaceutical Statistics). Since 1990, SFK has been collecting dispensing data from more than 90% of all Dutch community pharmacies [11]. Outpatient dispensing by hospital pharmacies is still an uncommon phenomenon in The Netherlands.

To link pharmacy dispensing data to GP prescription data, we contacted all pharmacies that were pointed out by the GPs as the pharmacies were their patients filled prescriptions. We excluded 11 dispensing GP practices, as their dispensing data is not collected by SFK. All relevant pharmacies were asked to participate in our study and to give permission to retrieve dispensing data of the GP practices from the SFK database.

Since the Dutch healthcare system lacks sofar a unique identifier for each individual patient, we identified the GPs' patients in neighbouring pharmacies by applying a deterministic record linkage approach. Detailed information on the identification of individual patients in pharmacies is presented in **Chapter 2.1**. In short, 110,102 patients from 83 GP practices were identified in 112 pharmacies based on the patient's gender, year of birth, postal code and prescription characteristics, such as anatomical therapeutic codes (ATC) [12], and prescribing dates. For these patients complete prescribing and dispensing data were available. The prescribing data contained only prescriptions of the GPs who participated in the DNSGP-2, whereas the dispensing data contained besides the prescriptions of GPs also prescriptions from other prescribers, such as medical specialists.

Study design and outcome measures

We assessed to what extent GP prescribing data cover patients' actual drug exposure by estimating primary drug defaulting and the proportion of prescriptions patients receive from other prescribers than their own GP. We regarded the patients' pharmacy dispensing data as their actual exposure to drugs.

Firstly, primary drug defaulting, or primary non-compliance, occurs when patients fail to claim their prescriptions in a pharmacy. We calculated for each patient their filling rate, defined as the proportion of GP prescriptions claimed in a pharmacy out of the total number

of prescriptions patients received during the DNSGP-2 registration period. A prescription was considered filled if the dispensing database contained a record for that patient dated within 14 days after the drug was prescribed and if the first three ATC-characters of the dispensed drug were the same as those of the drug prescribed. The reason for applying a 14 day time window was that patients do not always fill prescriptions on the same day as they are prescribed. In addition, the ATC-code of the dispensed drug may differ from the prescribed drug due to interventions of pharmacists [13,14]. Influenza vaccines (ATC-code=J07BB02) were excluded from our comparison because these are frequently dispensed directly by GPs in The Netherlands.

Secondly, we estimated the proportion of prescriptions patients received from other prescribers than the DNSGP-2 GPs out of the total number of prescriptions present in the dispensing database. Each dispensing record contains an ID-number identifying the individual physician as well as the type of physician, such as a medical specialist, GP, dentist, or midwife.

For each patient, we calculated their chronic disease score (CDS) [15] to test the hypothesis that patients with multiple co-morbidities are more consistent in filling their prescriptions since their conditions require chronic treatment. The patient's CDS was calculated based on their prescriptions in the DNSGP-2 prescription database. The CDS was calculated over the 365 days before the patient's last prescription during the DNSGP-2 registration period. To test the hypothesis that the patients with multiple co-morbidities are also the patients receiving more prescriptions from other prescribers, we calculated the proportion of prescriptions patients received from other prescribers than a DNSGP-2 GP out of the total number of filled prescriptions.

Results

Of the 110,102 patients included in our study, 58.0% were female and the mean age was 42.2 years (SD=21.8). The prescribing database contained 858,307 prescriptions and the dispensing database contained 1,070,791 prescriptions during the DNSGP-2 registration period.

Overall, 92.4% (N=793,076) of all prescriptions was filled indicating that overall primary drug defaulting occurred in 7.6% (N=65,231) of all prescriptions from GPs (Figure 1). Table 1 lists the 10 drug classes most frequently not filled by patients. These 10 drug classes contributed 46.1% (N=30,079) of all prescriptions not filled.

In total, 20.0% (N=213,979) of all prescriptions patients filled in the pharmacy were not prescribed by a DNSGP-2 GP and therefore not covered by the GP prescribing database (Figure 1). Patients received most of these prescriptions from medical specialists (53.4%), followed by other GPs (38.6%), dentists (2.1%), and others (0.6%). For 5.3% of the prescriptions the type of physician was unknown. Table 2 shows the 10 drug classes that patients most often received from medical specialists.

Table 1: *The 10 drug classes most often not filled by patients.*

ATC-code	Therapeutic drug class	N (%) *
1. N05	Anxiolytics, hypnotics	4,556 (7.0%)
2. R03	Anti-asthmatics	3,349 (5.1%)
3. G03	Sex hormones and modulators of the genital system	3,264 (5.0%)
4. M01	Anti-inflammatory and antirheumatic agents	3,174 (4.9%)
5. N06	Antidepressants	2,821 (4.4%)
6. J01	Antibacterials for systemic use	2,793 (4.3%)
7. B01	Antithrombotic agents	2,664 (4.1%)
8. C07	Beta blocking agents	2,577 (4.0%)
9. N02	Analgesics	2,534 (3.9%)
10. A02	Antacids	2,347 (3.6%)

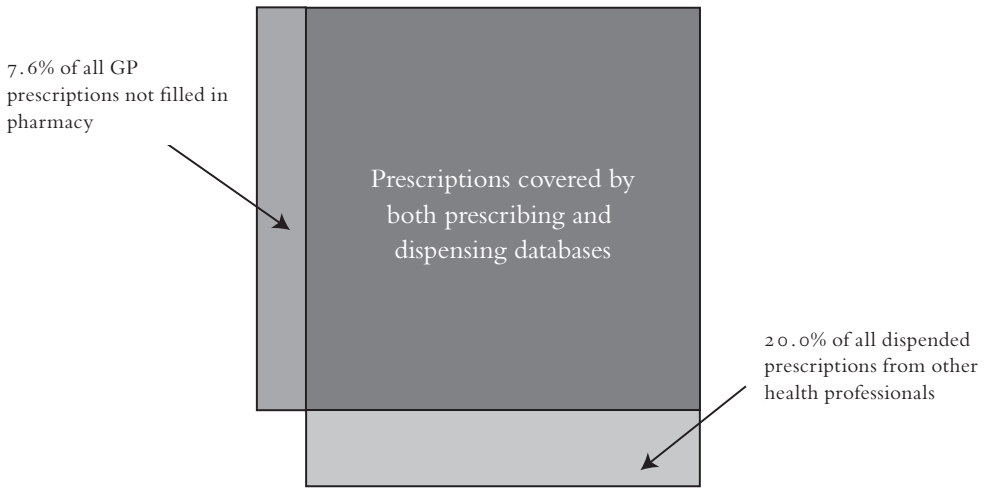
* Proportion calculated over the 65,231 prescriptions not found.

Table 2: *The 10 drug classes patient received from medical specialists.*

ATC-code	Therapeutic drug class	N (%) *
1. S01	Ophtalmologicals	10,288 (9.0%)
2. N05	Anxiolytics, hypnotics	9,564 (8.4%)
3. R03	Anti-asthmatics	5,844 (5.1%)
4. B01	Antithrombotic agents	5,682 (5.0%)
5. N06	Antidepressants	5,579 (4.9%)
6. C07	Beta blocking agents	4,191 (3.7%)
7. M01	Anti-inflammatory and antirheumatic agents	3,875 (3.4%)
8. C09	ACE and AII antagonists	3,680 (3.2%)
9. C10	Serum lipid reducing agents	3,493 (3.1%)
10. J01	Antibacterials for systemic use	3,407 (3.0%)

* Proportion calculated over the 114,265 prescriptions prescribed by medical specialists.

Figure 1: *Coverage of drug exposure in 110,102 patients in GP prescribing and pharmacy dispensing data.*



We noted a twofold higher primary drug defaulting in patients with four or more chronic diseases than in patients without any chronic diseases. Patients without any chronic diseases failed to claim on average 10.7% (SD=17.5%) of their prescriptions, whereas patients with four or more chronic diseases failed to claim 21.8% (SD=17.0%) of their prescriptions. In addition, the coverage of GP data of patients' drug exposure was lower in patients with multiple chronic diseases due to patients receiving prescriptions from other prescribers. Patients with no chronic diseases received on average 12.4% (SD=26.3%) of their prescriptions from other prescribers, compared to 19.8% (SD=25.9%) for patients with four or more chronic diseases (Figure 4).

Figure 3: *Primary drug defaulting in 110,102 patients as function of the patient's CDS.*

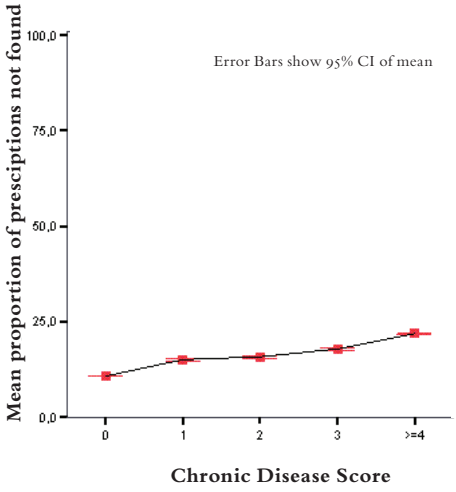
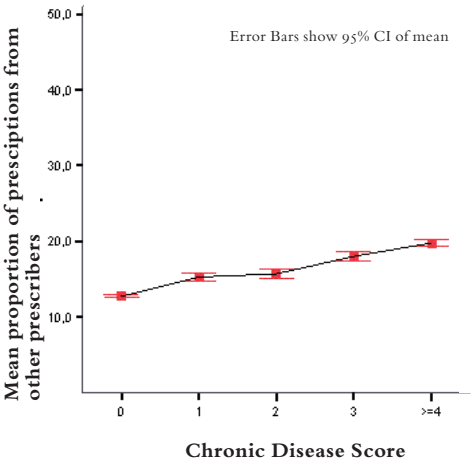


Figure 4: *Mean proportion of prescriptions patients received from other physicians as function of the patient's CDS.*



Discussion

The primary objective of this study was to assess to what extent GP prescribing data provide a accurate coverage of actual drug exposure in patients. Our study shows that GP prescribing data overestimate drug exposure up to 7.6% due to primary drug defaulting and miss up to 20% of prescriptions prescribed by other prescribers. Furthermore, we found that the differences between GP prescribing and pharmacy dispensing data became more pronounced for patients with multiple co-morbidities.

The main strength of this study is that it compared prescribing and dispensing data from a large number of patients registered in 83 different GP practices and 112 community pharmacies over a 12-month period. Previous studies estimating primary drug defaulting used data from only a limited number of GP practices or limited their study to a particular drug class or time period [16-21].

Our data showed primary drug defaulting to occur in 7.6% of all prescriptions written by GPs. This is in line with other studies showing that patients fill between 87.0% to 94.7% of all their prescriptions [19,20]. A wide variety of reasons have been suggested for patients failing to fill prescriptions, ranging from economical reasons, such as the availability of cheaper over

the counter alternatives, to the wish to regain control [18,22,23]. We identified 10 drug classes that accounted for 46.1% of all drugs not filled. The 10 drug classes cover a wide range of indications and are extensively prescribed in general practice. Higher non-filling rates for oral contraceptives and pain medication for which cheaper over-the-counter alternatives are available, such as paracetamol, ibuprofen and diclofenac, have been identified by others [19,21,23,24]. Although studies noted primary drug defaulting to be higher among antibiotics [25] and oral contraceptives [19], our data shows that patients fail to claim prescriptions from every therapeutic drug class and therefore primary drug defaulting to be uniformly distributed over all drug classes. The underestimation of drug exposure may is likely to affect incidence and prevalence estimation, and may also lead to biased estimates of exposure-risk outcome relationships.

Patients received 20.0% of their prescriptions from other physicians than their GP, which were not registered in the GP prescribing database. Most of these prescriptions were initiated and it is likely that these will be repeated by GPs during follow-up, at which point they will have a complete view on drug exposure. However, dispensing information at the pharmacy offers more timely and complete information on drugs prescribed by specialists. Other GPs accounted for the remainder of the prescriptions that were filled at the pharmacy, while not present in the GP database. These are most likely to be emergency, short-term prescriptions. To complicate matters, Beardon et al. noted that prescriptions issued in weekends presumably after emergency calls were less likely to be filled [19]. We have no data on prescriptions by other GPs that were not filled at the pharmacy.

The top 10 drug classes prescribed by medical specialists contain a high presentation of drugs indicated for cardiovascular diseases. For an accurate estimation of drug exposure the completeness of the data is vital and in especially the case of cardiovascular diseases the use of only GP prescribing data is not sufficient [26]. Pharmacy dispensing records may be a better reflection of the patients drug use. Lack of information on actual drug use in GP databases, not only leads to an underestimation of actual drug exposure in pharmacoepidemiological studies, but also is important information for the management of pharmacotherapy by GPs and community pharmacists.

Incomplete information on drug exposure when using only GP prescribing data becomes increasingly apparent when patients suffer from several chronic diseases that require multidisciplinary or specialist care. We noted that both primary drug defaulting and receiving prescriptions from other physicians were more common among patients treated for multiple chronic diseases. Other studies found evidence supporting our finding by identifying lower filling rates for drugs indicated for chronic diseases, such as cardiovascular deceases and repeat prescriptions [19,21].

The results of this study need to be interpreted in light of its limitations. Firstly, the data were sampled from a research network of Dutch GPs. Whether these data also reflect drug exposure information in other primary care research settings needs further investigation. Secondly, the dispensing and prescribing data used in this study were also an integral part of the identification of the GP patients in pharmacies. This may have resulted in an overestimation of the proportion of prescriptions found in the dispensing data. However, our estimation of primary drug defaulting lies in the range as found by others. Moreover, we used a broad definition of a filled prescription, in which we allowed for a 14-day time window and substitution within the ATC therapeutic group. However, sensitivity analyses on the time window and number of ATC-characters used to trace prescriptions showed that the filling rate was robust. The filling rate dropped from 93.1% when using only the first ATC-character of the prescribed drug to 91.4% when using all ATC-characters. A similar finding was apparent with the respect to the definition of the time window.

Conclusions

Our study shows that the validity of GP prescribing data to estimate actual drug exposure in patients may be compromised by primary drug defaulting and by patients receiving prescriptions from other physicians, especially from medical specialists. Particularly, when patients are treated for multiple chronic diseases, the coverage of GP data may deviate from the patient's actual drug exposure. No matter which source for drug exposure data is used in pharmacoepidemiology, the choice for a specific source is always a trade-off between various, frequently not equally valued, quality features (e.g. completeness of prescription and/or dispensing data, indication of prescribing, OTC drug usage, and compliance). There is no single source the best solution for every research question and therefore it remains always important to crosscheck or combine drug exposure data from other sources.

Chapter 3

NEW DRUGS IN GENERAL PRACTICE

Chapter 3.1

Who are the early prescribers of new drugs?

Five cases of rapid market introductions

Stefan R. Florentinus [1], Eibert R. Heerdink [1], Peter P. Groenewegen [2,3], Dinny de Bakker [2], Liset van Dijk [2], A.M.G. Fabiënne Griens [4], Hubert G.M. Leufkens [1]

[1] Utrecht University,
Division of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht, The Netherlands.

[2] NIVEL (Netherlands Institute for Health Services Research),
Utrecht, The Netherlands.

[3] Utrecht University,
Department of Sociology and Department of Human Geography,
Utrecht, The Netherlands.

[4] SFK (Foundation for Pharmaceutical Statistics),
The Hague, The Netherlands.

Abstract

Background: Innovation in pharmacotherapy is a cornerstone of clinical practice. However, when new drugs are adopted in an erratic fashion, there is valid concern about uncertain risk-benefit for patients and increased costs.

Objective: To identify characteristics of general practitioners (GPs) associated with prescribing of new drugs that showed rapid market uptake.

Methods: Measurement of adoption of five new drugs in a cohort of 103 GPs, working in 59 practices, over the period 1999 untill 2003. The main outcome measurement was starting on a new drug or another drug from the same therapeutic category within the first six months after market introduction. Multilevel modelling was used for analyses.

Results: A positive industry orientation (OR=1.37; 95% CI 1.17-1.61) and positive attitude towards new drugs (OR=1.65; 95% CI 1.26-2.15) were associated with rapid prescribing of new drugs. GPs working single-handed prescribed more new drugs (OR=2.55; 95% CI 1.70-3.83) than those in group practices. GPs who participated in well-developed pharmacotherapy audit meetings with community pharmacists prescribed less new drugs (OR=0.67; 95% CI 0.53-0.84).

Conclusions: Even for drugs that show rapid market penetration considerable variation exists in prescribing behaviour among GPs. Only a small proportion of GPs seems to be accountable for a disproportionate share of all early prescriptions for new drugs. New drug prescribing seems to be embedded in the GP's attitudes towards new drugs and orientation towards the pharmaceutical industry and pharmacotherapeutic consultation of colleagues and pharmacists.

Introduction

Yearly about 10-15 new molecular entities with indications applicable to general practice receive marketing authorisation [1]. New drug prescribing has many clinical, economical and societal dimensions. Prescribing of newly marketed drugs is not uniformly distributed among physicians and some new drugs are prescribed more than medical need can account for [2]. The rapid prescribing of new drugs fuels the ongoing discussion about the trade-off between the wish to treat patients more effectively and ensuring sustainable cost-containment in health care [3,4]. Despite the positive contributions of new drugs, Lasser et al. showed that 10.2% of the new molecular entities approved between 1975-1999 acquired a new black box warning or were withdrawn [5]. More recently, reported side effects of two rapidly adopted drugs again raised questions about early new drug prescribing and drug safety [6,7].

As new drugs are aimed to be a cornerstone in pharmacotherapeutic innovation, it is important to acquire a better understanding of the causes of variation between physicians in adopting new drugs. Studies estimating the magnitude of new drug prescribing revealed that a minority of physicians was heavily inclined to prescribe new drugs during the early post-marketing period [8-10]. In a British study, 10% of the GPs who prescribed most heavily accounted for 42% of total prescribing of new drugs during the first six months after introduction [8]. These findings were iterated in a Canadian study that noted an eight to 17-fold difference in prescribing rates of new drugs [10]. These studies used only basic physician characteristics, such as age and gender, to profile early adopters and had little qualitative examination of whether the physician's attitude towards new drugs, the influences of peers, and guidelines contributed to variation. Qualitative studies, using semi-structured interviews, pinpointed differences in belief of physicians that may explain part of the variability in new drug prescribing [11]. High and low prescribers of new drugs clearly displayed differences in, among other things, their attitude towards new drugs, risk management, and conformation to group norms [12-14].

To understand the variability in prescribing of new drugs during the early post-marketing period and to tailor interventions to ensure appropriate prescribing of these new drugs accordingly, studies are needed that combine relevant characteristics of prescribers with accurate prescribing data. Such studies are currently lacking and this study attempts to fill this void. Accordingly, the purpose of the present study is to examine the association between heavy prescribing of newly marketed drugs in the first six months after market introduction and various GP-related attitudes and characteristics on industry relations, practice setting and demographics.

Methods

Study setting

In this study, we used drug dispensing data from patients of 103 GPs who participated in the second Dutch national survey of general practice (DNSGP-2), conducted by NIVEL (Netherlands Institute for Health Services Research) in 2001 [15,16]. The 103 GPs worked in 59 non-dispensing practices in all 12 provinces of The Netherlands. Dispensing data were collected by the network of SFK (Foundation for Pharmaceutical Statistics) and covered the period 1999 untill 2003 [17]. Because virtually all patients in The Netherlands designate a single pharmacy to fill prescriptions from GPs or medical specialists, dispensing data provide a complete account of actual drug exposure in time [18].

In this setting, five new drugs were selected as study cases, namely the combination of the long-acting bronchodilator and inhalation corticosteroid (ICS) salmeterol/fluticasone, the cyclo-oxygenase-2 inhibitor rofecoxib, the proton pump inhibitor esomeprazole, the long-acting anticholinergic bronchodilator tiotropium, and the lipid lowering HMG-CoA reductase inhibitor rosuvastatin. Table 1 shows relevant characteristics of these case study drugs. All five drugs showed rapid market introduction and were listed within one year after market introduction in the top 10 drugs that were associated with the fastest growing expenditures in The Netherlands [17]. As reference drugs for the selected case study drugs we used all long-acting beta-2 antagonists and ICS for the combination salmeterol/fluticasone, all ipratropium bromide containing products for tiotropium, all nonsteroidal anti-inflammatory drugs (NSAIDs) (excl. low-dose aspirin) for rofecoxib, all proton pump inhibitors for esomeprazole and all HMG-CoA reductase inhibitors for rosuvastatin.

Detailed data on GPs and practices were collected by using the questionnaire of the DNSGP-2 that included, among other features, several questions related to prescribing of newly marketed drugs. Factor analyses with a varimax rotation procedure and a critical component loading>0.4 was used to identify underlying factors. Appendix 1 shows the questions used in the factor analyses and the component loadings after rotation. Five factors were identified, namely 'attitude towards new drugs' and 'guideline-, peer-, and patient and industry orientation'. Per item, a sum score ranging from 1 to 5 was calculated and used in further analyses. Other variables included were hours of continuing medical education (CME) per year, practice type (single-handed versus group), proportion of female patients, type of insurance, age including 65-79 years old, 80 years and older, and degree of urbanisation of the practice location. Information on collaboration between the GPs and community pharmacists were collected through a questionnaire sent to a network of 123 community pharmacies working together with the 103 GPs.

In The Netherlands, GPs and community pharmacists participate in regional pharmacotherapy audit meetings (PTAMs) to discuss and make decisions to improve the quality of pharmacotherapy. PTAMs can be stratified into four quality levels [19]. PTAMs functioning on level 1 or 2 only meet informally and no decisions are made. Level 3 groups have structured meetings that result in decisions about which drugs are prescribed, but these decisions are not evaluated. Level 4 is the highest level and the impact of the therapeutic decisions on actual prescribing behaviour are monitored and evaluated.

Table 1: *Characteristics of the five newly marketed drugs included in the study.*

New drug *(Brand name)*	**Market introduction**	**Main indication** ⋆	**Reference group**
Salmeterol/fluticasone *(Seretide/Advair®)*	1999, May	Asthma/COPD ¶	Long acting ß$_2$-agonist and ICS §
Rofecoxib *(Vioxx®)*	2000, Apr	Rheumatoid arthritis	NSAIDs # excl. low-dose aspirin
Esomeprazole *(Nexium®)*	2000, Nov	Gastro-oesophageal reflux disease	Proton pump inhibitors
Tiotropium *(Spiriva®)*	2002, Jun	COPD ¶	Ipratropium bromide containing products
Rosuvastatin *(Crestor®)*	2003, Mar	Hypercholesterolemia	HMG-CoA ¥ reductase inhibitors

⋆ Main indication at registration derived from Dutch Medicine Evaluation Board (www.cbg-meb.nl).

¶ COPD=Chronic Obstructive Pulmonary Disease.

§ ICS=Inhalation CorticoSteroid.

NSAIDs=NonSteroidal Anti-Inflammatory Drugs.

¥ HMG-CoA=3-Hydroxy-3-MethylGlutaryl Co-enzyme A.

Study design

With the introduction of a new drug, GPs can either treat a patient with the tried and proven existing drugs (if available) or the newly introduced drug. For this study, we included all patients receiving a new or a existing reference drug during the first six months after the market introduction. The primary outcome measure was starting on a new or a reference drug. Both new starters and switchers were included in the analysis. The date of the patient's first prescription for either the new or a reference drug was termed the index date. Starting was defined as receiving a prescription for a new or reference drug and no prescription for the same drug the six months before the index date. Patients who had less than six months of follow-up were excluded.

Data analysis

To identify GP characteristics that are associated with heavy new drug prescribing, we used a logistic multi-level model with two levels, namely patients nested within GPs using MLwiN [20]. For feasibility reasons we left out the practice as a level; a three level model turned out too difficult to converge. However, we added the variable whether or not a GP worked in single-handed practice. Using a multilevel model enabled us to correct for differences between patients and clustering of patients within GPs that might affect the GP's decision to prescribe new drugs [21]. Instead of running separate analyses for the five different new drugs and reference drug classes, we included dummies to represent the groups. In this way, we took into account that new drug prescribing in one group might be related to that in other groups. The groups were modelled as fixed effects to estimate the mean rate of new drug prescribing for each group, taking clustering into account. They were also modelled as random effects to estimate the variance and co-variance at GP-level. This allowed us to estimate the correlation at GP-level between new drug prescribing in the different groups. The patient's age, gender, and chronic disease score [22] were used to correct for any patient influences. The upper panel of Table 3 shows the coefficients for the drug classes and the patient characteristics that were include in all subsequent analyses. Odds ratios (ORs) with 95% confidence intervals were estimated for all GP characteristics one by one, corrected for all patient characteristics. Due to the relatively small sample size of our study population at the GP-level, we were unable to perform a multivariate multilevel analysis to correct for all GP characteristics simultaneously.

Results

In total, 1,012 patients were identified as starters on one of the 5 study case drugs and 15,567 patients started on one of the reference drugs. Of those patients starting on a new drug, 459 (4.6%) started with rofecoxib, 263 (26.7%) with tiotropium, 99 (5.4%) with esomeprazole, 123 (18.7%) with rosuvastatin, and 68 (2.3%) on the combination of salmeterol/fluticasone. Women received a new drug more frequently compared to men (OR=1.31; 95% CI 1.15-1.48). A positive trend was noted for patients with a higher age (OR=1.02; 95% CI 1.02-1.02) and multiple co-morbidities (OR=1.06; 95 CI 1.04-1.09) (Table 4).

The proportion of GPs prescribing new drugs during the first six months after market introduction ranged from 30.0% for esomeprazole to 66.3% for tiotropium. Rofecoxib was prescribed by 64.7%, rosuvastatin by 36.2%, and the combination salmeterol/fluticasone by 42.5% of the GPs. Figure 1 shows the rapid adoption of the five new drugs by GPs. Most striking was the presence of a minority of GPs who were heavily inclined to prescribe new drugs. The percentage GPs giving 50% of the early prescriptions ranged from 26.9% for the combination salmeterol/fluticasone to only 10.9% for rofecoxib. For tiotropium,

50% of the early prescriptions were prescribed by 18.5%, for rosuvastatin 23.5% and for esomeprazole 25.9% of the GPs (Table 2). However, GPs who were heavy prescribers of one drug were not by definition heavy prescribers of the other four drugs. The correlations between prescribing of the new drugs are presented in Table 3. The intraclass correlation (ICC) after correction for patient characteristics ranged from 32.4% for the combination salmeterol/fluticasone to 45.5% for rosuvastatin. The ICC for rofecoxib was 36.9%, for the tiotropium 35.3%, and for esomeprazole 42.3%.

Figure 1: *Adoption curve of five newly marketed drugs.*

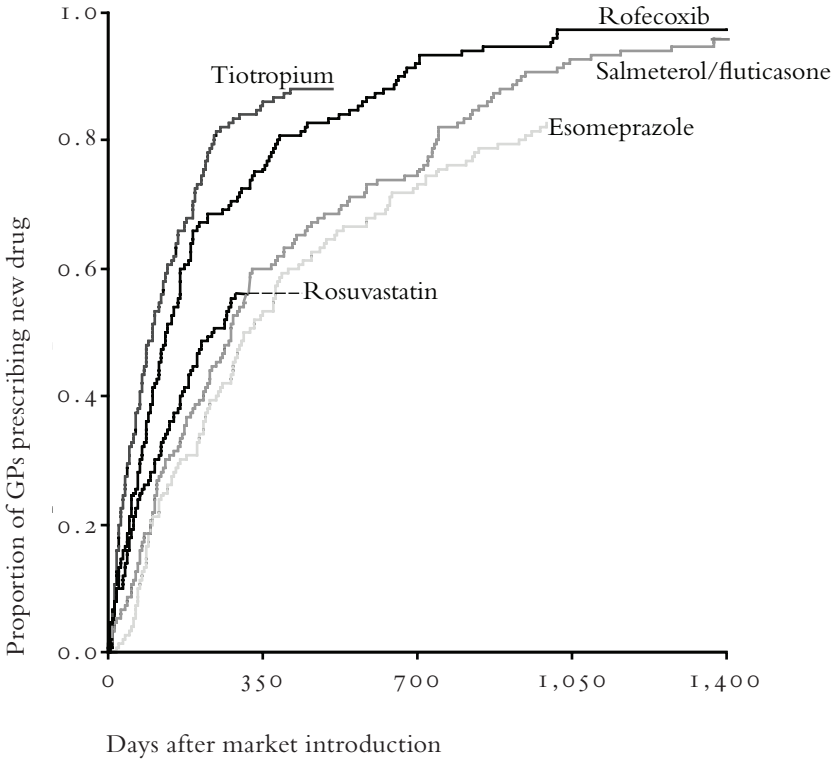


Table 2: *GP prescribing patterns of five newly marketed drugs.*

New drug *(Brand name)*	% giving 25% of early prescriptions	% giving 50% of early prescriptions
Salmeterol/fluticasone *(Seretide/Advair®)*	8.8	26.9
Rofecoxib *(Vioxx®)*	5.5	10.9
Esomeprazole *(Nexium®)*	6.2	18.5
Tiotropium *(Spiriva®)*	7.4	25.9
Rosuvastatin *(Crestor®)*	5.9	23.5

Table 3: *Correlation at GP-level between prescribing of the 5 new drugs by GPs during the first six months after market introduction, corrected for patient age, gender, and CDS.*

	Rofecoxib				
Rofecoxib	1.00	Salmeterol/Fluticasone			
Salmeterol/					
Fluticasone	0.31	1.00	Tiotropium		
Tiotropium	0.44	0.11	1.00	Rosuvastatin	
Rosuvastatin	0.37	-0.12	0.40	1.00	Esomeprazole
Esomeprazole	0.42	0.07	0.32	0.65	1.00

In Table 4, we present logistic multilevel modelling results on heavy new drug prescribing and the various characteristics of the GPs. A positive attitude towards new drugs was positively associated with prescribing of new drugs (OR=1.65; 95% CI 1.26-2.15). A similar finding was found for industry orientation. GPs who are more industry orientated were more likely to prescribe the new drugs (OR=1.37; 95% CI 1.17-1.61) compared to those more reluctant in their industry relations. GPs who are heavily involved in pharmacotherapy audit meetings with community pharmacists were much less willing to act as heavy prescribers of new drugs (OR=0.67; 95% CI 0.53-0.84). Moreover, GPs practising single-handed and in urbanised areas seem to be heavy new drug prescribers (OR=2.55; 95% CI 1.70-3.83), (OR=1.35; 95% CI 1.13-1.62), respectively.

Table 4: *Multilevel logistic regression analysis of prescribing five new drugs, compared to reference drugs, in the first six months after market introduction.*

Panel 1: Basic model including five drug classes and patient characteristics.		
New drugs	Coefficients (95% CI)	
Esomeprazole	1.5% (1.0%-2.5%)	
Rofecoxib	1.9% (1.3%-2.6%)	
Rosuvastatin	6.3% (4.0%-10.0%)	
Salmeterol/fluticasone	1.6% (1.1%-2.4%)	
Tiotropium	17.0% (12.0%-24.0%)	
Patient characteristics	N (%)	OR (95% CI)
Gender		
Female	9,706 (58.5%)	**1.31 (1.15-1.48)**
Age (mean; SD)	50.2 (20.2)	**1.02 (1.02-1.02)**
Chronic disease score (mean; SD)	2.32 (2.7)	**1.06 (1.04-1.09)**
Panel 2: basic model plus GP characteristics, introduced one at a time.		
GP characteristics	N (%)	OR (95% CI)
Gender		
Female	24 (23.5%)	1.12 (0.65-1.94)
Age (mean; SD)	46.6 (6.3)	0.98 (0.94-1.02)
Attitudes and orientation		
Industry orientation (mean; SD)	2.12 (1.41)	**1.37 (1.17-1.61)**
Attitude towards new drugs (mean; SD)	2.25 (1.02)	**1.65 (1.26-2.15)**
Peer orientation (mean; SD)	3.00 (1.33)	1.01 (0.82-1.24)
Patient orientation (mean; SD)	2.50 (1.12)	1.01 (0.68-1.49)
Guideline orientation (mean; SD)	3.63 (1.27)	0.87 (0.63-1.19)
Hours of CME per year (mean; SD)	47.0 (20.3)	1.00 (0.98-1.02)
Quality level PTAMs (mean; SD)	2.2 (1.53)	0.67 (0.53-0.84)
Single-handed practice		
Yes	39 (38.2%)	**2.55 (1.70-3.83)**
Proportion female (mean; SD)	50.3% (1.3%)	1.14 (0.99-1.32)
Proportion publicly insured (mean; SD)	64.9% (9.7%)	0.98 (0.96-1.00)
Proportion patients 65-79 years old (mean; SD)	9.6% (3.1%)	1.03 (0.96-1.10)
Proportion patients 80 years and older (mean; SD)	2.9% (1.6%)	1.07 (0.94-1.21)
Urbanisation (mean; SD)	3.02 (1.23)	**1.35 (1.13-1.62)**

Discussion

The objective of this study was to elucidate the associations between heavy new drug prescribing and specific GP characteristics. This study shows that new drug prescribing is embedded in the GP's general attitude towards new drugs and his/her orientation towards the pharmaceutical industry. Furthermore, several contextual factors, such as degree of urbanisation, type of practice, and professional collaboration with community pharmacists, are relevant in understanding the dynamics of prescribing of new drugs in general medical practice.

The main strength of this study is that it combines multilevel (i.e. individual patient and GP) data on new drug prescribing in a vast sample of 103 highly characterized GPs. This enabled us to quantify new drug prescribing by GPs while taking into account possible clustering of patients in GPs. Previous studies on new drug prescribing ignored clustering of patients within GPs or limited the study to only GPs working single-handed [10,23]. Associations between characteristics of GPs and new drug prescribing found in these studies may be biased due to differences between patients in and between GP practices. Furthermore, previous studies identified a minority of physicians heavily inclined in new drug prescribing during the early post-marketing period, but these studies were limited with respect to GP data [8,10]. Data on basic GP, and practice characteristics have been studied in relation to early new drug prescribing before. However, for profiling early adopters data on the GP's attitudes towards new drugs and their orientation towards guidelines, industry, patients and peers are key to elucidate important factors influencing new drug uptake.

As shown by the high ICCs and the low correlations between prescribing of the different new drugs, new drug prescribing is strongly dependent on the new drug in question and varies strongly between GPs. The estimated proportion of patients receiving a new drug differed from the found proportion due to this clustering of new drug prescribing in GPs. Dybdahl et al. also found that early adoption is probably not a trait of GPs [23].

We found that GPs with a positive attitude towards new drugs and with a positive industry orientation were more inclined in prescribing of new drugs. This draws attention to GPs' attitudes towards different aspects related to prescribing of new drugs. Explaining the variability in prescribing of new drugs with a few basic GP and practice characteristics is limited. Prior research has shown that prescribing of new drugs is not a simple dichotomy or the outcome of a biomedical evaluation, but rather a combination of GP characteristics and a matter of degree of attitude or influence [11,14]. Consistent with prior research, we found that GPs who are industry orientated prescribe more new drugs [11,24].

The association between practising single-handed and heavy prescribing of new drugs is an interesting finding. Literature reports inconsistency in the association between prescribing of

new drugs and type of practice. Some studies reported that group practices adopt faster due to a greater exposure to evaluative information engendered by their close intra-group colleague contact [25,26], while others found no association [23]. This discrepancy may be explained by differences in social norms within practices. De Jong et al. noted that GPs working in a partnership show more resemblance in attitudes and behaviour than GPs working in different partnerships [27]. This may lead to commonalities in social norms of which some are favouring while others limit prescribing of new drugs.

A novel finding is that structural collaboration with community pharmacists to improve pharmacotherapy is associated with lower prescribing rates of new drugs by GPs. Compared to GPs participating in informal PTAMs, those that participate in PTAMs that make decisions about which drugs are prescribed prescribe new drugs less often. For health authorities that strive to reduce drug expenses, stimulating GPs and pharmacists to organise structured counselling groups to improve pharmacotherapy may be a way to achieve their goal.

The effect of type of practice and collaboration with community pharmacists points out the importance of peer pressure perceived by GPs on their prescribing behaviour. Although self-reported peer orientation was not associated with new drug prescribing, GPs practising in group practices and those working closely with community pharmacists prescribed less new drugs. Prior research showed that the decision to prescribe new drugs is heavily influenced by 'who says what'. GPs mention, among others, colleague GPs as a legitimating role in the adoption process [24].

We found no association between the GP's gender, after adjusting for patient's influence, and prescribing of new drugs. Previous studies found a positive association between male gender and early new drug prescribing [8,10], but these studies did not correct for any influences of patients. Inman and Pearce explained the lower prescribing by female GPs as a result of working more part-time, but their results were based on numerator counts of prescriptions and could therefore be biased by differences in practice characteristics [8]. Although we found no association between the GP's gender and new drug prescribing, studies using semi-structured interviews have identified differences between high and low prescribers of new drugs in their perception of risks and strategies adopted for risk management [11,13,24,28,29]. Female GPs may manage the risks associated with prescribing new drugs by a 'wait and see' policy, while male GPs are more risk-taking.

The findings of this study need to be interpreted in light of its limitations. Although computerised drug-dispensing records of community pharmacies provide virtually complete dispensing histories in The Netherlands, no information was available on the indication of the prescriptions that may influence the likelihood to prescribe. To cope with that issue we

applied the approach of using drugs form the same therapeutic category as reference drugs. Furthermore, our findings are based on prescribing of five new drugs and this should be taken in to account when generalising the results to all new drugs. Finally, the GP's characteristics were obtained from the questionnaire of the DNSGP-2, which was conducted in 2001. The new drugs were on the other hand introduced between May 1999 and March 2003. Therefore, there may have been changes in GP or practice characteristics between the DNSGP-2 and the moment the new drug was introduced. However, we presumed the GPs attitudes, orientation and practice characteristics may be constant over a couple of years.

Conclusions

Even for drugs that show rapid market penetration considerable variation exists in the prescribing behaviour of GPs. A small number of GPs seem to be accountable for a striking disproportionate share of all early prescriptions for new drugs, as found in earlier studies as well. New drug prescribing is strongly influenced by the GP's attitude towards new drugs and orientation towards the pharmaceutical industry. Furthermore, peer pressure of colleagues and community pharmacists seems to result in less prescribing of new drugs. By a better understanding of this interplay between various prescribing and GP factors, we aim to improve sustained adoption of new drugs in general practice. Recent history has shown amply that erratic and marketing driven prescribing of new drugs may result in putting patient at unnecessary risk.

Appendix 1: *Questions for the questionnaire of the second Dutch national survey of general practice included in the factor analysis and rotated factor loadings.*

Item content	Factor 1 ¶	Factor 2	Factor 3	Factor 4	Factor 5
When a new drug is introduced, I want to know everything about it. (5 point scale: fully agree - fully disagree)	-0.584				
I am very conservative when it comes to prescribing newly marketed drugs. (5 point scale: fully agree - fully disagree)	0.525				
Before I write a prescription for new drugs, I first consult other GPs. (5 point scale: fully agree - fully disagree)	0.631				
How often do you use guidelines of the Dutch college of GPs during a consult? (5 point scale: several times per day - never)		0.584			
How often do you use the formulary present in your practice? (5 point scale: several times per day - never)		0.498			
How often do you use the pharmacotherapeutic compass when making a decision to prescribe? (5 point scale: daily - never)		0.466			
How often do you use the guidelines of the Dutch college of GPs when making decision to prescribe? (5 point scale: daily - never)		0.595			
Consulting of colleague GP(s). (5 point scale: completely my style - completely not my style)			0.453		
Consulting of hospital specialist(s). (5 point scale: completely my style - completely not my style)			0.426		
Do you consult colleague GP(s) when you want to prescribe newly marketed drugs? (no - yes)			-0.575		
Do you consult community pharmacists when you want to prescribe newly marketed drugs? (no - yes)			-0.416		
Do you consult hospital specialists when you want to prescribe newly marketed drugs? (no - yes)			0.587		
It is normal when patients look up to their GP. (5 point scale: fully agree - fully disagree)				-0.521	
More and more patient visits the surgery with complaints or problems that are hard to take serious. (5 point scale: fully agree - fully disagree)				-0.682	
Giving a clarification is useless for some patients, because they will not understand it. (5 point scale: fully agree - fully disagree)				-0.669	
A successful treatment depends more on the patient's confidence in the GP than in an extensive explanation. (5 point scale: fully agree - fully disagree)				-0.516	
How often do you use information from the industry when making a decision to prescribe? (5 point scale: daily - never)					-0.532
Do you use information from the pharmaceutical industry when you want to prescribe newly marketed drugs? (no - yes)					0.655
Do you receive visits from pharmaceutical representatives? (no - yes)					0.706

Only rotated component loading>0.4 are shown.

Cronbach's α for scales based on factor 1=0.50, 2=0.64, 3=0.56, 4=0.54, 5=0.65.

¶ Factor 1: Attitude towards new drugs; Factor 2: Guideline orientation; Factor 3: Peer orientation; Factor 4: Patient orientation; Factor 5: Industry orientation.

Chapter 3.2

Is new drug prescribing in general practice specialist induced?

Stefan R. Florentinus [1], Eibert R. Heerdink [1], Liset van Dijk [2],
A.M.G. Fabiënne Griens [4], Peter P. Groenewegen [2,3], Hubert G.M. Leufkens [1]

[1] Utrecht University,
Division of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht, The Netherlands.

[2] NIVEL (Netherlands Institute for Health Services Research),
Utrecht, The Netherlands.

[3] Utrecht University,
Department of Sociology and Department of Human Geography,
Utrecht, The Netherlands.

[4] SFK (Foundation for Pharmaceutical Statistics),
The Hague, The Netherlands.

Submitted

Abstract

Background: Medical specialists are often seen as the first prescribers of new drugs. However, the extent to which specialists influence prescribing of new drugs in primary care is largely unknown.

Objective: To estimate the influence of medical specialists on prescribing of new drugs in primary care shortly after market introduction.

Methods: The influence of specialists on prescribing of five new drugs was analysed in a retrospective cohort study comprised of all patients listed at 103 GPs over the period 1999 untill 2003. Their influence on new drug prescribing was compared to their influence on prescribing of existing drugs from the same therapeutic drug class (reference groups). Firstly, the proportion of patients receiving their first prescription for a new or reference drug from a specialist. Secondly, the proportion of GPs prescribing new drugs before waiting for prescriptions from specialists. Thirdly, we compared the time to the GP's first own prescribing between GPs who waited for prescriptions from specialists and those who did not.

Results: The influence of specialists showed considerable differences among the new drugs. The proportion of patients receiving their first prescription from a specialist was greatest for the combination salmeterol/fluticasone (60.2%), and lowest for rofecoxib (23.0%). The proportion of GPs prescribing new drugs before waiting for prescriptions from medical specialists ranged from 21.1% in the case of esomeprazole to 32.9% for rofecoxib. Prescribing new drugs by specialists did not shorten the GP's own time to prescribing.

Conclusions: This study shows that the influence of medical specialists is clearly visible for all new drugs and often greater than for the existing older drugs, but the rapid uptake of new drugs in primary care does not seem specialist induced in all cases. GPs are responsible for a substantial amount of all early prescriptions for new drugs and for a subpopulation specialist endorsement is not a requisite to initiate in new drug prescribing. This contradicts with the idea that the diffusion of newly marketed drugs always follows a two-step model, with medical specialists as the innovators and GPs as the followers.

Introduction

Prescribing of newly marketed drugs is not uniformly distributed among physicians. A minority of physicians is responsible for the majority of all early prescriptions for new drugs shortly after market introduction [1-3]. The interface between primary and specialist care is an important factor in the mixture of drugs prescribed by general practitioners (GPs) [4]. In healthcare systems, like in the UK and The Netherlands, where GPs function as gatekeepers for accessing specialist care, referral of patients and repeat prescribing of specialist initiated prescriptions are important mechanisms through which specialists influence the GP's prescribing behaviour [5,6].

Two studies noted that GP prescribing behaviour to be a derivative of specialist prescribing by showing that 60-66% of all drugs prescribed by GPs was initiated by medical specialists[7,8]. However, these studies did not differentiate between new and old drugs. Tamblyn et al. found no indication that repeat prescribing of specialist prescriptions influenced the GP's prescribing of new drugs [3]. In addition, Robertson et al. noted that prescriptions for more recently introduced drugs were not more likely to have been specialist initiated than older drugs [9]. So, despite the acknowledged impact that specialists have on the prescribing of existing drugs by GPs, little data are available when it comes newly marketed drugs.

Better understanding of the interplay between primary and specialist care, and thereby the mechanisms by which new drugs diffuse into medical practice, contribute to the discussion on ensuring patient safety and a sustainable cost-containment in health care [10,11]. Therefore, the aim of this study was to estimate the influence of medical specialists on prescribing of new drugs by GPs shortly after market introduction. We were interested in three questions. Firstly, are newly marketed drugs in primary care mainly prescribed by medical specialists during the early post-marketing period? Secondly, how many GPs start prescribing new drugs before any medical specialists do so? Thirdly, does specialist prescribing shorten the GP's time to adoption?

Methods

Study setting

In this study we used dispensing data from patients of 103 GPs who participated in the second Dutch national survey of general care (DNSGP-2), conducted by NIVEL (Netherlands Institute for Health Services Research) in 2001 [12,13]. The 103 GPs worked in 59 non-dispensing practices in all 12 provinces of The Netherlands. Dispensing data were collected by the network of the Foundation for Pharmaceutical Statistics (SFK) and covered the period 1999 untill 2003 [14]. Because virtually all patients in The Netherlands designate a single pharmacy to fill prescriptions from both GPs and medical specialists, dispensing data provide an almost complete account of drug exposure in time [15].

Study design

For this study, we selected five new drugs as study cases, namely the combination of a long-acting bronchodilator and inhalation corticosteroid (ICS) salmeterol/fluticasone, the cyclo-oxygenase-2 inhibitor rofecoxib, the proton pump inhibitor esomeprazole, the long-acting anticholinergic bronchodilator tiotropium, and the lipid lowering HMG-CoA reductase inhibitor rosuvastatin. Table 1 shows some relevant characteristics of these study case drugs. With the introduction of a new drug, physicians can either treat a patient with the tried and proven existing drug (if available) or the newly introduced drug. As reference drugs for the selected study case drugs we used all long-acting beta-2 antagonists and ICS for the combination salmeterol/fluticasone, all ipratropium bromide containing products for tiotropium, all nonsteroidal anti-inflammatory drugs (NSAIDs) (excl. low-dose aspirin) for rofecoxib, all proton pump inhibitors for esomeprazole and all HMG-CoA reductase inhibitors for rosuvastatin. All five new drugs showed rapid market introduction and were listed within one year after market introduction in the top 10 drugs associated with the fastest growing expenditures in The Netherlands [14]. All drugs were fully reimbursed by all health insurance companies and could be prescribed without limitation by both GPs and medical specialists.

For this study, we included patients starting on a new or a reference drug during the first six months after market introduction. We included both new starters and switchers. The date of the patient's first prescription for either the new or reference drug was termed the index date. Starting was defined as receiving a prescription for a new or reference drug and no prescription for that same drug during the six months before the index date. Patients in whom dispensing follow-up of less than six months was present were excluded. Market introduction was defined as the date of the first prescription for the new drug in the database.

Table 1: *Characteristics of the five newly marketed drugs included in the study.*

New drug *(Brand name)*	**Market introduction**	**Main indication** ⋆	**Reference group**
Salmeterol/fluticasone *(Seretide/Advair®)*	1999, May	Asthma/COPD ¶	Long acting ß$_2$-agonist and ICS §
Rofecoxib *(Vioxx®)*	2000, Apr	Rheumatoid arthritis	NSAIDs # excl. low-dose aspirin
Esomeprazole *(Nexium®)*	2000, Nov	Gastro-oesophageal reflux disease	Proton pump inhibitors
Tiotropium *(Spiriva®)*	2002, Jun	COPD ¶	Ipratropium bromide containing products
Rosuvastatin *(Crestor®)*	2003, Mar	Hypercholesterolemia	HMG-CoA ¥ reductase inhibitors

⋆ Main indication at registration derived from Dutch Medicine Evaluation Board (www.cbg-meb.nl).

¶ COPD=Chronic Obstructive Pulmonary Disease.

§ ICS=Inhalation CorticoSteroid.

NSAIDs=NonSteroidal Anti-Inflammatory Drugs.

¥ HMG-CoA=3-Hydroxy-3-MethylGlutaryl Co-enzyme A.

Main outcome measurements

We recorded the type of physician (GP or medical specialist) using the patient's prescription for a new or reference drug on the index date. To answer the first research question, we calculated for each new drug the proportion of patients receiving their first prescription for a new drug from a medical specialist out of the total number of patients receiving the drug from both GPs and medical specialists. The same proportion was calculated for the reference groups to calculate a relative rate. To answer the second research question of how many GPs start prescribing new drugs before waiting for any prescriptions of medical specialists, we calculated the proportion of GPs that started prescribing the new drug before any of their patients received the drug from a medical specialist. To answer the third research question we calculated for each GP the time between market introduction and the date on which the GP prescribed the new drug for the first time to a patient who never used the drug before. We compared the time to prescribing between GPs that initiate therapy before one of their patients received the drug from a medical specialist and GPs that waited for specialists to prescribe first before prescribing themselves.

Results

In total 1,687 patients received one of the five new drugs during the first six months after market introduction. Most patients received rofecoxib (N=596), followed by tiotropium (N=556), rosuvastatin (N=212), the combination salmeterol/fluticasone (N=171) and esomeprazole (N=152). The average age was 61.7 years (SD=15.3 years) and 57.2% was female. Overall, 16,797 patients received a drug from the reference groups (mean age 51.9 years (SD=18.7); 58.8% female). Complete dispensing data were available for 80 GPs for the combination salmeterol/fluticasone. The number of included GPs for rofecoxib was 85, 90 for esomeprazole, 98 for tiotropium, and 94 for rosuvastatin.

During the first six months following market launch, three drugs were more frequently prescribed by GPs than by medical specialists. Most patients starting on rofecoxib, esomeprazole, or rosuvastatin, received their first prescription from their own GP. The proportion of patients receiving their first prescription from a GP was 77.0% for rofecoxib, 65.1% for esomeprazole, and 58.0% for rosuvastatin. On the other hand, tiotropium and salmeterol/fluticasone were more frequently initiated by medical specialists. Of the patients starting on tiotropium, 52.7% received their first prescription from a specialist. The proportion was 60.2% for salmeterol/fluticasone. Table 2 shows for each new drug the number of patients receiving a new or reference drug and the corresponding probability of receiving a new drug from a specialist compared to a reference drug. Except for rosuvastatin, receiving a new drug from a specialist was more likely than receiving a reference drug from a GP. The relative rate was greatest for tiotropium (RR=3.64; 95% CI 3.03-4.36) and salmeterol/fluticasone (RR=3.56; 95% CI 3.03-4.17). For rosuvastatin, no difference was observed (RR=1.06; 95% CI 0.89-1.27).

The proportion of GPs with at least one patient in their practice that received a new drug during the first six months after market introduction ranged from 53.3% for esomeprazole to 94.9% for tiotropium (Table 3). Not all GPs started prescribing the new drugs themselves. The proportion of GPs starting therapy ranged from 30.0% for esomeprazole to 66.3% for tiotropium. A substantial proportion of GPs that started prescribing new drugs before any of their own patients received a prescription from a specialist. The proportion of GPs prescribing new drugs before a specialist prescription ranged from 21.1% for esomeprazole to 32.9% for rofecoxib.

Table 2: *New drug prescribing on a patient level. Number of patients receiving their first prescription for a new or a reference drug from a medical specialist or GP six months after market introduction.*

	New drug N (%)	Reference drug N (%)	Relative Rate (95% CI)
Salmeterol/fluticasone			
Medical specialist	103 (60.2%)	302 (16.9%)	**3.56 (3.03-4.17)**
GP	68 (39.8%)	1,481 (83.1%)	REF.
Rofecoxib			
Medical specialist	137 (23.0%)	1,445 (13.0%)	**1.77 (1.51-2.06)**
GP	459 (77.0%)	9,656 (87.0%)	REF.
Esomeprazole			
Medical specialist	53 (34.9%)	424 (19.6%)	**1.78 (1.41-2.25)**
GP	99 (65.1%)	1,741 (80.4%)	REF.
Tiotropium			
Medical specialist	293 (52.7%)	123 (14.5%)	**3.64 (3.03-4.36)**
GP	263 (47.3%)	726 (85.5%)	REF.
Rosuvastatin			
Medical specialist	89 (42.0%)	355 (39.5%)	1.06 (0.89-1.27)
GP	123 (58.0%)	544 (60.5%)	REF.
Overall			
Medical specialist	675 (40.0%)	2,649 (15.8%)	**2.53 (2.37-2.71)**
GP	1,012 (60.0%)	14,148 (84.2%)	REF.

The time between market introduction and actual prescribing of the different new drugs showed considerable variation among GPs (Table 4). For all new drugs, the average time to prescribing was shorter (not significantly) for GPs that started prescribing before one of their patients received a prescription from a specialist compared to GPs waiting for a prescription from a medical specialist.

Table 3: *New drug prescribing on a GP level. Number of GPs with at least one patient in their practice receiving a new drug, GPs initiating therapy with a new drug, and GPs initiating new drug therapy without waiting for a specialist prescription.*

	Total number of GPs	GPs with at least one patient in their practice receiving new drug	GPs initiating therapy with new drugs	GPs initiating therapy without waiting for a specialist prescription
Salmeterol/fluticasone	80	59 (73.8%)	34 (42.5%)	23 (28.8%)
Rofecoxib	85	68 (80.0%)	55 (64.7%)	28 (32.9%)
Esomeprazole	90	48 (53.3%)	27 (30.0%)	19 (21.1%)
Tiotropium	98	93 (94.9%)	65 (66.3%)	26 (26.5%)
Rosuvastatin	94	61 (64.9%)	34 (36.2%)	23 (24.5%)

Table 4: *The influence of medical specialist prescribing on the mean number of days (SD) to the GP's first prescription for a new drug in the first six months after market introduction.*

	GPs starting therapy before repeating a specialist prescription		GPs starting therapy after repeating a specialist prescription		
	N (%)	Mean days (SD)	N (%)	Mean days (SD)	p-value
Salmeterol/fluticasone	23 (67.6%)	88.6 (36.3)	11 (32.4%)	109.0 (41.3)	0.69
Rofecoxib	28 (50.9%)	71.7 (56.1)	27 (49.1%)	87.8 (42.5)	0.56
Esomeprazole	19 (70.4%)	53.8 (43.8)	8 (29.6%)	87.3 (48.9)	0.56
Tiotropium	26 (40.0%)	45.0 (46.5)	39 (60.0%)	88.0 (52.7)	0.60
Rosuvastatin	23 (67.6%)	43.1 (40.1)	11 (32.4%)	108.8 (48.1)	0.34

Discussion

The primary objective of this study was to estimate the influence of medical specialists on new drug prescribing in primary care shortly after market introduction. This study shows that the influence of medical specialists is clearly visible for all new drugs and often greater than for the existing older drugs, but the rapid uptake of new drugs in primary care does not seem specialist induced by definition and very much drug dependent. A substantial proportion of GPs that prescribe new drugs do so without awaiting specialist prescribing.

The main advantage of this study was the possibility to identify within individual GP practices patients that received a new drug from a specialist and those receiving a prescription from their own GP. This clear distinction enabled us to estimate the influence of medical specialists on new drug prescribing in primary care. In addition, we measured the specialists' influence on new drug prescribing shortly after a new drug's market introduction in comparison to their influence on the prescribing of drugs from the same therapeutic category already present on the market.

Research on diffusion of innovations postulated a two-step model by which innovations are adopted by a population with innovators as the individuals who adopt first, followed by others copying their behaviour [16,17]. Because GPs regard medical specialists as the opinion leaders in specific medical area, they often mention specialists as the early prescribers of new drugs [18,19]. It is therefore reasonable to assume that the diffusion of new drugs also follows this two-steps model with medical specialists as innovators and GPs as followers. However, our data show that this is not the case for all new drugs. Even in the early post-marketing period in which new drug prescribing by specialists should be predominant, GP prescribing outweighed specialist prescribing in three out of the five new drugs. Moreover, we noted that specialist endorsement was not a requisite for a subpopulation of GPs. Especially rofecoxib, and to a lesser extent rosuvastatin and esomeprazole, were adopted by the majority of GPs and 32.9% adopted before ever having seen a prescription for rofecoxib from a medical specialist. Although the influence of specialists is clearly visible, GPs are innovators too.

The level of specialist prescribing differs per new drug. Especially for rosuvastatin, esomeprazole, and rofecoxib, GP were in most cases the first prescribers. On the other hand, tiotropium and the combination salmeterol/fluticasone were mostly initiated by specialists. This finding is in line with other studies [8,9,20,21]. Robertson et al. noted in a study among 88 Australian GPs that the proportion of specialist-initiated prescriptions ranged from 8% to 85% for different drug classes [9]. The smaller influence of medical specialists for rosuvastatin, esomeprazole, and rofecoxib may partly be explained by extensive marketing and the relative low perceived risk associated with prescribing of these drugs [22-24]. Extensive marketing campaigns may have resulted in less reluctance of GPs to adopt the new drugs fast. Moreover, rofecoxib, esomeprazole, and rosuvastatin are clear examples of new drugs showing rapid uptake in primary care that is not specialist induced.

We found that for four new drugs the probability of receiving a new drug from a medical specialist was significantly higher than receiving a reference drug. Only for rosuvastatin, no difference was observed. The difference between drugs may partly be explained by differences between patients receiving new drugs and those receiving reference drugs. In general, medical specialists treat a different patient mix primarily composed of more severely ill patients that may be more likely to benefit from new drugs [25,26]. In previous studies on new drug prescribing we have identified channelling of new marketed drugs in high-risk patients and those with poor a response existing therapies [25,26,27].

Based on the classical model of innovation, specialist prescribing could serve as a catalyst for GPs to try out the new drugs themselves. Rapid prescribing of newly marketed drugs by specialists could convince GPs through a learning-by-demonstration effect to adopt too. However, this was not confirmed by our data because the time to first prescription was not

shorter for GPs who awaited specialist prescribing compared those prescribing before any of their patients received the drug from a medical specialist. The absence of any differences may partly be explained by seemingly great willingness among GPs to prescribe these newly marketed drugs.

The findings in this study need to be interpreted in light of its limitations. Firstly, the results are based on five new drugs and this should be taken into account when generalising the results to all new drugs. Our dispensing data contained no information on the diagnosis that may have influenced the likelihood the patient may have referred to medicals. Furthermore, we used dispensing data as a proxy of physician prescribing. Patients do not fill all prescriptions they receive from their physician in a pharmacy. It is therefore possible that the dispensing data are conservative estimations of the real prescribing of physicians. However, we had no indication that the filling rate of patients was more selective for one of the five new drugs or differed between GPs and specialists. Hospital pharmacies that dispense medication to patients visiting the hospital are still limited in The Netherlands. It is therefore unlikely that we missed prescriptions of specialists to the patients of the study GPs.

Conclusions

This study shows that the influence of medical specialists is clearly visible for all new drugs and often greater than for older drugs, but the rapid uptake of new drugs in primary care does not seem specialist induced in all cases. GPs are responsible for a substantial amount of all early prescriptions for new drugs and for a subpopulation of GPs specialist endorsement is not a requisite to initiate in new drug prescribing. This contradicts with the idea that the diffusion of newly marketed drugs always follows a two-step model, with medical specialists as the innovators and GPs as the followers.

Chapter 3.3

The effect of pharmacotherapy audit meetings on early new drug prescribing by general practitioners

Stefan R. Florentinus [1], Rolf van Hulten [1], Marjolein E.M. Kloth [1], Eibert R. Heerdink [1], A.M.G. Fabiënne Griens [4], Hubert G.M. Leufkens [1], Peter P. Groenewegen [2,3]

[1] Utrecht University,
Division of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht, The Netherlands.

[2] NIVEL (Netherlands Institute for Health Services Research),
Utrecht, The Netherlands.

[3] Utrecht University,
Department of Sociology and Department of Human Geography,
Utrecht, The Netherlands.

[4] SFK (Foundation for Pharmaceutical Statistics),
The Hague, The Netherlands.

Submitted

Abstract

Background: New drugs are cornerstones in clinical practice. However, when adopted in an imprudent fashion, there is valid concern about uncertain risk-benefit for patients and increased health care expenditures. In several countries, general practitioners (GPs) and community pharmacists work closely together to ensure proper use of new drugs in daily medical practice.

Objective: To estimate the effect of pharmacotherapy audit meetings (PTAMs) between GPs and community pharmacists on prescribing of newly marketed drugs by GPs.

Methods: Case-control design nested in a cohort of 103 GPs working in 59 practices over the period 1999 untill 2003. The main outcome measures were the decisions to start therapy with a new drug or with an existing older drug from the same therapeutic category within the first six months after market introduction. Multi-level modelling was used for analyses.

Results: Overall, in 6.1% of the decisions to start drug therapy, the choice for the latest drug on the market was made. The GPs attending low-quality PTAMs made 1,861 decisions to start therapy in which 112 (6.0%) times a new drug was preferred over an older alternative. GPs participating in high-quality PTAMs preferred a new drug in only 1.7% of the 2,092 decisions made. Compared to GPs participating in PTAMs on the highest quality level (level 4), the GPs attending level 1 or level 2 PTAMs were more than twice as likely to start therapy with new drugs than with older drugs (OR=2.24; 95% CI 1.04-4.81 resp. OR=2.31; 95% CI 1.30-4.09).

Conclusions: PTAMs may be an effective way to control early new drug prescribing in general practice. For PTAMs to be effective, it is vital that GPs and pharmacists set common goals on how to optimise pharmacotherapy. This concordance should be reflected in PTAMs that result in concrete decisions with auditing of GP prescribing behaviour. Pharmacists should take up an active role in organising PTAMs to extent their influence on drug prescribing.

Introduction

Innovation in pharmacotherapy is a cornerstone in clinical practice. However, prescribing of newly marketed drugs is not uniformly distributed among physicians and some new drugs are prescribed more than medical need can account for [1-3]. Erratic adoption of new drugs fuels the ongoing discussion about the trade-off between the wish to treat patients more effectively and ensuring sustainable cost-containment in health care [4-6]. With an ageing population and an increasing ability to treat many chronic diseases with medicines, general practitioners (GPs) report difficulties to stay up-to-date with medical innovations [7-9]. To ensure optimal care given to patients, a teamwork approach is important in which different health professionals each with their own clinical expertise work together [10,11].

In The Netherlands, community pharmacists and GPs practising in the same catchment area regularly organise pharmacotherapy audit meetings (PTAMs) to improve the quality of prescribing by making decisions about first choice treatment [12,13]. Clinical assessment of newly marketed drugs is an important topic on the agenda of more than 70% of all PTAMs [13,14]. In 2003, 794 PTAMs consisting on average of nine GPs and two pharmacists were active, meaning that nearly all Dutch GPs and community pharmacists participate in PTAMs [13,14]. The literature pertaining to the effects of PTAMs on GP prescribing behaviour is limited and neglected the effect on prescribing of new drugs [13,15]. Therefore, the purpose of the present study was to estimate the effect of PTAMs on prescribing of newly marketed drugs by GPs.

Methods

Study setting

This study used dispensing data from patients of 103 GPs who participated in the second Dutch national survey of general practice (DNSGP-2), conducted by NIVEL (Netherlands Institute for Health Services Research) in 2001 [16]. The 103 GPs worked in 59 non-dispensing practices in all 12 provinces of The Netherlands. Dispensing data were collected by the network of SFK (Foundation for Pharmaceutical Statistics) and covered the years 1999 untill 2003 [17]. Because virtually all patients in The Netherlands designate a single pharmacy to fill prescriptions from GPs and medical specialists, dispensing data provide an almost complete account of drug exposure in time [18].

Data on PTAMs were collected through a questionnaire sent in December 2003 to 123 community pharmacies that worked closely together with the 103 GPs. The pharmacist most actively involved in the PTAMs filled in the questionnaire. The questionnaire contained questions about the quality, composition, and content of the PTAMs. In The Netherlands, PTAMs are categorised into four levels based on the capability to make decisions [13], namely

level 1: no structured meetings, level 2: frequent meetings without concrete decisions, level 3: frequent meetings with concrete decisions, and level 4: frequent meetings with concrete decisions and evaluation of these decisions. In case more than one pharmacist attended the same PTAMs and there was a difference in their assessment of the PTAMs' quality, the lowest value was used in the analysis to make sure not to overestimate the effectiveness of the PTAMs.

Table 1: *Characteristics of the five newly marketed drugs included in the study.*

New drug *(Brand name)*	**Market introduction**	**Main indication** ⋆	**Reference group**
Salmeterol/fluticasone *(Seretide/Advair®)*	1999, May	Asthma/COPD ¶	Long acting β_2-agonist and ICS §
Rofecoxib *(Vioxx®)*	2000, Apr	Rheumatoid arthritis	NSAIDs # excl. low-dose aspirin
Esomeprazole *(Nexium®)*	2000, Nov	Gastro-oesophageal reflux disease	Proton pump inhibitors
Tiotropium *(Spiriva®)*	2002, Jun	COPD ¶	Ipratropium bromide containing products
Rosuvastatin *(Crestor®)*	2003, Mar	Hypercholesterolemia	HMG-CoA ¥ reductase inhibitors

⋆ Main indication at registration derived from Dutch Medicine Evaluation Board (www.cbg-meb.nl).

¶ COPD=Chronic Obstructive Pulmonary Disease.

§ ICS=Inhalation CorticoSteroid.

NSAIDs=NonSteroidal Anti-Inflammatory Drugs.

¥ HMG-CoA=3-Hydroxy-3-MethylGlutaryl Co-enzyme A.

In this setting, five new drugs were selected as study cases, namely the combination of the long-acting bronchodilator and inhalation corticosteroid (ICS) salmeterol/fluticasone, the cyclo-oxygenase-2 inhibitor rofecoxib, the proton pump inhibitor esomeprazole, the long-acting anticholinergic bronchodilator tiotropium, and the lipid lowering HMG-CoA reductase inhibitor rosuvastatin. Table 1 shows some relevant characteristics of these case study drugs. All five new drugs showed rapid market uptake and were listed within one year after market introduction in the top 10 drugs associated with the fastest growing drug expenditures in The Netherlands [17]. As reference drugs for the selected case study drugs we used all long-acting beta-2 antagonists and ICS for the combination salmeterol/fluticasone, all ipratropium bromide containing products for tiotropium, all nonsteroidal anti-inflammatory drugs (NSAIDs) (excl. low-dose aspirin) for rofecoxib, all proton pump inhibitors for esomeprazole and all HMG-CoA reductase inhibitors for rosuvastatin.

Study design

With the introduction of a new drug, GPs can choose to either treat a patient with the tried and proven existing drug (if available) or the newly introduced drug. In this study, we included all patients receiving a new or an older reference drug during the first six months after the market introduction. The primary outcome measure was the GP's decision to start drug therapy in patients with a new or a reference drug. The date of the patient's first prescription for either a new or a reference drug was termed the index date. Starting was defined as receiving a prescription for a new or reference drug and no prescription for the same drug the six months before the index date. Patients in whom dispensing follow-up of less than six months was present were excluded. Both starters and switchers were included in the analysis.

Data analysis

To estimate the effect of PTAMs on new drug prescribing, we used a logistic multi-level model with two levels, namely patients nested within GPs. For practical reasons we left out the practice or the pharmacy where their patients usually go to as a level; a three level model turned out very difficult to converge. Characteristics of PTAMs were modelled as characteristics of GPs. Using a multi-level model enabled us to adjust for differences between patients and clustering of patients within GPs that might affect the GP's decision to prescribe new drugs [19]. Instead of running separate analyses for the five different new drug and reference drug classes, we included dummies to represent the groups. In this way, we took into account that new drug prescribing in one group might be related to that in other groups. The patient's age, gender, and chronic disease score (CDS) [20] were used to correct for any patient influences. Odds ratios (ORs) with 95% confidence intervals (CI) were estimated for all PTAM characteristics one by one and corrected for all patient characteristics. Due to the relatively small sample size of our study population at GP-level, we were unable to perform a multivariate multi-level analysis to correct for all characteristics simultaneously.

Results

For 86 (83.5%) of the 103 GPs both dispensing data and information on PTAMs was available. The mean age was 46.6 years (SD=6.3), 26.7% were female and 53.5% worked single-handed. The GPs for whom no information about PTAMs was available did not differ from the other GPs with respect to age and gender. The proportion of GPs prescribing new drugs during the first six months after market introduction ranged from 31.6% for esomeprazole to 74.0% for tiotropium. Rofecoxib was prescribed by 69.0%, rosuvastatin by 43.2%, and the combination salmeterol/fluticasone by 43.3% of the GPs.

In total, 849 patients were identified as starters on one of the five new drugs and 13,149 patients as starters on one of the older reference drugs (Table 2). This means that in 6.1% of the choices to initiate new therapy, the choice for the latest drug on the market was made. The number of patients starting on a newly marketed drug was highest for tiotropium (29.5%) and lowest for the combination salmeterol/fluticasone (2.2%).

As shown by Table 2 the preference for the latest drug on the market increased when GPs participated in low-quality PTAMs. Out of the 1,861 decisions to initiate new therapy, in 112 (6.0%) cases a new drug was chosen over an older alternative by the GPs attending low quality PTAMs. The decision to prescribe a newly marketed drug was made in 36 (1.7%) of the total of 2,092 times therapy was started by the GPs attending high-quality level 4 PTAMs.

Table 2: *Number (%) of decisions to start therapy with a new drug out of the total number of decisions made by GPs per PTAM level.*

PTAM	Nr GPs	Esomeprazole	Rofecoxib	Rosuvastatin
Level 4	25 (29.1%)	14/358 (3.9%)	36/2,092 (1.7%)	10/148 (6.8%)
Level 3	17 (19.8%)	19/336 (5.7%)	110/2,186 (5.0%)	35/134 (26.1%)
Level 2	35 (40.7%)	39/671 (5.8%)	161/3,222 (5.0%)	50/218 (22.9%)
Level 1	9 (10.5%)	12/142 (8.5%)	46/1,129 (4.1%)	14/67 (20.9%)
Total	**86 (100%)**	**84 /1,507(5.6%)**	**353/8,629 (4.1%)**	**109/567 (19.2%)**

PTAM	Salmeterol/ Fluticasone	Tiotropium	Overall
Level 4	4/394 (1.0%)	44/146 (30.1%)	108/3,138 (3.4%)
Level 3	7/617 (1.1%)	73/241 (30.3%)	244/3,514 (6.9%)
Level 2	37/1005 (3.7%)	98/368 (26.6%)	385/5,484 (7.0%)
Level 1	6/433 (1.4%)	34/90 (37.8%)	112/1,861 (6.0%)
Total	**54/2,449 (2.2%)**	**249/845 (29.5%)**	**849/13,997 (6.1%)**

Level 4: Frequent meetings with concrete decisions and evaluation of these decisions (Highest quality).
Level 3: Frequent meetings with concrete decisions.
Level 2: Frequent meetings without concrete decisions.
Level 1: No structured meetings (Lowest quality).

Our findings from Table 2 were confirmed by our multi-level analysis. When adjusted for the patient's age, gender, and CDS, the GPs attending level 1 PTAMs (OR=2.24; 95% CI 1.04-4.81) or level 2 PTAMs (OR=2.31; 95% CI 1.30-4.09) were more than twice as likely to prescribe drugs in the early post-marketing period than GPs participating in PTAMs on the highest level (level 4).

Table 3: *Multilevel regression analysis of new drug prescribing showing effect of PTAMs on GP prescribing of five newly marketed drugs during first six months after introduction.*

Panel 1: Basic model including five drug classes and patient characteristics.		
New drugs	Coefficients (95% CI)	
Esomeprazole	1.5% (1.0%-2.5%)	
Rofecoxib	1.9% (1.3%-2.6%)	
Rosuvastatin	6.3% (4.0%-10.0%)	
Salmeterol/fluticasone	1.6% (1.1%-2.4%)	
Tiotropium	17.0% (12.0%-24.0%)	
Patient characteristics	N (%)	OR (95% CI)
Gender		
Female	9,706 (58.5%)	**1.31 (1.15-1.48)**
Age (mean; SD)	50.2 (20.2)	**1.02 (1.02-1.02)**
Chronic disease score (mean; SD)	2.32 (2.7)	**1.06 (1.04-1.09)**
Panel 2: basic model plus PTAM characteristics, introduced one at a time.		
Quality level of PTAMs	N (%)	OR (95% CI)
Level 4	25 (28.1%)	REF.
Level 3	17 (19.1%)	1.49 (0.77-2.88)
Level 2	35 (39.3%)	**2.31 (1.30-4.09)**
Level 1	9 (10.1%)	**2.24 (1.04-4.81)**
Composition of PTAMs (Mean;SD)		
Number of pharmacists	3.5 (2.0)	1.06 (0.97-1.16)
Number of pharmacies	2.2 (1.0)	1.05 (0.98-1.12)
Number of GPs	9.5 (3.1)	**1.05 (1.01-1.09)**
Total participants	13.0 (5.3)	**1.06 (1.02-1.10)**
Other PTAM characteristics		
Are newly marketed drugs discussed during PTAMs?		
Yes	82 (92.1%)	0.59 (0.12-2.87)
Are decisions about which new drugs should or should not be prescribed made during PTAMs?		
Yes	27 (30.3%)	0.82 (0.50-1.33)
Are decisions about which drugs are first choice made during PTAMs?		
Yes	68 (76.4%)	0.88 (0.50-1.54)
Are pharmaceutical representatives invited to attend the PTAMs?		
Yes	11 (12.4%)	1.54 (0.81-2.96)
Are decisions about who receives pharmaceutical representatives made during PTAMs?		
Yes	41 (46.1%)	**0.36 (0.24-0.56)**

In addition, we noted that the effect of PTAMs became smaller as the number of GPs attending the PTAMs increased (OR=1.05; 95% CI 1.01-1.09). The same trend was observed for the total number of participants (OR=1.06; 95% CI 1.02-1.10). GPs participating in PTAMs that made decisions about who receives pharmaceutical representatives were less likely to prescribe new drugs (OR=0.36; 95% CI 0.24-0.56).

Discussion

The objective of this study was to study the effect of PTAMs on prescribing of new drugs by GPs during the first six months following market introduction. Our study shows that rapid prescribing of new drugs by GPs is restricted when GPs and community pharmacists collaborate in high-quality PTAMs that make concrete decisions to optimise pharmacotherapy and evaluate GP's prescribing behaviour.

The main strength of our study is that we analysed new drug prescribing by GPs in a multi-level structure of patients clustering in GPs while also taking into account the GPs professional interactions with community pharmacists. We noted that GPs participating in low-quality PTAMs, namely those that do not have frequent meetings and fail to make decisions to optimise pharmacotherapy, prescribe more new drugs than GPs participating in high-quality PTAMs. There may be several explanations for this finding. One explanation, of course, is a direct effect of PTAMs on the GP's decision to prescribe new drug. Making decisions to optimise pharmacotherapy may result in restrainment of the number of drugs GPs can prescribe, especially when the GP's prescribing behaviour is evaluated. Another explanation may be the participants' attitudes towards new drugs. GPs that are willing to professionalize PTAMs to function on level 4 may have different attitudes about new drugs than those attending noncommittal PTAMs. Prosser and Walley noted that prescribing of new drugs dependents heavily on the GP's subjective beliefs [21]. GPs with a negative attitude towards new drugs might also influence and support each other [22]. In addition, GPs participating in the same PTAMs show more resemblance in their prescribing behaviour than GPs participating in different PTAMs [13]. Therefore, further research is needed to elucidate whether the GP's restraint in new drug prescribing is the result of decisions made during PTAMs.

Some conditions need to be met before PTAMs may be effective in influencing the prescribing behaviour of GPs. A key prerequisite for PTAMs to reach decisions about optimising pharmacotherapy is a group of willing GPs and pharmacists. Firstly, we found that only the GPs that participated in PTAMs with sufficient internal basis for making decisions prescribed less new drugs. Secondly, GPs participating in smaller PTAMs prescribed new drugs less frequently. As the number of participants per PTAM increases, the effectiveness

seems to decrease and GPs prescribe more new drugs. Veninga et al. identified that the optimal number of participants for PTAMs is about 5 to 6 persons and that participants of smaller groups were shown to be more satisfied with the climate in the group [23].

Our data shows that PTAMs that made decisions about who receives visits from pharmaceutical representatives had a limiting effect on the prescribing of new drugs. Moreover, our results may indicate that inviting pharmaceutical representatives during PTAMs results in more new drugs being prescribed. Numerous studies have shown that receiving visits from pharmaceutical representatives is a strong predictor for adopting new drugs [24,25]. The wish to stay up-to-date with medical innovation is often mentioned by GPs as a important reason for seeing pharmaceutical representatives [7,21]. In our study, some GPs decided not to see pharmaceutical representatives themselves, but instead agreed that visits were only accepted by pharmacists. The information can be filtered and assessed on its scientific merits by pharmacists and subsequently discussed during PTAMs. This may offer a valuable opportunity for GPs to save time and still staying up-to-date while limiting commercial influences.

The results of our study need to be interpreted in light of its limitations. Our findings are based on prescribing of five new drugs, so generalising our results to all new drugs should be done with restraint. However, our study case drugs are clear examples of drugs with rapid market uptake and sharp increases in health care expenditures. The main limitation of our study is that due to our relatively limited sample size at GP-level, we were unable to estimate the effect of PTAMs in a multivariate model. Furthermore, characteristics of PTAMs were collected through a questionnaire filled in only by pharmacists of which the most conservative assessments were used in the analysis. Other studies have identified differences between the GP's and the pharmacist's perception regarding the quality of PTAMs [13,26]. In general, GPs rate the quality of PTAMs higher than pharmacists do.

Conclusions

Professional collaboration between GPs and community pharmacists in PTAMs may be an effective way to control early prescribing of new drugs in general practice. For PTAMs to be effective, it is vital that GPs and pharmacists set common goals on how to optimise pharmacotherapy. This concordance should be reflected in PTAMs with frequent meetings that result in concrete decisions with auditing of GP prescribing behaviour. Pharmacists should take up an active role in organising PTAMs to extent their influence on drug prescribing.

Chapter 3.4

Which pharmacists contribute to high-level pharmacotherapy audit meetings with GPs?

Stefan R. Florentinus [1], Rolf van Hulten [1], Marjolein Kramer [1], Liset van Dijk [2], Eibert R. Heerdink [1], Hubert G.M. Leufkens [1], Peter P. Groenewegen [2,3]

[1] Utrecht University,
Division of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht, The Netherlands.

[2] NIVEL (Netherlands Institute for Health Services Research),
Utrecht, The Netherlands.

[3] Utrecht University,
Department of Sociology and Department of Human Geography,
Utrecht, The Netherlands.

Submitted

Abstract

Background: Community pharmacists are challenged to become important professionals in the care provided to patients in general practice. In The Netherlands, community pharmacists collaborate with general practitioners (GPs) in pharmacotherapy audit meetings (PTAMs) to rationalise and optimise pharmacotherapy.

Objective: To find characteristics of pharmacists associated with high-quality PTAMs.

Methods: Cross-sectional questionnaire design. The main outcome measure was the self-reported quality level of PTAMs by pharmacists. Multinomial logistic regression analysis was used.

Results: Compared to pharmacists participating on lowest level, pharmacists participating on the highest level reported significantly more to undertake initiatives (OR=2.98; 95% CI 1.07-8.26).

Conclusions: In light of existing evidence, the role of pharmacists in PTAMs seems to be important and pharmacists should expand their involvement by facilitating in the organisation of PTAMs. Pharmacists should create a distinct profile of their expertise and they can professionalise PTAMs by undertaking more initiatives. PTAMs offer pharmacists a great opportunity to become integral members of the prescribing process.

Introduction

Nowadays a growing interest exists to optimise patient care by applying a teamwork approach in which different professionals each with their own expertise work together [1-3]. Community pharmacists, for example, are challenged to become important players in the prescribing process or even prescribers of drugs themselves [2,4,5]. With the development of pharmaceutical care, the pharmacist's attention has shifted from preparing medicines to more patient-orientated services [6]. Based on current literature it can be assumed that the pharmacist's contribution to the quality of pharmacotherapy increases as co-operation with GPs improves [7-9]. In several countries, this process has led to closer collaborations between GPs and pharmacists [10,11].

In The Netherlands, GPs and community pharmacists practising in the same catchment area regularly organise pharmacotherapy audit meetings (PTAMs) to optimise pharmacotherapy [12]. In 2003, 794 PTAMs were active meaning that nearly all GPs and community pharmacists participated in PTAMs [13]. Studies pertaining to the effectiveness of PTAMs have charted inconclusive results. In a study by De Vries et al., 45% of the PTAMs had some effect on the GP's prescribing behaviour, but these were often limited [14]. Muijrers et al. noted that, although GPs and pharmacists have fruitful collaborations, PTAMs had no measurable effect on the quality of prescribing of single-handed GPs. In **Chapter 3.1** and **3.3**, we noted that GPs participating in well-structured PTAMs that make decisions with actual feedback to optimise pharmacotherapy prescribed less new drugs in the early post-marketing period. Despite conflicting findings on the effectiveness, these studies have also charted limited data on the profile of pharmacists contributing to high-level PTAMs. Therefore, the purpose of the present study was to examine the associations between the quality level of PTAMs and characteristics of pharmacists.

Methods

Study setting

This study was conducted in a network of 123 community pharmacies that participated in a larger study on new drug prescribing by GPs, conducted by UIPS (Utrecht Institute for Pharmaceutical Sciences) of Utrecht University. To participate in our study the pharmacies had to work closely together with one of the 104 GP practices that participated in the second Dutch national survey of general practice, conducted by NIVEL (Netherlands Institute for Health Services Research) in 2001 [15,16]. Data on PTAMs were collected through a questionnaire sent to all participating pharmacies in December 2003. All non-responders received a reminder letter and a phone call two weeks after receiving the questionnaire.

Variables and instruments

The questionnaire was drawn up based on the literature, discussions in the research team and existing questionnaires [17,16]. The final questionnaire was based on the comments of experts and seven practising community pharmacists. The questionnaire consisted of four topics, namely:

(a) Characteristics of the PTAMs. The pharmacist who was most actively involved in the PTAMs filled in this part of the questionnaire. The purpose was to measure the quality, composition, and content of the PTAMs and the pharmacy's involvement.

(b) The provision of pharmaceutical care activities [6]. The pharmacist responsible for co-ordinating the pharmacy's pharmaceutical care activities filled in this part. The purpose was to determine the quantity and content of the pharmacy's care providing services.

(c) Characteristics of the pharmacists. All pharmacists working in the pharmacy filled in this section. Several characteristics were assessed, including the pharmacist's attitudes towards 'pharmacists as health professionals', 'pharmacists as entrepreneurs', 'pharmaceutical care', and 'newly marketed drugs'. Furthermore, we determined their use of drug information sources, general perceived self-efficacy scale (GSE) [18], and their initiatives in PTAMs. All attitudes were measured by using a 5-points Likert scale (Appendix 1).

(d) Practice characteristics; Ownership of the pharmacy, presence of consulting room, and use of a chain formula.

Factor analysis with a varimax rotation procedure was used to verify whether the different questions related to the pharmacist's attitude identified a single construct. Cronbach's alphas were calculated for the different constructs to assure sufficient internal consistency in the questions. Questions related to one construct were used to calculate sum scores that were used in the analysis (Appendix 1).

Data analysis

To find characteristics of pharmacists associated with the quality level of PTAMs, we used a multinomial logistic regression model. The primary outcome variable was the quality level of the PTAMs as perceived and reported by pharmacists in the questionnaire. In The Netherlands, PTAMs are categorised into four levels based on the capability to make decisions [17], namely level 1 (lowest level): no structured meetings, level 2: frequent meetings without concrete decisions, level 3: frequent meetings with concrete decisions, and level 4 (highest level): frequent meetings with concrete decisions and evaluation of these decisions. When more than one pharmacist attended the same PTAMs and differed in their assessment, each pharmacist was considered to participate on the lowest reported level as reported by one of the pharmacists. This assured that the effect of the PTAMs was not overestimated. Odds ratios (ORs) with 95% confidence intervals (95% CI) were estimated for the different pharmacist characteristics per PTAM levels with the lowest level (level 1) as the reference level.

Results

In total, 109 (88.6%) pharmacists completed the questionnaire. Five pharmacists worked in a pharmacy that did not participate in PTAMs with one of the 104 GP practices. Furthermore, one pharmacist was excluded due to missing data, leaving a total of 103 pharmacists to be included in the analysis. The 103 pharmacists participated in 62 different PTAMs. Table 1 shows for the PTAMs the quality-level, composition, and content related to prescribing of new drugs. On average, the PTAMs consisted of 3.9 (SD=2.2) pharmacists, working in 2.6 (SD=1.4) pharmacies, and 10 (SD=3.7) GPs. The majority of the PTAMs (74.2%) made decisions about which drugs were first choice treatment. Only 3 (4.8%) PTAMs never discussed newly marketed drugs. Although the majority did discuss newly marketed drugs, 42 (67.7%) did not make any decisions about which new drugs should or should not be prescribed. Pharmaceutical representatives were invited to attend nine (14.5%) PTAMs and eight (12.9%) PTAMs decided that only the pharmacist, and not the GPs, received visits of pharmaceutical representatives.

Of the pharmacists assigned to be the pharmacy's representative at PTAMs, 54 (52.4%) were male, 76 (73.8%) managing pharmacist and 42 (40.8%) the pharmacy's owner. The mean years practising in community pharmacy was 12.0 (SD=8.1) years. In total, 17 pharmacists participated in level 1 PTAMs, 57 in level 2 PTAMs, 21 in level 3 PTAMs, and 8 in PTAMs on the highest level (Table 2).

The multinomial logistic regression analysis identified a trend for the reported initiatives in PTAMs. Pharmacists who reported to undertake more initiatives in PTAMs were more likely to participate on a higher PTAM level. Compared to pharmacists participating on lowest level, those participating on the highest level reported to undertake initiatives more frequently (OR=2.98; 95% CI 1.07-8.26).

Table 1: *Quality level and content of the 62 PTAMs attended by the 103 pharmacists .*

Quality level of PTAMs.	N (%)
Level 1	7 (11.3%)
Level 2	33 (53.2%)
Level 3	14 (22.6%)
Level 4	8 (12.9%)
Are decisions made about which drugs are first choice during PTAMs?	
No	16 (25.8%)
Yes, oral decisions	16 (25.8%)
Yes, written decisions without feedback	18 (29.0%)
Yes, written decisions with feedback	12 (19.4%)
Are drugs prescribed following a (regional) formulary?	
No	46 (74.2%)
Yes	16 (25.8%)
Are newly marketed drugs discussed during PTAMs?	
No	3 (4.8%)
Yes, sometimes	29 (46.8%)
Yes, always	30 (48.4%)
Are decisions made about which new drugs should or should not be prescribed?	
No	42 (67.7%)
Yes, oral decisions	12 (19.4%)
Yes, written decisions without feedback	5 (8.1%)
Yes, written decisions with feedback	3 (4.8%)
Are prescribing data of GPs discussed during PTAMs?	
No	10 (16.1%)
Yes, sometimes	45 (72.6%)
Yes, always	7 (11.3%)
Are pharmaceutical representatives invited to attend PTAMs?	
No	53 (85.5%)
Yes, sometimes	8 (12.9%)
Yes, always	1 (1.6%)
Are decisions made during PTAMs who sees pharmaceutical representatives?	
No	47 (75.8%)
Yes, both pharmacists and GPs	7 (11.3%)
Yes, only pharmacists	8 (12.9%)

Discussion

The aim of this study was to find characteristics of pharmacists that were associated with the quality level of PTAMs. Although studies have been conducted at the GP-pharmacist interface, none focussed on the characteristics of pharmacists in relation to the quality of PTAMs. In this sense, our study may be a valuable contribution to research focussing on the effect of pharmacists on the prescribing behaviour of GPs.

The key prerequisite for PTAMs to reach decisions to optimise pharmacotherapy is a group of willing GPs and pharmacists. Studies have identified perceived interprofessional barriers between pharmacists and GPs [2,3,19]. Muijrers et al. showed that the majority of GPs wants pharmacists to have an advisory role rather than a codetermining role [19]. Two aspects make it difficult for pharmacists to have extensive influence on the likelihood that decisions are being made during PTAMs. Firstly, to function on at least level 3 decisions have to be made and for this consensus between participants is needed. This may be difficult to achieve for an individual pharmacist in a PTAM that is attended by GPs and a few other pharmacists. Secondly, pharmacists are eventually not the ones that prescribe medicines and therefore do not have to conform to the decisions made during PTAMs. Making decisions means in almost all cases a restriction in the GPs freedom of prescribing and assigns a controlling function to pharmacists. This is something that not all GPs are willing to do [19]. The discrepancy is also reflected in the findings of other studies identifying differences in the perceptions of pharmacists and GPs regarding the quality-level of the PTAMs [11,17,19]. In general, pharmacists express a greater wish for a more binding character of agreed policies and guidelines than GPs [11,17].

Although the pharmacist's influence seems at first limited, we did find the pharmacist's self-reported initiatives regarding PTAMs to be associated with the quality-level of the PTAMs. Pharmacists that regularly undertake initiatives and fulfil an important role in the organisation of PTAMs are also the pharmacists who participate in high-quality PTAMs. This gives a clear sign for pharmacists who are willing to professionalise the PTAMs they attend. Van Dijk et al. noted that the quality of PTAMs was strongly influenced by the organisation and the ethos of the meetings [17]. An open ethos, making and auditing concrete decisions, an optimal balance between the length and frequency of the meetings, and assigning a chairperson, were among other things important determinants of the quality level reached. Given the studies showing synergy when GPs and pharmacists work together, pharmacists should focus on two things, namely on positioning themselves more as experts on pharmacotherapy and on expanding their involvement in PTAMs by facilitating in the organisation of PTAMs.

Interestingly, the typical profile of an active care-providing pharmacist (active counselling at first- and second-dispensing, private consultation room, and actively inviting patients to audit their medication) does not seem to be the profile of a pharmacist involved in high-quality PTAMs. However, Storimans et al. showed that pharmacies working in close relationships with other healthcare providers provided more care to diabetes patients [20]. This might imply that pharmacies involved in high-quality PTAMs are indeed more care-providing pharmacists, but their extra services are limited to the areas on which agreements have been made during PTAMs. Even high-quality PTAMs discuss only a limited number of topics each year [21]. New developments in community pharmacy, such as forward integration of wholesales buying retail pharmacies and the development of chain formulas, fuelled the discussion about the care-providing efforts of pharmacists. However, our results do not show that pharmacists working in pharmacies owned by wholesalers or in pharmacies consolidated in chain formulas participated in a lower or higher quality of PTAMs.

The results of this study need to be interpreted in light of its limitations. Although 88.6% of the pharmacists completed the questionnaire, the results are based on data as reported by only pharmacists. The most important limitation of our study was the relative limited number of pharmacists per PTAM level, especially on level 1 and 4. However, a logistic regression analysis with the number of quality levels reduced to two, namely with level 1 and 2 as 'low-quality' PTAMs and level 3 and 4 as 'high-quality' PTAMs, yielded identical results.

Conclusions

In light of existing evidence, the role of pharmacists in PTAMs seems to be important and pharmacists should expand their involvement by facilitating in the organisation of PTAMs. However, given the differences in opinion between GPs and pharmacists about the role of pharmacists and the fact that pharmacists are outnumbered during PTAMs, pharmacists should create a distinct profile of their expertise and they can professionalise PTAMs by undertaking more initiatives. PTAMs offer pharmacists a great opportunity to become integral members of the prescribing process, but further research is recommended to determine which pharmacist related factors are critical for fruitful PTAMs.

Appendix 1: *Results of the reliability analysis and the survey used to calculate sum scores.* ¶

	Factor loading	% Fully disagree	% Partly disagree	% Neutral	% Partly agree	% Fully agree
Attitude to pharmacists as healthcare provider (α=0.75)						
The pharmacist primarily focuses on the patient's wellbeing.	0.82	1.1	1.1	5.0	32.8	60.0
The pharmacist is primarily guided in his management by what is essential from a healthcare point of view.	0.82	0.6	1.1	12.8	40.0	45.6
The pharmacist is in the first place a link in the health care system.	0.67	1.7	1.1	9.4	27.8	60.0
The pharmacist should always devote his entrepreneurship to the healthcare.	0.73	1.1	7.8	13.4	40.2	37.4
Attitude towards pharmacists as entrepreneurs (α=0.66)						
Pharmacists should take up a purely businesslike position.	0.80	29.1	35.8	22.3	11.7	1.1
A good pharmacist is primarily an enterprising pharmacist.	0.80	21.9	27.5	24.7	23.6	2.2
A pharmacy is comparable to other commercial organisations operating based on a profit motif.	0.72	41.7	32.8	12.8	11.1	1.7
Attitude towards new drugs (α=0.64)						
Older drugs are in general equally effective as new drugs.	0.66	4.5	19.6	30.2	38.5	7.3
Prescribing of new drugs should occur with restraint.	0.81	16.2	46.4	27.9	8.9	0.8
New drugs are often me-too's.	0.82	2.2	12.8	20.0	49.4	15.6
Initiatives regarding PTAMs (α=0.93)						
I regularly undertake initiatives within the PTAMs.	0.82	7.3	9.6	23.2	29.4	30.5
Without me the PTAMs will function on a lower level.	0.92	17.5	13.6	27.7	23.2	18.1
I am the driving force behind the PTAMs.	0.93	24.9	16.4	30.5	17.5	10.7
Without me less will be undertaken within the PTAMs.	0.95	21.5	15.3	27.7	20.9	14.7

¶ Fully agree=5 points; Partly agree=4 points; Neutral=3 points; Partly disagree=2 points; Fully disagree=1 point

Chapter 4

CASE STUDIES ON NEW DRUG PRESCRIBING

Chapter 4.1

Off-label use of the new drug rofecoxib

Stefan R. Florentinus [1], Liset Van Dijk [2], Karin J. Velthove [1], Eibert R. Heerdink [1], Peter P. Groenewegen [2,3], Hubert G.M. Leufkens [1]

[1] Utrecht University,
Division of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht, The Netherlands.

[2] NIVEL (Netherlands Institute for Health Services Research),
Utrecht, The Netherlands.

[3] Utrecht University,
Department of Sociology and Department of Human Geography,
Utrecht, The Netherlands.

Submitted

Abstract

Background: New drugs are usually registered for a limited number ofindications. However, the clinical applications may be different than scientific evidence can account for.

Objective: To determine the extent of off-label prescribing of rofecoxib and to find characteristics of GPs associated with this off-label prescribing.

Methods: Case-control design. The main outcome measure was receiving the first rofecoxib prescription for an on-label diagnosis (osteoarthritis and rheumatoid arthritis) or for an off-label indication (all other diagnoses).

Results: 82.6% (1,654) of the patients received rofecoxib for an off-label indication. No GP characteristics were associated with the extent of off-label prescribing. Patient characteristics that were significantly associated with a lower probability of receiving rofecoxib off-label were older age (OR_{adj}=0.95; 95% CI 0.94-0.96), female gender (OR_{adj}=0.70; 95% CI 0.50-0.97), private insurance (OR_{adj}=0.71; 95% CI 0.52-0.95), and a history of prior NSAID use (OR_{adj}=0.66; 95% CI 0.51-0.93). Patients who rated their health status as 'bad' were, compared those who rated their health as 'good', more likely to receive rofecoxib off-label (OR_{adj}=3.41; 95% CI 1.75-6.65).

Conclusions: Although approved for only limited indications in 1999, GPs determined a wider clinical application for rofecoxib. Off-label prescribing of rofecoxib was extensive but not restricted to a sub-population of GPs with distinct characteristics. Therefore, when prescribing a newly marketed drug, especially for an off-label indication, GPs must be aware of the risks this may entail.

Introduction

Safety, effectiveness, and quality of new drugs are of great importance to ensure public health. To safeguard this, new drugs are subjected to licensing procedures by drug regulatory agencies. These organisations evaluate the scientific evidence for new products handed over by the manufacturer and can subsequently authorise market approval for specific indications. However, the official indication of the drug may not always be the reason for prescribing in individual cases. Moreover, because the risk-benefit ratio is unclear for off-label indications, patients may be exposed to potential danger. This is especially true for newly marketed drug since clinical evidence of long-term effectiveness and safety is still limited.

In September 2004, rofecoxib, a cyclo-oxygenase-2 (COX-2) selective inhibitor, was withdrawn from the market due to an excess risk of myocardial infarctions and strokes [1]. Rofecoxib was introduced in 1999 and had an annual sale of $2.5 billion [2]. This recent market withdrawal, reaffirmed the fact that prescribing newly marketed drugs, irrespective of its volume of use, comes with uncertainties for physicians and risks for patients [3]. In the past, several studies have shown high percentages of off-label prescribing for various drugs [4-6]. Off-label prescribing is often associated with use in patient groups for which little or no pre-registration studies have been done, like for example in neonatal and paediatric care settings [7]. The situation is different when drugs are prescribed to adults for whom other drugs are available, such as for rofecoxib. Especially with new drugs, off-label prescriptions may have a non-clinical explanation. We, therefore, hypothesise that although drug regulatory agencies authorise new drugs only for limited indications, other parties, especially physicians, will determine the real application for the new drug. This actual application may be for other indications than for which evidence is available.

We studied off-label prescribing by using rofecoxib as an example. Rofecoxib was registered in The Netherlands for the symptomatic treatment of arthritis in November 1999. It became available for reimbursement by all health insurance companies in April 2000. Meanwhile the manufacturer promoted rofecoxib by stressing its gastroprotective qualities and significant pain reduction, and had to compete with a vast number of nonsteroidal anti-inflammatory drugs (NSAIDs). While rofecoxib was registered in The Netherlands for only the indications mentioned above, internationally it was registered and prescribed for a much wider array of indications, notably primary dysmenorrhoea and the management of acute pain in adults [8]. Furthermore, during this period results from clinical studies were published in which rofecoxib was tested for postoperative dental pain [9], and rheumatoid arthritis [10]. In the light of this evidence, the Dutch Medicines Evaluation Board granted a label extension for the treatment of rheumatoid arthritis in adults (December 2001) followed by the approval for the treatment of acute pain and primary dysmenorrhoea (January 2002). This initially made rofecoxib a drug that had to gain GPs' acceptance,

while competing with a vast number of existing NSAIDs that are heavily prescribed in general practice. Because of its narrow initial indications and the wide range of applications of its market competitors, off-label use of rofecoxib was likely to occur as physicians extended rofecoxib's therapeutic applications to those used for the NSAIDs. We assessed the GP adherence to the indications of rofecoxib, as approved by the regulatory agency, and whether off-label prescribing was limited to a sub-population of GPs with distinct characteristics. Furthermore, we evaluated how GPs positioned rofecoxib by comparing the indications of rofecoxib with the indications used for the three most prescribed NSAIDs in The Netherlands, namely ibuprofen, diclofenac, and naproxen.

Methods

The analysis used data derived from the second Dutch national survey of general practice (DNSGP-2) conducted by NIVEL (Netherlands Institute of Health Services Research) in 2001 [11,12]. This survey provided background data on a patient, GP and practice level, including 2,143,558 prescriptions prescribed to 262,817 patients in 101 GP practices. The prescriptions contained diagnoses coded according to the International Classification for Primary Care (ICPC) [13]. The patient population is representative for the Dutch population concerning age, gender, and insurance. The sample of GPs is representative for all Dutch GPs regarding age, gender, region of residence, degree of urbanisation, and patient population. GPs filled out a questionnaire resulting, among other things, in data on usage of information sources about pharmacotherapy, visits from pharmaceutical representatives, hours of continuing medical education (CME), and participation in pharmacotherapy audit meeting with community pharmacists.

We used a case-control design to study the association between patient- and GP characteristics and off-label prescribing. Cases were first-time users of rofecoxib with an off-label indication; controls were first-time rofecoxib users with an on-label indication. A prescription for rofecoxib was defined as on-label when prescribed for osteoarthritis (ICPC L84, L89, L90, and L91), after December 4, 2001 rheumatoid arthritis (ICPC L88) was also an on-label indication. All other indications were regarded as off-label. Starters were defined as patients with a prescription for rofecoxib and who did not receive the drug in the previous six months.

The data were analysed using a logistic multilevel regression model with a random intercept, because of the hierarchical nature of the data. The model consisted of two levels with patients as the lower level and GPs as the higher level. A binary outcome variable was calculated using the indication of the patient's first prescription for rofecoxib. There were no data

available for the period after the label extensions for acute pain and primary dysmenorrhoea. The analyses were performed using MLwiN v1.1 [14,15].

Results

A total of 145 GPs working in 99 practices prescribed rofecoxib 5,806 times to 2,770 patients during 2001. After excluding 768 (27,7%) patients, because no diagnoses were available for their prescriptions, 2,002 patients were included in the analyses. There were no statistically significant differences between included and excluded patient concerning age, gender, and type of insurance. The 2,002 patients were treated by 125 GPs who worked in 90 practices. There were no statistical significant differences between included and excluded GPs concerning age, gender, and type of practice.

Overall, 82.6% (1,654) of the patients' first prescription contained an off-label indication. The majority of the first time users were treated for musculoskeletal related complaints (85.2% (N=1,706)), followed by 'general and unspecified' (3.2% (N=65)), 'neurological' (2.6 (N=53)) and 'digestive' (1.5% (N=31)). The indications low back symptoms without radiation (ICPC L03), shoulder syndrome (ICPC L92), and osteoarthritis of the knee (ICPC L90) were the listed the most. The top 15 indications, listed in Table 1, contains all five on-label indications, but these contribute for only 21.8% of all prescriptions. As much as 65.3% of all first-time rofecoxib users are diagnosed with an indication from the top 15 indications. For first-time users of ibuprofen, diclofenac, and naproxen this proportion was lower; 48,8% of the patients received a drug for one of the 15 indications. Only 2.8% of the patients starting on one of the three NSAIDs received it for the treatment of osteoarthritis or rheumatoid arthritis. Therefore, although rofecoxib was extensively prescribed off-label it did not spread out over as many indications as the other three NSAIDs.

Of 120 (96.0%) GPs all background data were available. 79.2% (99) was male and the average age was 47.8 years (SD=6.1). Table 2 shows the results of the multivariate logistic multilevel analysis. After adjusting for patient characteristics, no GP characteristics were associated with the extent of off-label prescribing. However, the intra-class correlation was 0.16 meaning that there was clustering of off-label prescribing among GPs. GPs that prescribed off-label to one patient also prescribed rofecoxib more often off-label to other patients.

Table 1: *The 15 indications made most in first-time rofecoxib users and the number of patients starting on ibuprofen, naproxen, and diclofenac treated for the same indications.*

Indication (ICPC-coded)	First time users of rofecoxib (N=2,002) N (%)	First time users of ibuprofen, naproxen and/or diclofenac (N=29,655) N (%)
L03 Low back symptoms/complaints without radiation	160 (8.0%)	3,906 (13.2%)
L92 Shoulder syndrome	142 (7.1%)	1,671 (5.6%)
L90 Osteoarthritis of knee	**125 (6.2%)**	**226 (0.8%)**
L88 Rheumatoid arthritis and allied conditions	**103 (5.1%)**	**288 (1.0%)**
L91 Other osteoarthritis and allied conditions	**95 (4.7%)**	**130 (0.4%)**
L20 Joint symptom/complaint NOS	89 (4.4%)	310 (1.0%)
L08 Shoulder symptoms/complaints	88 (4.4%)	1,432 (4.8%)
L99 Other disease musculoskeletal	77 (3.8%)	1,202 (4.1%)
L02 Back symptoms/complaints	76 (3.8%)	1,700 (5.7%)
L89 Osteoarthritis of hip	**69 (3.4%)**	**114 (0.4%)**
L15 Knee symptoms/complaints	65 (3.2%)	896 (3.0%)
L86 Back pain with radiating symptoms	60 (3.0%)	1,148 (3.9%)
L13 Hip symptoms/complaints	58 (2.9%)	422 (1.4%)
L18 Muscle pain	51 (2.5%)	988 (3.3%)
L84 Osteoarthritis of spine	**49 (2.4%)**	**53 (0.2%)**
Total	1,307 (65.3%)	14,480 (48.8%)

Bold: licensed indication for rofecoxib.

As for patients, those that were older were less likely to receive rofecoxib off-label compared to younger patients (OR_{adj}=0.95; 95% CI 0.94-0.96). Women were less likely to receive rofecoxib off-label than men were (OR_{adj}=0.70; 95% CI 0.50-0.97). Compared to publicly insured patients, those privately insured were less likely to receive rofecoxib off-label (OR_{adj}=0.71; 95% CI 0.52-0.95). Furthermore, patients with a history of NSAID use were less likely to receive rofecoxib off-label compared to patients with no NSAID history (OR_{adj}=0.69; 95% CI 0.51-0.93). Patients who rated their health as bad were compared to patients rating their health as good more likely to receive rofecoxib off-label (OR_{adj}=3.41; 95% CI 1.75-6.65).

Table 2: *Associations between patient or GP and off-label prescribing of rofecoxib.*

	N(%)	Adjusted OR (95% CI)
Patient characteristics	N=2,002	
Gender		
Male	549 (27.4%)	REF.
Female	1,453 (72.6%)	**0.70 (0.50-0.97)**
Age (mean;SD)	62.2 (16.3)	**0.95 (0.94-0.96)**
Insurance		
Public	1,467 (73.3%)	REF.
Private	532 (26.6%)	**0.71 (0.52-0.95)**
Medication history		
No prior use of PPIs ¶	1,704 (85.1%)	REF.
Prior use of PPIs	298 (14.9%)	1.45 (0.96-2.20)
No prior use of NSAIDs	1,433 (71.6%)	REF.
Prior use of NSAIDs	569 (28.4%)	**0.69 (0.51-0.93)**
Education		
None or primary school	594 (29.7%)	REF.
High school	820 (41.0%)	0.93 (0.69-1.26)
University	159 (7.9%)	0.70 (0.40-1.24)
Self reported health		
Good	753 (37.6%)	REF.
Average	645 (32.2%)	1.24 (0.93-1.67)
Bad	159 (7.9)	**3.41 (1.75-6.65)**
GP characteristics	N=125	
Gender		
Male	99 (79.2%)	REF.
Female	26 (20.8%)	1.66 (0.85-3.24)
Age (Mean;SD)	47.8 years (6.1)	1.01 (0.98-1.04)
Use of guidelines		
Monthly	83 (66.4%)	REF.
Weekly or daily	39 (31.2%)	1.39 (0.86-2.26)
PTAMs/year (Mean;SD)	8.7 (8.4)	1.03 (0.98-1.08)
Hours of CME/year (Mean;SD)	51.0 (13.7)	1.05 (0.95-1.16)
Oral information sources		
None	18 (14.4%)	REF.
1	30 (24.0%)	1.44 (0.74-2.81)
2	35 (28.0%)	1.81 (0.90-3.63)
3	37 (29.6%)	0.98 (0.52-1.85)
Number of visits by drug reps per month (Mean;SD)	3.5 (3.0)	1.01 (0.65-1.57)
Type of office		
Solo	50 (40.0%)	REF.
Duo	29 (23.2%)	1.08 (0.62-1.88)
Group	46 (36.8%)	1.01 (0.57-1.79)
Dispensing		
No	110 (88.0%)	REF.
Yes	15 (12.0%)	1.09 (0.52-2.26)
Deprived area		
No	114 (91.2%)	REF.
Yes	11 (8.8%)	1.57 (0.58-4.25)
Workload (patients per FTE)	2,607 (SD=601)	0.99 (0.94-1.04)

Numbers do not add up due to missing data.
¶ Proton pump inhibitors

Discussion

For new drugs entering crowded markets, such as the market for anti-inflammatory and pain medication, it is essential to display a real or at least a perceived advantage over direct competitors to gain a viable market share. To safeguard proper use of new products, physicians should be reserved in prescribing. For rofecoxib, two phenomena emerged namely the high extent of off-label use and the prescribing while evidence was advocating restraint. In previous studies, we identified patterns of channelling of rofecoxib in high-risk patients [16-19].

A perceived improved safety or effectiveness of rofecoxib over conventional NSAIDs may be reasons for GPs to incorporate new drugs into their personal evoked set and subsequently allows the drug to diffuse into the market. The high percentage off-label may partly be a reflection of the GP's perception that rofecoxib offered a gastrointestinal safety over conventional NSAIDs. Furthermore, due to its similarity with other NSAIDs GPs may have been more confident in prescribing rofecoxib and extended its clinical application to those of the NSAIDs. This is in line with other studies [20,21]. Cutts et al. found in a study among 72 Australian GPs that in 30.6% of the patients, gastrointestinal side effects from conventional NSAIDs were a reason for prescribing rofecoxib. In 23.8% of the cases GPs had the perception of rofecoxib as a safer alternative for conventional NSAIDs [20].

After the initial introduction of a new drug on the market, the drug starts to exhibit its own unique fingerprint. This fingerprint is a reflection of its application in daily practice and is shaped by among other things the accumulation of scientific evidence, reported side effects, label changes, and patients treated [22,23]. GPs are important factors in establishing the fingerprint of rofecoxib [24]. The indications for rofecoxib were broadened in The Netherlands with the use for acute pain and primary dysmenorrhoea in January 2002. However, GPs seemed to anticipate the label extension a year earlier. Although GPs anticipated this label extension, during the period that rofecoxib was on the market there were discussions about the side effects of the COX-2 inhibitors, such as gastro-intestinal side effect [25,26], cardiovascular events [27], and possible pro-thrombotic risk [28] that eventually led to the voluntary withdrawal of rofecoxib. This accumulation of scientific evidence should have made GPs reluctant to prescribe rofecoxib.

The existing NSAIDs not only influenced the market penetration of rofecoxib, but also influenced the range of applications of rofecoxib as can be concluded from off-label indications. However, although rofecoxib was widely prescribed off-label, we found that it was not prescribed for as many indications as the widely prescribed NSAIDs ibuprofen, diclofenac, and naproxen. Fifteen indications, including the five on-label indications, accounted for 65.3% of the patients starting on rofecoxib. These 15 indications accounted

for 48.8% of new users of the three most prescribed NSAIDs. Not all patients were as likely to receive rofecoxib for an off-label indication. Older, female patients with a history of prior NSAID use and private insurance are less likely to receive rofecoxib for other indications than osteoarthritis and rheumatoid arthritis. Possible explanations for these findings may lie in the fact that the prevalence of both diseases increases with age and that rheumatoid arthritis affects more women [29]. These patients are likely to have a history of NSAID use. The finding that patients who rate their own health as bad and receive rofecoxib more off-label may be due to increased co-morbidity.

The multilevel analyses showed some clustering of off-label prescribing within certain GPs. The intra-class correlation was 0.16, meaning that 16% of the variation in off-label prescribing was caused by differences between GPs. Therefore, other GP characteristics that were not included in the analyses may explain the variation in off-label prescribing.

In The Netherlands, there were no restrictions for GPs to prescribe rofecoxib. Reimbursement is not diagnosis dependent and therefore there is no incentive for Dutch GPs to code off-label prescriptions as on-label. The high percentage off-label may also be related to the marketing efforts of the producer of rofecoxib. During the marketing campaign for rofecoxib, the COX-2 specificity of the drug was stressed suggesting less gastrointestinal side effects [30]. This perceived advantage might have made GPs to decide to prescribe rofecoxib to patients with gastrointestinal complaints or to those who are susceptible for it. Although the number of drug representatives seen by the GP is not associated with off-label prescribing this does not mean that the marketing is ineffective. Another possible explanation for the high percentage off-label is that GPs code the prescriptions using the complaints of the patients rather than the true diagnosis. To minimise the effect of wrong coding, GPs who participated in the DNSGP-2 were instructed before the study to code diagnosis only when they felt certain. However, it is not unlikely that a GP diagnosed a patient with vague musculoskeletal complaints and changes the diagnosis to osteoarthritis or rheumatoid arthritis after subsequent consults.

There are several caveats in interpreting the outcomes of this study. Firstly, only off-label prescribing of rofecoxib was studied. Therefore, no generalisations can be made about off-label prescribing of other drugs. Secondly, since the study used data from the DNSGP-2 only data on prescriptions of GPs were available. Although representative for all Dutch GPs and the patient population, prescriptions of medical specialists were not registered during the DNSGP-2. Therefore, the influence of medical specialists on the prescribing of rofecoxib by GPs could not be taken in to account.

Conclusions

Although registration authorities approved market introduction of rofecoxib for only limited indications in 1999, GPs determined a wider clinical application for rofecoxib, continued prescribing while scientific evidence advocated restrained. Off-label prescribing of rofecoxib was extensive but not restricted to a sub-population of GPs with distinct characteristics. Therefore, when prescribing a newly marketed drug, especially for off-label indications, GPs must be aware of the risks this may entail.

Chapter 4.2

Patient characteristics associated with prescribing of a newly introduced drug: *the case of rofecoxib*

Stefan R. Florentinus [1], Merete W. Nielsen [1,2], Liset van Dijk [3], Hubert G.M. Leufkens [1], Ebba H. Hansen [2,4], Eibert R. Heerdink [1]

[1] Utrecht University,
Division of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht, The Netherlands.

[2] The Danish University of Pharmaceutical Sciences,
Department of Social Pharmacy,
Copenhagen, Denmark.

[3] NIVEL (Netherlands Institute for Health Services Research),
Utrecht, The Netherlands.

[4] FKL (Research Centre for Quality in Medicine Use),
Copenhagen, Denmark.

Eur J Clin Pharmacol, 2005. 61(2):p.157-159

Abstract

Background: Selective prescribing of new drugs shortly after marketing may jeopardise a soft landing of the new agent in medical practice and may place patients in avoidable risks.

Objective: To identify sociodemographic characteristics of the first patients receiving the new drug rofecoxib.

Methods: Matched case-control design. The main outcome measure was starting on rofecoxib or another nonsteroidal anti-inflammatory drug (NSAID) and who did not receive any other NSAIDs the 90 days before starting.

Results: Starting on rofecoxib was associated with an increasing age (OR_{adj}=in age 80 and older = 8.7; 95% CI 6.7-11.2), a poor self-perceived health (OR_{adj}=2.4; 95% CI 1.8-3.3), female gender (OR_{adj}=1.4; 95% CI 1.2-1.6), private insurance (OR_{adj}=1.3; 95% CI 1.1-1.5), and previous acetaminophen use (OR_{adj}=1.3; 95% CI 1.1-1.7).

Conclusions: This study noted that specific patient characteristics were associated with getting rofecoxib prescribed shortly after marketing. GPs should be aware of selective prescribing new drugs to specific patients because it may place patients at unintentional and avoidable risk.

Introduction

Reasons for general practitioners (GPs) to prescribe new drugs may vary from an ongoing pursuit of alternative therapies for patients refractory to existing medications to a plethora of erratic market forces, such as industry promotion and reimbursement [1-4]. In an 'ideal' world, each prescribing decision would be based on careful weighing of the benefits, risks, and costs of the new agent in the context of alternative options. Various studies have focused on quantification and characterisation of physicians responsible for early prescriptions for new drugs [5-8]. To date, little attention has been paid to socio-demographic characteristics of the first patients receiving the new drugs. We chose the introduction of rofecoxib to study such patient factors. Rofecoxib was launched in The Netherlands for the symptomatic treatment of osteoarthritis in November 1999. The aim of this study was to identify early users of rofecoxib by socio-demographic characteristics. The reason for choosing rofecoxib was that we expected to find effects of patients on the decision to prescribe because of its marketing and similarity to the existing nonsteroidal anti-inflammatory drugs (NSAIDs) [9]. We hypothesised that patients with higher social economic status would be more likely to get rofecoxib prescribed.

Methods

We obtained data from the second Dutch national survey of general practice (DNSGP-2) conducted by NIVEL (Netherlands Institute for Health Services Research) in a representative sample of 195 Dutch GPs in 104 practices and 385.461 listed patients in 2001 [10,11]. These data provided background information on practice, GP, and patient level, including prescription data. Patient data included socio-demographic factors such as educational status, type of insurance and self-reported health. Patients were asked to rank their health on a 5-points Likert scale ranging from 'very bad' to 'very good'. For educational status, we used the highest completed level of education. The prescription database contained 57,381 NSAID-users. We compared the starters on rofecoxib (N=954) with patients starting on other non-selective cyclo-oxygenase inhibitors NSAIDs (N=25,231). Starters were defined as patients who did not receive a prescription for a NSAID during the 90 days before starting on either rofecoxib or another NSAID. Logistic regression analysis was applied to estimate odds ratios (OR) including 95% confidence intervals (CI) of characteristics in patients starting on rofecoxib compared with patients starting other NSAIDs.

Results

In total, 99 GPs working in 101 practices prescribed rofecoxib during the study period. We noted that rofecoxib starters were more likely to be elderly (OR_{adj} in age 80 and older 8.7; 95% CI 6.7-11.2) and patients with a poor self-perceived health (OR_{adj}=2.4; 95% CI 1.8-3.3). Furthermore, rofecoxib starters were more frequently female (OR_{adj}=1.4; 95% CI 1.2-1.6), privately insured (OR_{adj}=1.3; 95% CI 1.1-1.5), and previous paracetamol users (OR_{adj}=1.3; 95% CI 1.1-1.7). Moreover, rofecoxib starts were also more frequently seen in patients with a higher education although this association diminished after adjustment for other variables in Table 1.

Discussion

Immediately following product launch, the diffusion of rofecoxib showed a steep adoption curve. There has been ample public debate about the effectiveness and safety of rofecoxib [12-16]. Concerns regarding cardiovascular safety in high-risk patients, in particular the elderly with poor health and other co-morbidity evolved [17]. However, our data show that rofecoxib was preferentially prescribed to such patients. In previous work, we have identified patterns of 'channelling' of NSAIDs in susceptible patients as threats to patient safety [18]. Industry promotion of the preferable profile of the new drug, in particular for patients with a poor response to existing therapies, is an important factor [3]. Although direct-to-consumer advertisement is still prohibited in The Netherlands, the role of patients should not be underestimated. GPs have reported that patients often request rofecoxib in particular [3]. Our data show that private insurance is associated with receiving rofecoxib, but this only partly supports our hypothesis about patients with a higher social economic status were more likely to start on rofecoxib. The finding that previous paracetamol use was associated with starting on rofecoxib may be explained by the wish of GPs to provide gastroprotection. In the Dutch health care system, privately insured patients, about 25% of the population, have a higher income, but are frequently not fully insured, unless under various co-payment schemes. The reimbursement of rofecoxib is not limited to any type of insurance, age category, or indication.

Conclusions

We found that specific patient characteristics were associated with receiving a prescription for rofecoxib shortly after marketing. GPs should be aware of selective prescribing new drugs to specific patients because it may place patients at unintentional and avoidable risk.

Table 1: *Rofecoxib starters compared to other NSAID starters. Prevalence (%) and results of logistic regression analyses expressed as crude and adjusted OR and 95% confidence intervals.*

	Rofecoxib (N=954) N (%)	**NSAID (N=25,231) N (%)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)**
Gender				
Male	321 (33.6%)	11.303 (44.8%)	REF.	REF.
Female	633 (66.4%)	13.928 (55.2%)	**1.6 (1.4-1.8)**	**1.4 (1.2-1.6)**
Age				
25-44	140 (14.7%)	10,543 (41.8%)	REF.	REF.
45-64	355 (37.2%)	9,985 (39.6%)	**2.7 (2.2-3.3)**	**2.5 (2.0-3.0)**
65-79	309 (32.4%)	3,706 (14.7%)	**6.3 (5.1-7.7)**	**5.5 (4.4-6.8)**
80 years and older	150 (15.7%)	997 (4.0%)	**11.3 (8.9-14.4)**	**8.7 (6.7-11.2)**
Insurance				
Public	668 (70.0%)	18,496 (73.3%)	REF.	REF.
Private	286 (30.0%)	6,735 (26.7%)	**1.2 (1.0-1.4)**	**1.3 (1.1-1.5)**
Educational status				
University	76 (8.0%)	2,870 (11.4%)	REF.	REF.
Secondary school	414 (43.4%)	1,1641 (46.1%)	**0.6 (0.5-0.7)**	1.1 (0.9-1.3)
None or primary school	261 (27.4%)	4,124 (16.3%)	**0.4 (0.3-0.5)**	0.9 (0.7-1.2)
Unknown	203 (21.3%)	6,596 (26.1%)	**0.5 (0.4-0.6)**	1.0 (0.7-1.3)
Self reported health				
Good	384 (40.3%)	1,3141 (52.1%)	REF.	REF.
Moderate	292 (30.6%)	4,255 (16.9%)	**2.3 (2.0-2.7)**	**1.7 (1.4-2.0)**
Poor	63 (6.6%)	653 (2.6%)	**3.3 (2.5-4.4)**	**2.4 (1.8-3.3)**
Unknown	215 (22.5%)	7,182 (28.5%)	1.0 (0.9-1.2)	1.2 (0.9-1.7)
Previous use of paracetamol				
No	862 (90.4%)	24,245 (96.1%)	REF.	REF.
Yes	92 (9.6%)	986 (3.9%)	**2.6 (2.1-3.3)**	**1.3 (1.1-1.7**

Chapter 4.3

The trade-off between cardiovascular and gastrointestinal effects of rofecoxib

Stefan R. Florentinus [1], Eibert R. Heerdink [1], Antonius de Boer [1], Liset van Dijk [2], Hubert G.M. Leufkens [1]

[1] Utrecht University,
Division of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht, The Netherlands.

[2] NIVEL (Netherlands Institute for Health Services Research),
Utrecht, The Netherlands.

Pharmacoepidemiol Drug Saf, 2005. 14(7):p.437-41

Abstract

Background: The COX-2 inhibitor rofecoxib was registered in 1999. By 2000, the first reports were published indicating that the agent was possibly associated with an increased risk of myocardial infarction. Since then a surge of data supporting this association has become available. To interpret these data it is essential to ascertain the cardiovascular risk profile of users of rofecoxib relative to other NSAID recipients.

Objective: To assess differences in cardiovascular risk between starters of rofecoxib versus starters of any other NSAID.

Methods: Data were sampled from a representative research network of Dutch general practitioners in 2001. New users (starters) of rofecoxib were compared to starters of any other NSAID, unmatched and matched on age, gender and indication nested in the cohort of the second Dutch National Survey of General Practice.

Results: A total of 40.4% of patients starting on rofecoxib had cardiovascular co-morbidity. Patients starting on rofecoxib were twice more likely to have a history of gastrointestinal morbidity, compared to patients starting on other NSAIDs (OR_{adj}=2.09; 95% CI 1.65-2.66). These patients were also more likely to have cardiovascular co-morbidity (OR=1.90; 95% CI 1.60-2.24) compared to recipients of rofecoxib with no gastrointestinal co-morbidity. Cardiovascular morbidity was present at the time of rofecoxib exposure in over 61% of carriers of a composite risk profile including age 60 years or older, gastrointestinal co-morbidity and diagnosis of rheumatoid arthritis and osteoarthritis.

Conclusions: In general, a typical recipient of an NSAID is aged and carrier of a serious cardiovascular risk profile. Selective prescribing of rofecoxib to provide gastroprotection, indirectly and unintentionally resulted in prescribing rofecoxib in a population with high frequencies of cardiovascular morbidities.

Introduction

The risk-benefit balance of new drugs is of great importance to ensure public health. To safeguard this, new drugs are subjected to licensing procedures by drug regulatory agencies. These organisations evaluate the scientific evidence for new products handed over by the manufacturer and can subsequently authorise market approval. However, the post-marketing clinical application of the drug is shaped by several factors, such as the dissemination of new scientific evidence about safety and efficacy and the subsequent reaction of doctors and patients. In 1999, rofecoxib, a nonsteroidal anti-inflammatory drug (NSAID) that selectively inhibits cyclo-oxygenase-2 (COX-2) was introduced as the first representative of the COX-2 inhibitors. The idea that COX-2 causes the anti-inflammatory effects and COX-1 the gastrointestinal (GI) side effects led to the development of drugs selectively blocking COX-2 [1,2]. Since the results of the Vioxx Gastrointestinal Outcomes Research (VIGOR) study were published on November 23rd, 2000 the cardiovascular safety profile of rofecoxib has been questioned [3]. The VIGOR-study showed a gastroprotective effect of rofecoxib over naproxen, but also a five-fold higher incidence of myocardial infarction in the rofecoxib group. This finding fuelled the ongoing discussion about the trade-off between the cardiovascular risk and gastrointestinal protective effects of COX-2 inhibitors [3-6]. Meanwhile, the gastrointestinal safety was the spearhead of the marketing campaigns, resulting in an estimated 80 million users world-wide and US$2.5 billion in sales in 2003 [7]. September 30, 2004 rofecoxib was withdrawn from the market after the APPROVE-study had shown a twofold increased risk of myocardial infarctions and strokes in rofecoxib patients compared to placebo [8]. In the aftermath of the withdrawal of rofecoxib, a passionate debate has been held about the regulatory and clinical consequences [8,7]. A fundamental question underlying the full understanding of this safety issue is the a priori cardiovascular risk of patients starting with the drug, particularly in the context of a trade-off between GI- and cardiovascular risk factors [4].

Methods

Data sources

We used prescribing data of general practitioners (GPs) who participated in the second Dutch national survey of general practice (DNSGP-2) [9,10]. The NIVEL (Netherlands Institute for Health Services Research) conducted the DNSGP-2 among 195 GPs, practising in 104 practices, and 385.461 patients in 2001. The GPs were considered representative for all Dutch GPs (N=7,217). No statistically significant differences for age, gender, region of residence and urbanization were found. The patients captured by the 104 practices were a good representation of the Dutch population on age, gender, and type of health insurance [10]. All eligible patients were approached to co-operate in a census to determine among other things their socio-demographic characteristics, including their self-reported health. Computerized

clinical and prescribing data, including ICPC-coded (International Classification of Primary Care) diagnoses [11], were obtained. The DNSGP-2 was conducted nine months after the introduction of rofecoxib in The Netherlands.

Study design

We compared patients starting on rofecoxib with patients starting on any other NSAID. The date of the first prescription in the study period for either rofecoxib or another NSAID was defined as the index date. Starting was defined as a prescription for rofecoxib or another NSAID and no prescription for the same type of drug the six months before the index date. In The Netherlands, medicines are dispensed for a maximum of three months. Due to differences in age, gender and diagnosis between the group of patients starting on rofecoxib or any other NSAID the comparison was conducted unmatched as well as matched on age, gender and indication. Rofecoxib's initial licensed indication was the treatment of osteoarthritis. In December 2001, a label extension for the treatment of rheumatoid arthritis was granted, followed by the approval for the treatment of acute pain and primary dysmenorrhoea in January 2002.

In order to assess the patient's cardiovascular and GI co-morbidity a time window of six months around the index date was used. Cardiovascular co-morbidity was defined as receiving a prescription with a diagnosis from ICPC chapter 'K' (Circulatory), except 'K95' (Haemorrhoids) and 'K96' (Varicose veins of leg) or a drug with an ATC-code starting with 'C' (Cardiovascular system). GI co-morbidity was estimated by using ICPC-codes 'D02' (Abdominal pain epigastric), 'D03' (Heartburn), 'D84' (Oesophagus disease), 'D85' (Duodenal ulcer), 'D86' (Peptic ulcer other), 'D87' (Stomach function disorder), and 'D90' (Hiatus hernia) and the ATC-code 'A02' (Drugs for acid related disorders).

Results

A total of 2,770 patients received rofecoxib during the study period, of whom 1,655 (59.7%) patients could be defined as newly starting on rofecoxib. Of these patients 1,505 (90.9%) started on a daily dose of 25mg, 120 patients started on 12.5mg (7.3%) and 30 patients (1.8%) started on a daily dose of 50mg or more. Only 15.3% of the patients starting on rofecoxib received it for the in 2001 licensed indications osteoarthritis and rheumatoid arthritis. A total of 31,403 patients were defined as new starters on any other NSAID. Most patients started on diclofenac (44.1%), ibuprofen (24.5%), or naproxen (20.2%), which are the three most frequently prescribed NSAIDs in The Netherlands.

The characteristics of all patients newly starting on rofecoxib or any other NSAID are shown in Table 1. Clear differences were noted between starters on rofecoxib and all other starters on any other NSAID. Gastrointestinal (OR_{adj}=2.00; 95% CI 1.73-2.30) and

cardiovascular co-morbidity (OR_{adj}=1.19; 95% CI 1.04-1.36) were more common among patients starting on rofecoxib. Furthermore, rofecoxib was more often prescribed to older (mean age 60.9 vs. 46.6 years) and female (OR_{adj}=1.43; 95% CI 1.26-1.62) patients, who reported their own health as bad (OR_{adj} compared to good=1.93; 95% CI 1.52-2.44). Osteoarthritis and rheumatoid arthritis were diagnosed more frequently in patients starting on rofecoxib (OR_{adj}=4.39; 95% CI 3.64-5.27) than in starters on any other NSAID.

The discrepancies in gastrointestinal and cardiovascular co-morbidity between starters on rofecoxib and any other NSAID might be caused due to differences in age, gender and indications. However, pair wise comparison using a conditional logistic regression model revealed significant differences in gastrointestinal co-morbidity and self-reported health. Table 2 shows the characteristics of starters on rofecoxib or other NSAIDs, matched on age, gender and indication. Patients starting on rofecoxib were twice as likely to have gastrointestinal complaints, compared to patients starting on other NSAIDs (OR_{adj}=2.09; 95% CI 1.65-2.66). Cardiovascular co-morbidity was univariately associated with starting on rofecoxib (OR=1.34; 95% CI 1.15-1.56), but after adjusting for the other covariates the association became weaker (OR_{adj}=1.22; 95% CI 0.991.49). Still 40.3% of the patients starting on rofecoxib had cardiovascular co-morbidity.

Table 1: *Characteristics of patients newly starting on rofecoxib or any other NSAID.*

	Rofecoxib N (%)	**Any other NSAID N (%)**	**OR (95% CI)**	**Adjusted OR (95% CI)**
Nr. of patients	1,655	31,403		
Gender				
Male	506 (30.5%)	13,644 (43.4%)	REF.	REF.
Female	1,149 (69.4%)	17,759 (56.6%)	**1.7 (1.6-1.9)**	**1.43 (1.26-1.62)**
Age (SD) (increase per 10 years)	60.9 (16.4)	46.6 (17.5)	1.0 (1.0-1.0)	**1.04 (1.03-1.04)**
Indication				
Other	1,401 (84.7%)	30,709 (97.8)	REF.	REF.
RA and OA	254 (15.3%)	694 (2.2%)	**8.0 (6.9-9.4)**	**4.39 (3.64-5.27)**
Self-reported health				
Good	658 (51.5%)	13,262 (42.2%)	REF.	REF.
Average	512 (30.9%)	5,034 (16.0%)	**2.5 (2.2-2.8)**	**1.46 (1.28-1.66)**
Bad	108 (6.5%)	773 (2.5%)	**3.5 (2.8-4.3)**	**1.93 (1.52-2.44)**
Cardiovascular co-morbidity				
No	986 (59.6%)	25,312 (80.6%)	REF.	REF.
Yes	669 (40.4%)	6,091 (19.4%)	**2.8 (2.5-3.1)**	**1.19 (1.04-1.36)**
Gastrointestinal co-morbidity				
No	1,211 (73.2%)	28,295 (90.1%)	REF.	REF.
Yes	444 (26.8%)	3,108 (9.9%)	**3.3 (3.0-3.7)**	**2.00 (1.73-2.30)**

Table 2: *Characteristics of patients newly starting on rofecoxib or any other NSAID - matched on age, sex, and indication.*

	Rofecoxib N (%)	**Any other NSAID N (%)**	**OR (95% CI)**	**Adjusted OR (95% CI)**
Nr. of patients	1,640	1,640		
Gender				
Male	497 (30.3%)	497 (30.3%)	Matched on	
Female	1,143 (69.7%)	1,143 (69.7%)		
Age (SD)	60.8 (16.3)	60.8 (16.3)	Matched on	
Indication				
Other	1,399 (85.3%)	1,399 (85.3%)	Matched on	
RA and OA	241 (14.7%)	241 (14.7%)		
Self-reported health *				
Good	652 (39.8%)	763 (46.5%)	REF.	REF.
Average	506 (30.9%)	408 (24.9%)	**1.35 (1.11-1.64)**	**1.25 (1.02-1.52)**
Bad	108 (6.6%)	56 (3.4%)	**2.09 (1.44-3.04)**	**1.82 (1.24-2.67)**
Cardiovascular co-morbidity				
No	979 (59.7%)	1,074 (65.5%)	REF.	REF.
Yes	661 (40.3%)	566 (34.5%)	**1.34 (1.15-1.56)**	1.22 (0.99-1.49)
Gastrointestinal co-morbidity				
No	1,198 (73.0%)	1,399 (85.3%)	REF.	REF.
Yes	442 (27.0%)	241 (14.7%)	**2.27 (1.88-2.74)**	**2.09 (1.65-2.66)**

* Numbers do not add up due to missing values.

Table 3: *Association between cardiovascular co-morbidity and risk factors for NSAID or rofecoxib prescribing.*

	Nr. patients	% Cardiovascular
Co-morbidity		
No risk factors	22,523	9.9% (2,235)
Age ≥ 60	8,197	48.6% (3,986)
Age ≥ 60 + GI co-morbidity	1,587	61.0% (968)

Among all matched patients, cardiovascular co-morbidity was higher among those with gastrointestinal co-morbidity, compared to patients with no gastrointestinal co-morbidity (OR=1.90; 95% CI 1.60-2.24). The clinical profile of a typical rofecoxib user (with GI co-morbidity and age>60) results in prescribing these drugs to patients with cardiovascular co-morbidity. The percentage of patients with cardiovascular co-morbidity increased to 61.0% when rofecoxib or any other NSAID is prescribed to patients older than 60 years with GI morbidity (Table 3).

Discussion

The primary objective of this study was to assess differences in cardiovascular and gastrointestinal co-morbidity between patients starting on rofecoxib versus starters on any other NSAID. Our findings show that Dutch GPs prescribed rofecoxib in 2001 more often to patients with gastrointestinal co-morbidity, as expected based on the claimed differential GI risk of the COX-2 inhibitors, also leading to a surplus of cardiovascular morbidity in these patients.

For new drugs entering crowded markets, such as the market for anti-inflammatory and pain medication, it is essential to display a real or at least a perceived advantage over its direct competitors to gain a viable market share [12]. The higher percentage of gastrointestinal co-morbidity among starters on rofecoxib was expected and in line with other studies [13-15]. Cutts et al. found in a study among 72 Australian GPs that in 30.6% of the patients gastrointestinal side effects from conventional NSAIDs were reasons for prescribing rofecoxib. In 23.8% of the cases, GPs had the perception of rofecoxib as a safer alternative for conventional NSAIDs [13].

The legitimate reasons for prescribing rofecoxib to patients susceptible to gastrointestinal adverse effects, namely older patients with gastrointestinal co-morbidity, and morbidities like osteoarthritis and rheumatoid arthritis, consequently fuelled prescribing of rofecoxib to patients with cardiovascular co-morbidity. Therefore, the trade-off between gastrointestinal and cardiovascular safety is affected even when only considering gastroprotection.

In a recent meta-analysis, Jüni et al. argued that already at the end of 2000 enough evidence was available to conclude that rofecoxib caused an increased risk of myocardial infarction [6]. Some of the studies used by Jüni et al. in their meta-analysis were never published so it is unlikely that GPs in 2001 had a complete picture of the risk-benefit ratio of rofecoxib. However, in 2000 the results of the VIGOR-study noted a five-fold higher incidence of myocardial infarction for rofecoxib compared to naproxen [3]. The differences in cardiovascular risk were attributed to the cardioprotective effects of naproxen rather than to cardiotoxic properties of rofecoxib. The discussion about the trade-off between gastroprotection and cardiotoxicity was further encouraged by other studies [16] iterating the protective effect of naproxen, while others advocated the opposite [17]. Our findings show that the percentage of patients with cardiovascular co-morbidity among those starting on rofecoxib was higher than in patients starting on any other NSAID. Perhaps due to conflicting reports about the cardiovascular safety of rofecoxib, and therefore the absence of unequivocal evidence in 2001, cardiovascular safety was not reflected in the decision to prescribe rofecoxib. The finding that only 15.3% of the patients received rofecoxib for approved and licensed indications strengthens this notion.

Several studies showed that rofecoxib was channelled towards patients with high-risk of gastrointestinal haemorrhage [18,19] and congestive heart failure [20]. What this study shows is that the channelling of rofecoxib into patients with cardiovascular co-morbidity was partly the result of a focus on gastrointestinal safety and the clustering of cardiovascular co-morbidity in patients with gastrointestinal co-morbidity.

The results of this study need to be interpreted in light of its limitations. For this study, we used prescribing data of GPs. Although representative for all Dutch GPs and the patient population, prescriptions of hospital specialists were not captured in the data. Some of the patients starting on rofecoxib or another NSAID may have received a prescription of a hospital specialist before the index date. This may have led to misclassification by defining patients as starters. However, GPs adopted rofecoxib instantly and by 2001 rofecoxib alone contributed for 6.1% to the total volume of for NSAIDs prescribed in The Netherlands [21].

Conclusions

As expected gastrointestinal co-morbidity was more common among patients starting on rofecoxib. Selective prescribing of rofecoxib to provide gastroprotection, indirectly and unintentionally resulted in the channelling of rofecoxib in more severely ill patients with cardiovascular risk factors relevant to take into account when weighing the pros and contras of COX-2 inhibitors against other NSAIDs.

Chapter 4.4

The use of rosuvastatin shortly after marketing

Stefan R. Florentinus, Eibert R. Heerdink, Olaf H. Klungel, Antonius de Boer

Utrecht University,
Division of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences (UIPS),
Utrecht, The Netherlands.

An adjusted version was published in Lancet, 2004.364(9445):p.1577

Abstract

Background: Even prior to its market introduction rosuvastatin was surrounded by controversy regarding its safety profile. In light of this controversy, it is important to see what the attitude of clinical practice was towards prescribing of rosuvastatin and which patients were the first users of this new agent.

Objective: To describe the uptake of rosuvastatin in general practice.

Methods: Early prescribing of rosuvastatin was analysed using dispensing data from patients who participated in the second Dutch national survey of general practice (DNSGP-2). All patients who received a prescription for rosuvastatin from both general practitioners and medical specialists during the first nine months following rosuvastatin's market introduction were included in the study.

Results: In over one third of all decisions to initiate a (new) statin therapy, the choice for the latest drug on the market was made, not only for patients with lack of effect on previous lipid-lowering drugs but over 40% for de novo patients. Over 90% of patients use rosuvastatin in a maximum daily dosage of 10 mg or 20 mg, limiting the renal risk associated with high dosages. However, at least 22.9% of patients that use rosuvastatin have additional risk factors for myopathy or rhabdomyolysis.

Conclusions: Given the yet unproven safety record of rosuvastatin, it is of concern that both general physicians and specialists are so keen to prescribe a new drug in such large groups of patients who often have had no previous experience with lipid lowering drugs, and in many cases have predisposing risk-factors for a potentially lethal side effect.

Introduction

The rapid prescribing of new drugs fuels the ongoing discussion about the trade-off between the wish to treat patients more effectively and ensuring the patient's safety [1,2]. Despite positive contributions of new drugs to the treatment of many diseases, about 10% of the new chemical entities approved in the USA between 1975-1999 acquired a new black box warning or were withdrawn [3]. More recently, reported side effects of two rapidly adopted new drugs again raised questions about early new drug prescribing and drug safety, which has lead to a debate about promotional activities by pharmaceutical companies [4-8].

In March of 2003 rosuvastatin, a HMG-CoA reductase inhibitor or statin, was marketed as one of the most potent lipid lowering agents available on the market [7,8]. Its initial indication covered primary hypercholesterolemia and homozygous familial hypercholesterolemia [9]. However, even before market introduction rosuvastatin was surrounded by controversy regarding its safety profile, suggesting an increased risk of proteinuria and heamaturia with increased rosuvastatin dose, as well as a possibly higher rate of reports of rhabdomyolysis [7,10]. In June 2004, important safety information was made available by the registration authorities stressing to be aware of predisposing factors for myopathy/rhabdomyolysis, such as among other things, renal impairment, hypothyroidism, age above 70 years, and concomitant use of fibrates [9]. In previous studies, it was shown that newly marketed drugs are often prescribed by only a small fraction of physicians, and possibly channelled into an idiosyncratic patient group [11-13].

In light of the controversy surrounding rosuvastatin and the given previous concerns about the safety of another potent statin cerivastatin that eventually led to its withdrawal from the global pharmaceutical market, it is important to see what the attitude is in clinical practice towards prescribing and which patients are the first users of rosuvastatin. Therefore, the aim of this study is to describe the uptake of rosuvastatin in primary care.

Method

This study used dispensing data from patients who participated in the second Dutch national survey of general practice (DNSGP-2) [14-16]. In 2000, NIVEL (Netherlands Institute for Health Services Research) launched the DNSGP-2 to obtain up-to-date and national representative data on Dutch general practice. The rationale and design of the DNSGP-2 is discussed in detail elsewhere [17,16]. The patient dispensing histories were collected through the network of SFK (Foundation for Pharmaceutical Statistics) and covered the period January 1999 untill December 2003 [18]. Because virtually all patients in The Netherlands designate a single pharmacy to fill prescriptions from GPS or hospital specialists, dispensing data provide a complete account of drug exposure in time [19].

Study design

For this study, we selected all patients who received a prescription for rosuvastatin during the first nine months following rosuvastatin's market introduction. Market introduction was defined as the date of the first prescription for rosuvastatin in the database. The date on which the patient received his/her first prescription for rosuvastatin was defined the index date. We recorded the type of prescriber (GP versus medical specialist) of the prescription and the patient's age on the index date. The maximum prescribed dose the patient received during the study period was obtained using all prescriptions for rosuvastatin following the index date. By using the patient's dispensing history, we were able to assess the presence of predisposing factors for myopathy/rhabdomyolysis other than the age, namely concomitant use of fibrates (ATC-code=C10AB) and levothyroxin (ATC-code=H03AA01) for hypothyroidism. In addition, we assessed whether patients starting on rosuvastatin had a history of other lipid lowering drugs (LLD) (ATC-code=C10A) use prior to the index date.

Results

In total, 599 patients were identified in which rosuvastatin was prescribed during our study period of which 275 (45.9%) were woman and the average age was 59.3 (SD=11.9) years. Interestingly, we noted that 251 (41.9%) patients had no previous use of lipid lowering drugs (Table 1). Most of the patients (67.4%) used a maximum daily dose of 10 mg, and only 2 patients (0.3%) used a daily dose of 80 mg. Rosuvastatin is not recommended for patients with predisposing factors for myopathy/rhabdomyolysis, including concurrent use of fibrates, hypothyroidism and age above 70 years. However, we found concurrent fibrate use in 14 patients (2.3%), concurrent levothyroxin use in 4 patients (0.7%) and 124 patients (20.7%) that were aged 70 years or older. This resulted in a total of 137 (22.9%) patients on rosuvastatin with additional risk factors for rhabdomyolysis. For 50 (36.5%) of the 137 patients at increased risk for rhabdomyolysis, rosuvastatin was the first lipid-lowering drug they used.

Table 1: *Characteristics of patients using different maximum doses of rosuvastatin in the first nine months after market introduction.*

		Maximum daily dose			
	N (%)	**10 mg**	**20 mg**	**40 mg**	**80 mg**
Number of patients	599 (100.0%)	404 (100.0%)	146 (100.0%)	47 (100.0%)	2 (100.0%)
No previous use of LLD	251 (41.9%)	198 (49.0%)	46 (31.5%)	7 (14.9%)	0 (0.0%)
Prescribed by specialist	271 (45.2%)	157 (38.9%)	81 (55.5%)	32 (68.1%)	1 (50.0%)
Aged over 70 years	124 (20.7%)	97 (24.0%)	22 (15.1%)	5 (10.6%)	0 (0.0%)
Concomitant use of fibrates	14 (2.3%)	5 (1.2%)	6 (4.1%)	3 (6.4%)	0 (0.0%)
Concomitant use of levothyroxin	4 (0.7%)	0 (0.0%)	0 (0.0%)	4 (8.5%)	0 (0.0%)

Discussion

The primary objective of this study was to describe the uptake of rosuvastatin in primary care shortly after market introduction. Our findings show a very rapid adoption of rosuvastatin by prescribers directly following introduction. In over one third of all decisions to initiate a (new) statin therapy, the choice for the latest drug on the market was made, not only for patients with lack of effect on previous lipid lowering drugs, but over 40% for de novo patients. Over 90% of patients use rosuvastatin in a maximum daily dosage of 10 mg or 20 mg, limiting the renal risk associated with high dosages. However, at least 22.9% of patients that use rosuvastatin have additional risk factors for myopathy or rhabdomyolysis.

The controversy about rosuvastatin's safety is not solemnly based on scientific findings, but also follows the market withdrawal of one of its potent predecessors. In August 2001, the lipid lowering drug cerivastatin was withdrawn from he market after its use was found to be associated with the deaths of 52 patients due to rhabdomyolysis in Europe and the US [20]. The safety concerns of rosuvastatin are part of sequential reports on safety concerns of widely used other drugs such as serotonin reuptake inhibitors (SSRIs) and selective cyclo-oxygenase-2 (COX-2) inhibitors. In June 2003, the British registration authority issued a negative advice on the use of the antidepressant paroxetine in children and adolescents based on a meta-analysis of nine studies testing paroxetine in 1,697 children. The meta-analysis concluded that there was not enough evidence to support paroxetine effectiveness, but also a threefold increase in relative risk of suicidal behaviour [21]. In November 2000 the results of the VIGOR-study were published showing an increased incidence of myocardial infarction in patients treated with the new COX-2 inhibitor rofecoxib compared to those receiving naproxen [22]. Since the publication, a surge of data supporting this association has become available [4,5,23-26]. Despite the ongoing debate about drug safety, including that of rosuvastatin, GPs and medical specialists were still eager to adopt a new agent with an unproven safety profile and for which existing alternatives were easily available. In September 2003, SFK reported a shift in statin prescribing with a rapid preference towards rosuvastatin. They reported that within three months after introduction, rosuvastatin was the first choice in 5% of the cases a statin was prescribed [27].

Conclusions

Given the yet unproven safety record of rosuvastatin, it is of concern that both GPs and medical specialists are so keen to prescribe new drugs in such large groups of patients, that often have had no previous experience with lipid lowering drugs, and in many cases have predisposing risk-factors for a potentially lethal side effect. Further post-marketing surveillance should clarify the trade-off between the observed increased adverse drug reactions and the potential benefit of its greater potency for LDL-C reduction.

Chapter 5

GENERAL DISCUSSION

Introduction

Innovation in pharmacotherapy is essential for the prevention, diagnosis, and treatment of many diseases [1]. However, even after years of extensive clinical testing there is still a high degree of uncertainty at the moment of market introduction about the new agent's surplus value in daily practice, both in clinical and economic terms [2]. This uncertainty not only applies to the new drug's clinical effectiveness, but also to its safety profile when used by large numbers of patients and its socio-economic impact on society in general [3-7]. So, despite the acknowledged positive contributions of new drugs, there is valid concern about uncertain risk-benefit for patients and potential negative effects on cost containment in health care when new drugs are adopted in an imprudent fashion [6,8]. Understanding the dynamics of new drug prescribing and reasons for doctors to adopt new drugs not only helps to improve patient benefit and optimal allocation of financial resources in health care, but also provides essential data to maintain sustainable pharmaceutical innovation. The uncertain risk-benefit ratio at market introduction is not only made clear by identification of unknown side effects, but also by identifying possible beneficial effects beyond those tested on in clinical trials.

In this thesis several studies have been presented with the objective to detect and elucidate patterns of new drug prescribing by GPs and to profile GPs according to their variability in adopting new drugs. In addition, we studied the influences of medical specialists and community pharmacists as one of the influences on the GP's decision to prescribe new drugs during the early post-marketing period. In this final chapter, the individual studies on new drug prescribing by GPs will be put into a broader perspective. For a discussion of the shortcomings and merits of the studies in the preceding chapters on new drug prescribing the reader is referred to the discussion section of the individual studies. Here, two topics will be addressed, namely 1) the applicability of the 'diffusion of innovations' theory to explain prescribing of new drugs, and 2) the possible consequences of rapid new drug prescribing.

Does the diffusion of innovations theory apply to new drug prescribing?

In the introductory chapter of this thesis we showed a theoretical model illustrating how the private consultations of GPs and patients may result in a decision to prescribe a new drug. When aggregated, these decisions form the diffusion patterns by which new drugs disseminate in primary care. In the following section, the 'diffusion of innovations' theory as hypothesised by Rogers is evaluated for its applicability in the context of new drugs being the innovations and GPs the adopters [9].

The innovative GP

Following years of basic research and extensive clinical testing about 10-15 new drugs with an indication applicable in general practice receive market authorization every year [10,11].

Figure 1 broadly illustrates the development, diffusion, and use of new drugs. The process by which new drugs, or innovations in general, enter and become part of daily medical practice has been coined as 'diffusion' [9,12-16]. In this thesis the marketing phase (rightmost part of Figure 1), following the clinical trial phase, was studied in particular. The phenomenon of new drug prescribing is composed of a micro-level component, i.e. the decisions of individual physicians made during specific doctor-patient encounters, and a macro-level component, that is the aggregation of these micro-level decisions into patterns of diffusion of new drugs. The diffusion of innovations has been extensively studied by Rogers and described in his landmark book 'Diffusion of innovations' [9]. Rogers' theory aims to explain why some people quickly adopt an innovation that is turned down by others and why some innovations diffuse faster into a social network than others.

The adoption of innovations is usually depicted in a typical S-shaped adoption curve (Figure 1). In an adoption curve the cumulative proportion of persons who decided to adopt the innovation is plotted over time. Based on their time to adopt a particular innovation, Rogers categorises persons into five groups, namely innovators, early adopters, early majority, late majority and laggards. However, this categorisation of adopters is not universal. During the last decades a myriad of studies in the field of new drug prescribing have reported a variety of different patterns depending on type of medication, clinical area, economic constraints, and others [14,17-19]. In addition, others have shown different diffusion patterns for medical innovations other than new drugs [20-22]. However, extrapolating Rogers' typology to new drug prescribing suggests that rapid adoption of new drugs is a trait of a small group of doctors, usually coined as the 'innovators'. Implicitly, it is assumed that GPs who rapidly adopt one new drug may also adopt other new drugs quickly.

In **Chapter 3.1**, we analysed the decisions of GPs to prescribe a newly marketed drug, or as an alternative scenario to treat a patient with an older existing drug from the same therapeutic category. Five new drugs were studied, namely a combination of a long-acting bronchodilator and inhalation corticosteroid salmeterol/fluticasone (Seretide®), the cyclo-oxygenase-2 inhibitor rofecoxib (Vioxx®), the proton pump inhibitor esomeprazole (Nexium®), the long-acting anticholinergic bronchodilator tiotropium (Spiriva®), and the lipid lowering HMG-CoA reductase inhibitor rosuvastatin (Crestor®). We noted rapid adoption of all five drugs and identified a small group of innovative GPs responsible for a large part of all early prescriptions for new drugs during the first six months of the post-marketing period. This is in line with the concept of the early adopter, but the interesting finding of our study was that the GP's decision to prescribe was very drug dependent. Prescribing one new drug does not seem to be a strong predictor for the GP to prescribe other new drugs as well. This finding contradicts with the image of early adopters as being related to a general innovative predisposition. At least two other studies have also shown

that the GP's decision to prescribe is heavily dependent on the new drug in question [14-19]. The obviously idiosyncratic component of GP's decision to quickly adopt one new drug while being reluctant to prescribe other new drugs fuels the question whether the diffusion of innovations theory needs to be re-evaluated for its applicability in today's pharmaceutical market place.

Figure 1: *A Scheme for development and diffusion of medical innovations.*

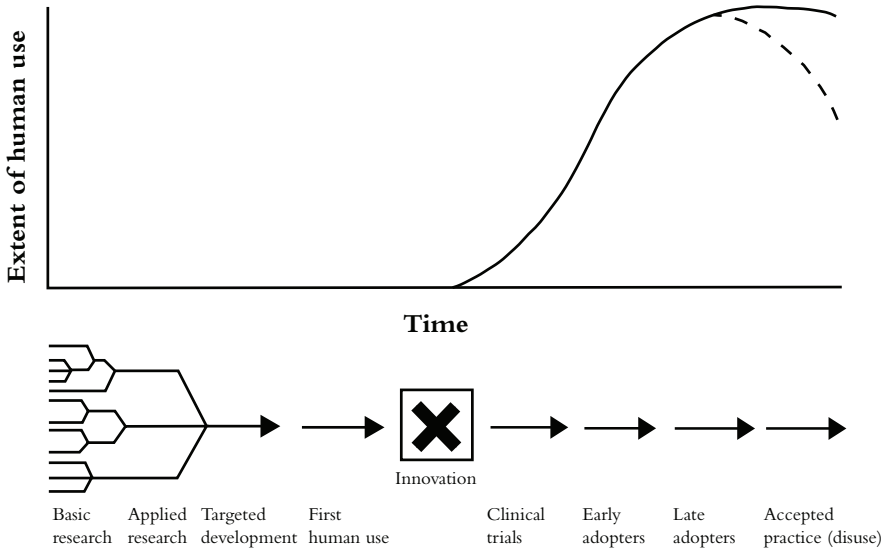


Figure derived from Banta, H.D., *Social science research on medical technology: utility and limitations*. Soc Sci Med, 1983. **17**(18): p. 1363-9.

Medical specialists as the real innovators with GPs as followers

When extending Rogers' diffusion of innovations theory to new drugs, medical specialists might be regarded as the 'real' innovators or early adopters of new drugs. Medical specialists are often seen as the (key) opinion leaders in pharmacotherapy, of course within their specific field of expertise and interest [23-30]. Their state-of-the-art working environment, in which clinical trials with new drugs are often conducted, drives them in the expected role of front-runners in medical innovation [31]. Moreover, medical specialists treat a patient population that due to their complex co-morbidity and failure to previous treatment, often requires new drugs. The interaction between GPs and medical specialists through referral of patients and repeat prescribing of specialist's initiated prescriptions was seen in several other studies as an important determinant for the variety of drugs prescribed by GPs [32-38].

A common concept of how new drugs diffuse into general practice is a two-step model with medical specialists as the innovators and GPs as the followers [12,39]. Shortly after market introduction medical specialists take the initiative to prescribe the new drug to patients visiting the hospital and through repeat prescribing by GPs the new drugs diffuse either gradually or erratically into primary care. The metaphor of an oil drop (specialist's influence) spreading unchecked over water (general practice) is often used to illustrate this mechanism. The two-step model, in addition to new drugs being sold to hospitals with high discounts, is a well known strategy used by pharmaceutical companies to obtain or increase the drug's market share [40,41]. Patients admitted to the hospital receive or are switched to the new drug and leave the hospital with a repeat prescription to fill at their local community pharmacy. The consequence may be a rapid introduction of the new drug in primary care and an increase in costs since high purchasing discounts, obtained in a hospital setting, are usually not valid in extramural care.

Other studies have shown that more than 25-75% of all prescriptions issued by GPs are initiated by medical specialists, but whether this also applies to prescriptions for new drugs shortly after market introduction remains unclear [32,33,36-38,42]. In **Chapter 3.2**, we estimated the influence of medical specialists on new drug prescribing of GPs during the first six months after market introduction. Our findings contradict the general and expected concept that the diffusion of newly marketed drugs generally follows a two-step model, with medical specialists as the innovators and GPs as the followers. Although the influence of medical specialists is clearly visible for the new drugs we studied, and often greater than for existing older drugs, the rapid uptake of new drugs may not always be specialist induced. We found that GPs themselves are responsible for a considerable amount of all early prescriptions for new drugs. Moreover, for a substantial group of GPs specialist endorsement is not even a requisite to initiate in new drug prescribing at all.

The profile of new drugs with rapid market uptake

After the initial introduction of a new drug on the market, the drug will start to develop its own unique fingerprint [43]. This fingerprint is a reflection of its application in daily clinical practice and is shaped by, among other things, the accumulation of scientific evidence, reported side effects, label changes, pharmaceutical marketing, reimbursement criteria, and the experiences with patients treated with the drug [44-46]. We hypothesised that these fingerprints may be unique to every new drug, a notion that may be reflected by our findings that some GPs are attracted to one new drug while ignoring other new drugs or that for some new drugs specialists more often take the initiative to prescribe than with other new drugs. This signifies that the decision to adopt a new drug is heavily dependent on the interaction between the innovation (the characteristics of the new drug) and the innovators (doctors).

The five new drugs investigated in this thesis as case study drugs all entered crowded markets with multiple competitors already available. For new drugs entering competitive markets, it is essential to display a real or at least a perceived advantage over its direct competitors to gain a viable market share [47]. Rogers hypothesised five important characteristics for an innovation to be successful [9].

In the case of a new drug being the innovation the five characteristics are:
1. Relative advantage: the degree to which the new drug is perceived as better (e.g. increased effectiveness or safety) than the existing drug it supersedes;
2. Compatibility: the degree to which the new drug connects to existing values, past experiences, and needs of GPs and/or patients;
3. Complexity: the degree to which the new drug is perceived as difficult to understand or use (e.g. oral or intravenous administration);
4. Trialability: the degree to which the new drug may be experimented with on a limited basis;
5. Observability: the degree to which the pharmacological effect of the new drug is visible to others.

Rofecoxib has been a classic example of an innovation, at least perceived, with high scores on all five characteristics, namely an improved gastrointestinal safety profile (relative advantage), innovative but similar pharmacological mode of action as the existing NSAIDs (compatibility), oral tablet with once daily recommended dose frequency compared to multiple daily dosing for existing NSAIDs (complexity), previous experience with NSAIDs made GPs confident to experiment (trialability), and the reduction of pain and inflammation is easy to observe for both GPs and patients (observability). This ideal mix of characteristics likely contributed to the rapid and large-scale adoption of rofecoxib in general practice, leading to the status of standard NSAID prescription within just a few years [48,49].

The new drug's relative advantage, such as improved efficacy or safety, over its direct competitors is probably the most important characteristic of the five [30]. This relative advantage is not without a reason the spearhead in most marketing campaigns by pharmaceutical companies [47]. For the new drugs studied in this thesis, Table 1 gives their position on the scale of the five characteristics.
Except for rofecoxib, the new drugs differ mainly in their relative advantage over the existing older drugs. Although all five new drugs contain a relative advantage, it was only small and of minor clinical importance for some of the new drugs. Esomeprazole, for example, was marketed for its faster mode of action, or so-called on-demand use [50]. Rosuvastatin was marketed as the most potent representative of the statins, but whether these claimed advantages were of any clinical importance was still unclear [51-54]. Salmeterol/fluticasone

and tiotropium require a lower dose frequency that has been shown to result in better compliance [55]. Improved asthma or COPD control was the main marketing message. Tiotropium with its longer mode of action made a once daily administration sufficient, compared to a four times daily of its predecessor. The four new drugs did not differ from the older drugs in the same therapeutic drug class on compatibility, complexity, trialability, and observability due to the identical pharmacological profile. This implies that the new drugs do not have to excel on all five characteristics defined as by Rogers to be adopted rapidly and on a large scale by GPs.

Table 1: *The differences between the new drugs and reference drugs on five characteristic hypothesised by Rogers as important for successful adoption.*

	Esomeprazole (Nexium®)	**Rofecoxib (Vioxx®)**	**Rosuvastatin (Crestor®)**	**Salmeterol/ fluticasone (Seretide®)**	**Tiotropium (Spiriva®)**
Relative advantage	On demand use	Improved gastrointestinal safety profile	High potency to lower cholesterol	Combines 2 drugs in 1 product	Improved dosage scheme
Compatibility	Identical to existing PPIs	Improved pharmacological mode of action	Identical to existing statins	Identical to existing products	Identical to ipratropium
Complexity	Identical to existing PPIs	Once daily dose frequency	Identical to existing statins	Identical to existing products	Identical to ipratropium
Trialability	Identical to existing PPIs	Similar to existing NSAIDs	Identical to existing statins	Identical to existing products	Identical to ipratropium
Observability	Identical to existing PPIs	Similar to existing NSAIDs	Identical to existing statins	Identical to existing products	Identical to ipratropium

Reference drugs: all proton pump inhibitors for esomeprazole, all NSAIDs for rofecoxib, all HMG-CoA reductase inhibitors (statins) for rosuvastatin, all long-acting β_2-agonists and inhalation corticosteroids for the combination salmeterol/fluticasone, and all ipratropium containing products for tiotropium.

Consequences of rapid new drug prescribing

The discrepancy between the population in which the new drug is tested and the patients treated in daily medical practice is an important factor in safety issues associated with new drug prescribing [56]. Although new drugs are subject to extensive clinical testing, there are well known and recognized limitations to the way new drugs are evaluated before receiving market approval [6,57,58]. New drugs are approved on the basis of studies of usually limited duration, relatively small numbers of patients, and ample differences with respect to disease

severity, complexibilies from the real-life target population [59]. The limitations to this clinical testing system result in insufficient data on several topics: the effects of long-term exposure, the frequency of rare adverse effects, the effects in special populations or for indications not studied before marketing, and the efficacy of a new drug relative to others for the same indications. These uncertainties about the risk-benefit ratio in large populations advocate restraint in prescribing new drugs during the early post-marketing period. Moreover, rapid and large-scale adoption will always enclose uncertainties about patient safety and long-term efficacy and may jeopardize rational and safe use of the new agents. The studies in this thesis identified several patterns by which new drugs are prescribed. Based on these, we would like to elaborate more on the following four topics, namely 1) the small group of GPs generating a disproportional number of early new drug prescriptions, 2) marketing driven adoption leading to hyperprescribing, 3) off-label prescribing of new drugs, and 4) channelling of new drugs.

Disproportional new drug prescribing by a small group of GPs

As mentioned earlier, rapid prescribing of new drugs is not uniformly distributed over all GPs and the uptake differs between drugs. Despite all the reasons for being critical and reserved when it comes to prescribing of new drugs shortly after marketing, a small group of GPs seems to be very quick to adopt the newly available agent. In **Chapter 3.1**, we noted that this small group of GPs generated a disproportionate number of new drug prescriptions. The proportion of GPs responsible for 50% of all early prescriptions ranged from 26.9% for the combination salmeterol/fluticasone to only 10.9% for rofecoxib. For tiotropium, 50% of the early prescriptions were prescribed by 18.5%, for rosuvastatin 23.5% and for esomeprazole 25.9% of the GPs.

The existence of a small group of hyperprescribers has been identified earlier by Inman in 1993 and confirmed by others in The Netherlands [60], Canada [24], and Denmark [14,19]. Since Inman's study in *The Lancet*, the impression prevailed that this small group of hyperprescribers was responsible for all new drugs, but as our results show, GPs who are heavy prescribers of one new drug may ignore others. This lack of predictability has important implications for policy makers who would like to control prescribing of new drugs. Attempts to alter behaviour of the early adopters may not achieve the desired effects when the composition of these groups changes between different new drugs. The interaction between the innovation, in our case the new drug, and the innovator (the GPs) needs to be analysed and used as a starting point before developing any policy to ensure optimal use of new drugs.

One strategy to influence new drug prescribing by GPs has been the establishment of so-called pharmacotherapeutic audit meetings (PTAMs; in Dutch called FTO [61]) between GPs and community pharmacists. Although other approaches have shown to be successful,

among others academic detailing [62-64], the studies in this thesis only focused on PTAMs. In The Netherlands, community pharmacists and GPs practising in the same catchment area regularly organise PTAMs to improve the quality of prescribing by making decisions on first choice treatment [65]. Clinical assessment of newly marketed drugs is an important topic on the agenda in more than 70% of all PTAMs [66,67]. Studies pertaining to PTAMs have charted conflicting results about their effectiveness to influence GP prescribing behaviour and, in addition, neglected the possible influences on new drug prescribing [65]. In **Chapter 3**, we showed that PTAMs are probably more effective to control early new drug prescribing in general practice than expected on the basis of earlier studies. New drug prescribing was more common among GPs attending noncommittal PTAMs than among GPs participating in PTAMs that set common goals about optimising pharmacotherapy and audit GP prescribing. Moreover, we showed in **Chapter 3.4** that pharmacists participating in high-quality PTAMs that make decisions and audit the GP's prescribing behaviour are also the pharmacists that report to play a pivot role in the organisation, maintenance, and endorsement of PTAMs.

Marketing driven adoption leads to hyperprescribing

In addition to the GP making his/her own decision to experiment and depending on their first clinical experiences decide to incorporate the new drug in their evoked set, other circumstances, in particular pharmaceutical marketing efforts, affect the drug's market penetration [68]. A new drug's success in terms of market penetration may be difficult to predict on forehand, but the success of pharmaceutical marketing on influencing prescribing behaviour is beyond dispute [18,25]. In **Chapter 3.1**, we noted that a positive industry orientation and a positive attitude towards new drugs were commonly seen determinants in the GP's decision to prescribe new drugs.

The interactions between pharmaceutical companies, doctors, and pharmacists are inevitable and not by definition always undesirable [69]. At market introduction an information asymmetry about the new drug's clinical profile exists between the drug company and GPs [70,71]. The drug company has been collecting information about the drug's effectiveness and safety for years through extensive clinical testing, while the drug is rather unknown to GPs, pharmacists, and patients. Drug companies use this information asymmetry to inform GPs and pharmacists about their products. Others have shown that commercial information is often the only source GPs consult before deciding to prescribe a new product [26,72]. This can cause friction with the implementation of evidence-based medicine in general practice at the time of marketing when the uncertainties about the pros and contras of a new drug are most important.

The controversy about pharmaceutical marketing stimulating irrational prescribing of new drugs is often channelled into a discussion about me-too drugs [73-76]. Me-too drugs are chemically very similar to existing drugs and largely exert the same pharmacological profile, but are sometimes more expensive than the original compounds in that class. The rapid prescribing of esomeprazole and rosuvastatin are examples of what some call me-too drugs with dubious clinical surplus value [77]. In **Chapter 3.1**, we noted one relatively high correlation namely the correlation between prescribing of esomeprazole and rosuvastatin, meaning that GPs who quickly prescribed esomeprazole were also likely to prescribe rosuvastatin. Although it seems unlikely that the labelling of the new agents as me-too drugs is a reason for prescribing, it may be a reason for not prescribing.

The labelling of new products as me-too drugs may show considerable variation among GPs. Some consider me-too drugs are part of a process of stepwise innovation leading to better new drugs through gradual improvements of existing drugs [78]. Despite personal opinions on the permissibility of pharmaceutical marketing, marketing campaigns are an expression of the intense economic pressure on pharmaceutical companies to earn back the increasing development costs of high risk investments and during the remaining period of applicable patent protection [4,77,79].

There is always a certain amount of tension between commercial entrepreneurship and the interests of public health. The belief that commercial and socially acceptable entrepreneurship can go hand in hand has led to self-regulation concerning pharmaceutical marketing in The Netherlands. Although pharmaceutical companies operate on the boundaries of the legal framework, there is also a demand side, e.g. the GPs and pharmacists that receive visits from pharmaceutical representatives and invite them to attend PTAMs. The information offered by pharmaceutical representatives can be very valuable to GPs and pharmacists, but GPs and pharmacists have the professional and social responsibility to critically appraise the information on its scientific and clinical merits. PTAMs can provide a good platform to assess the information on its scientific and clinical merits.

Off-label prescribing of new drugs

New drugs are subjected to licensing procedures by drug regulatory agencies to ensure their safety, effectiveness, and quality. Regulatory agencies evaluate the scientific evidence for new products handed over by the manufacturer and can subsequently authorise market approval for specific indications. However, the official indication of a drug may not always be the reason for prescribing in individual cases. Prescribing for indications other than the licensed indications is referred to as off-label prescribing [80-83]. Some even consider prescribing a new drug to patients with a disease that could have benefited from older drugs

as off-label prescribing [84]. Because the risk-benefit ratio is unclear for off-label indications, patients may be exposed to potential danger. This is especially true for newly marketed drugs since clinical evidence of long-term effectiveness and safety is still limited as discussed earlier [85].

In **Chapter 4**, we analysed the prescribing of rofecoxib one year following introduction, in a period when a surge of conflicting information about cardiovascular safety issues surrounded the new drug. Rofecoxib was registered in November 1999 for the initial indication symptomatic treatment of arthritis, followed by a label extension in December 2000 for the treatment of rheumatoid arthritis in adults. Rofecoxib showed a rapid market introduction in a market consisting of a vast number of competitors [86]. The claimed improved gastrointestinal safety over its direct competitors was the spearhead of rofecoxib's marketing campaign [87]. Shortly after rofecoxib's landmark VIGOR-study public debate arose about an increased risk of myocardial infarction associated with the use of rofecoxib which eventually lead to the voluntary withdrawal of rofecoxib in 2004 [88-95]. The fact that rofecoxib was a relatively new drug with limited data supporting long-term efficacy and safety, its initial narrow therapeutic indications, and the debate about the drug's cardiovascular safety profile, should have resulted in restraint when it came to prescribing rofecoxib. However, in **Chapter 4.1** a different picture emerged. In over 80% of the decisions made by GPs to prescribe rofecoxib, the drug was prescribed for off-label indications. So, while intended for a small group of patients with distinct indications, rofecoxib was accepted by GPs with open arms and prescribed for more than the clinical evidence at that time justified.

Although evident for rofecoxib, in **Chapter 4.4** a similar adoption pattern for rosuvastatin is described. Rosuvastatin was registered in 2003 and is the most recent representative of the lipid lowering drugs, the HMG-CoA reductase inhibitors or so-called statins. The introduction of rosuvastatin was accompanied by an extensive marketing campaign positioning rosuvastatin as the most potent member of the group [96,97]. However, the marketing campaign was companied by a public debate about the drug's safety [51,53,54,87,98-102]. Even prior to its market introduction rosuvastatin was already surrounded by controversy about an increased risk of proteinuria and heamaturia with an increased rosuvastatin dose, as well as a possible higher rate of reports of rhabdomyolysis. Given the availability of similar drugs with well-known efficacy and safety, rosuvastatin's place in the treatment of hypercholesterolemia is clearly for the patients with failure of effect on the existing products. In line with the adoption of rofecoxib, rosuvastatin was prescribed in over one third of all decisions to initiate statin therapy and not only for patients with lack of effect of previous lipid lowering therapy but also in over 40% of the patients starting without ever using any lipid lowering therapy. We observed for both rofecoxib and rosuvastatin that the drugs were easily adopted while evidence was advocating restraint.

Off-label prescribing was evident for both rofecoxib and rosuvastatin. Rofecoxib was prescribed extensively for non-licensed indications, whereas rosuvastatin was prescribed to patients that could be treated with existing drugs. The phenomenon of drug creeping (the tendency of a drug to be prescribed for other indications than registered or studied in clinical trials) [84] and thereby widening the clinical applicability to increase the drug's market share was present in both rofecoxib and rosuvastatin, and most likely not restricted to only these two agents [81,83,103,104].

Channelling

The individual and fairly rational decisions of doctors to prescribe new drugs for a specific patient may have unintentional consequences on a population level. A GP may decide that the new drug is the best option for a patient who had failed to respond satisfactorily to one or more of the older drugs, but if the majority of the GPs makes similar decisions in the same direction this can result in the drug being prescribed to patients with different characteristics than the population in which the new drug was tested in clinical trials. Channelling or selective prescribing is a common phenomenon in clinical practice and is not limited to a particular drug class and has been demonstrated for various drug classes, such as antidepressants, NSAIDs, and spasmolytics [56]. Channelling occurs when a drug is prescribed predominately to patients with multiple co-morbidities and risk factors. It is likely to happen to the latest representatives in a drug class entering the market since these are used to treat patients who experience lack of efficacy of the older drugs.

In **Chapter 4.1**, we showed that rofecoxib was preferentially prescribed to patients with concern about cardiovascular safety. Our findings were confirmed in **Chapter 4.3**, where we noted that gastrointestinal co-morbidity was more common among patients starting on rofecoxib. Selective prescribing of rofecoxib to provide gastroprotection, indirectly and unintentionally resulted in the channelling of rofecoxib in more severely ill patients with cardiovascular risk factors relevant to take into account when weighing the pros and contras of COX-2 inhibitors against other NSAIDs.

Rofecoxib was tested in patients with a high risk of gastrointestinal problems, namely those with rheumatoid arthritis and osteoarthritis, but these patients were not positioned on the high-end side of the cardiovascular disease severity scale [88]. The recipients of rofecoxib in general practice were, however, positioned on the high-end side on the cardiovascular risk scale and most of them did not (given the extensive off-label prescribing) suffer from rheumatoid arthritis or osteoarthritis [48,92,105,106]. This discrepancy in disease severity between the premarketing and post-marketing population, in combination with the tendency of rofecoxib to stimulate platelet aggregation and the imprudent prescribing, all contributed to the safety issues responsible for the worldwide withdrawal of rofecoxib in 2004.

Conclusions

In this final section a number of thoughts are shared with the reader on how to ensure sustainable adoption of new drugs in clinical practice. Moreover, we add suggestions on how further scientific research can contribute to our understanding of the dynamics of new drug prescribing. During the early post-marketing period not only unknown side effects are identified, but also unknown beneficial effects other than the ones identified in clinical testing. To ensure a safe landing of new drugs in general practice and to benefit the most of these new agents, the premarketing phase (particular the clinical trial phase) has to be as closely connected to the post-marketing phase as possible. For example, there is little point in conducting trials with a new drug exclusively in a hospital setting if virtually all of the treatments for the targeted disorder are carried out in primary care. Therefore, further understanding of how new drugs are adopted and prescribed, helps us to protect patients from possible side effects, while on the other hand to ensure the availability of new drugs and to stimulate innovation.

Re-evaluation of the diffusion of innovation theory

An important finding of our studies is the necessity to re-evaluate the applicability of Rogers' theory when it comes to introducing new drugs into today's medical practice. For a long time, the general perception prevailed that some doctors have an innovative predisposition to adopt all new drugs and that rapid hyperprescribing of these drugs was credited to a small group of doctors, in particular the medical specialists [9,12]. However, our studies show that, when it comes to adopting new drugs, the labelling GPs as innovators, early adopters, early majority, late majority, or laggards leads to an oversimplification of reality.

The perception of medical specialists being the real innovators in pharmacotherapy also needs to be re-assessed. The common concept of the two-steps model in which diffusion of new drugs starts by medical specialists rapidly prescribing new drugs followed by GPs repeating their prescriptions and later adopting the new agents themselves does not seem to apply for every new drug [12,39].

The composition of the small group of early prescribers seems to be different with every new drug introduced on the market. The five characteristics defined by Rogers to contribute to the success of an innovation may not all be of equal importance. Nowadays, where the majority of the new drugs does not represent a major innovation, a relative advantage over direct competitors seems to be sufficient for a show rapid and extensive adoption. However, without a continuous weighing of the new drug's pros and cons, this can lead to hyperprescribing that may jeopardize a soft landing of the new drug in general practice.

Further research on the dynamics of prescribing of new drugs

As for research on new drug prescribing, future studies need to address the interaction between the innovation (new drugs) and the innovators (the GPs and/or medical specialists). Elucidating these interactions may clarify why some new drugs show rapid and extensive adoptions, while others are rejected. Increasing the number of new drugs studied and stratifying them according to the type of new drug, for examples on a scale of innovativeness [5], could provide more data to validate the current findings based on the five study case drugs.

The decisions of GPs to prescribe new drugs during the early post-marketing period may seem 'erratic' on forehand, but can in fact be perceived as rational by an individual GP trying to tailor the therapy to a patient's individual medical needs [26,27,30,72,107,107]. Most studies in the field of new drug prescribing struggle with the trade-off between the richness (relevant information on the GPs) and the sample size of the data (number of GPs included). Extensive efforts have been put in to elucidate the decision making process of doctors [108-111], often using structured interviews or questionnaires. However, reported behaviour may deviate from actual behaviour in practice [26,112,113]. Other studies used large prescribing or dispensing data to analyse the GPs' decisions, but lack detailed information, such as their attitudes toward a particular new drug [14,17,19]. In light of the different composition of the small group of early prescribers for every new drug, future studies need to combine both methods of data collecting to gain a better understanding of the decisions resulting in prescribing of new drugs.

The traditional databases often used in pharmacoepidemiological studies, such as GP prescribing or pharmacy dispensing databases, may not fully cover the interaction between different important external influences, such as medical specialists, and the GP's decision to adopt a new drug. However, as shown in our studies, combining different databases makes it possible to eliminate the shortcomings of individual databases and can give more insight in the interaction between the different factors influencing the decision to adopt.

Implications

The change in the way we need to look at prescribing of new drugs not only has implications for further research, but also for policymakers who wish to control new drug prescribing. Efforts with a top down approach by targeting the a priori opinion leaders may not have the desired general effects. Moreover, relying on the passive diffusion of guidelines without an implementation strategy is unlikely to result in changes in practice [114]. In line with marketing campaigns that are completely tuned to the special features of a new drug, programs to influence new drug prescribing need to be tailored to every new drug individually or for a class of drugs with similar fingerprints [115].

Professionalizing and supporting PTAMs may be suitable for optimising prescribing of new drugs in general practice. PTAMs are existing platforms that provide close interaction between the GPs and pharmacists responsible for the prescribing and dispensing of the new drugs. Moreover, discussing new drugs is a frequent topic of the majority of the PTAMs and in our studies we found that GPs participating in high-quality PTAMs prescribe less new drugs than their colleagues attending more informal PTAMs [66,116,117]. Although the number of PTAMs functioning on the highest quality level is steadily increasing [117,118], there are still large regional differences in the quality of PTAMs and there is still much room for improvements. GPs and pharmacists should be strongly encouraged and supported where necessary to ensure that more PTAMs end with concrete decisions about pharmacotherapy.

Although different people can advise on how new drugs should be used – including policymakers, professional organisations, and educators – it are largely GPs, pharmacists, and their patients who have to implement the recommendations. To ensure the safe landing of new drugs in daily medical practice, interventions must be tailored to the audience and every individual new drug.

Chapter 6

SUMMARY/SAMENVATTING

Summary

The main objective of this thesis was to detect and elucidate prescribing patterns of newly marketed drugs by GPs and to profile GPs inclined to adopt new drugs rapidly. In addition, the studies presented in this thesis focussed on the influences of medical specialists, community pharmacists, and the pharmaceutical industry that shape the GP's decision to prescribe new drugs. During the last decades, innovation in pharmacotherapy has generated major changes in the ability to prevent, diagnose, and treat many diseases. The development and availability of new and innovative drugs has become a cornerstone in clinical practice. However, when new drugs are adopted in an imprudent fashion, there is valid concern about uncertain risk-benefit for patients and increased costs. Studying the patterns by which new drugs are prescribed contributes to better understanding on how to ensure patient safety and sustainable cost-containment in health care.

Chapter 2 describes the data sources used for our studies on prescribing of newly marketed drugs. As in most healthcare systems, medical information is increasingly stored in electronic form and made available for scientific research. GP prescribing and pharmacy dispensing data are, for example, often used for pharmacoepidemiological research. However, depending on the origin of the data, such databases have shortcomings that may limit their suitability to answer certain research questions. Combining different data sources make it possible to reduce the shortcomings of individual databases and could result in opportunities greater than those presently available. In **Chapter 2.1**, we determined the success rate of linking records from the dispensing database of SFK (Foundation for Pharmaceutical Statistics) to the prescribing database of the second Dutch national survey of general practice (DNSGP-2) conducted by NIVEL (Netherlands Institute for Health Services Research) in 2001. Working in a catchment area of 123 community pharmacies, 90 GP practices, and 170,000 individual patients, we were able to link records of 110,102 (64.8%) patients by using a deterministic record linkage approach. The linked database comprised both the complete prescribing and dispensing data of a vast number of highly characterised patients, GPs, and community pharmacists.

The availability of reliable data on drug exposure is of paramount importance in pharmacoepidemiology, as misclassification of exposure may lead to biased effect estimates. Using the linked database, we determined in **Chapter 2.2** whether GP prescribing data provide an accurate data source for estimating drug exposure in patients. We found that patients fill 92.4% of all prescriptions issued by GPs in their local pharmacy. Moreover, 20.0% of the total number of prescriptions filled were not present in the GP prescribing database, but instead were prescribed by other care providers than their own GP (mainly medical specialists). Non-filling prescriptions and receiving prescriptions from other prescribers was especially the case in patients with multiple chronic diseases. Our findings may indicate

that the validity of GP prescribing data to estimate actual drug exposure in patients may be compromised by primary drug defaulting and by patients receiving prescriptions from other prescribers.

Chapter 3 presents four studies on the decisions of GPs to prescribe new drugs and the context in which these decisions are made. In **Chapter 3.1**, we analysed the decisions of GPs to prescribe five new drugs, or existing drugs as an alternative, in the first six months after market introduction. The five drugs were esomeprazole, rofecoxib, rosuvastatin, tiotropium, and the combination salmeterol/fluticasone. We noted rapid market penetration for all five drugs, but still considerable variation in prescribing existed between GPs. A small number of GPs were accountable for a disproportionate share of all early prescriptions. Interestingly, we found that prescribing new drugs was very much dependent on the new drug in question and not so much on the prescriber. This contradicts the assumption of a universal adopter. Prescribing new drugs seemed to be embedded in the GP's attitudes towards new drugs and orientation towards the pharmaceutical industry. GPs with a positive attitude towards new drugs and those who are more industry-orientated prescribed more newly marketed drugs during the early post-marketing period. Furthermore, peer pressure of colleagues and community pharmacists seemed to result in less prescribing of new drugs.

The interface between primary and specialist care is an important factor in the mixture of drugs prescribed by GPs. Medical specialists are often considered as the early prescribers of new drugs, but the evidence supporting this presumption is weak. In **Chapter 3.2**, we studied the influence of medical specialists on prescribing of the afore mentioned five new drugs in primary care. We noted that the influence of specialists was clearly visible for all new drugs and in most cases greater than for existing drugs from the same therapeutic drug class. However, the influence of specialists differed considerably and the rapid prescribing of the five new drugs in primary care did not seem to be specialist induced in all cases. GPs themselves were responsible for a substantial amount of all early prescriptions. Moreover, a proportion of GPs, ranging from 21.1% for esomeprazole up to 32.9% in the case of rofecoxib, started prescribing before any of the patients received the new drug from a medical specialist. In addition, prior prescribing of these new drugs by medical specialist did not shorten the time to the GP's own prescribing. This finding contradicts with the idea that the diffusion of newly marketed drugs always follows a two-step model, with medical specialists as the innovators and GPs as the followers.

In **Chapter 3.3 and 3.4**, we studied the influences of community pharmacists, through their participation with GPs in pharmacotherapy audit meetings (PTAMs), on GPs' decisions to prescribe new drugs. The two studies show that this form of professional collaboration between GPs and pharmacists may be an effective way to control early new drug prescribing

in general practice. **Chapter 3.3** showed that GPs who participate in PTAMs on level 1 (lowest quality level) (OR=2.24; 95% CI 1.04-4.81) or level 2 (OR=2.31; 95% CI 1.30-4.09) prescribed more new drugs than their colleagues attending PTAMs on the highest level (level 4). We also noted that as more participants attended the PTAMs, the GPs were more likely to prescribe new drugs (OR=1.06; 95% CI 1.02-1.10). In addition, GPs participating in PTAMs that made decisions about who receives pharmaceutical representatives outside the PTAMs were less likely to prescribe new drugs (OR=0.36; 95% CI 0.24-0.56). In **Chapter 3.4**, we aimed to identify pharmacists that contributed to high-level PTAMs. We noted that the pharmacists attending level 4 PTAMs were more likely to undertake initiatives, compared to pharmacists participating on lowest level (OR=2.98; 95% CI 1.07-8.26). Interestingly, we found no evidence supporting the assumption that the active care-providing pharmacist (active counselling at first and second dispensing, private counselling room, and actively inviting patients to audit their medication) was also likely to be the pharmacist involved in high-quality PTAMs.

New drugs are subject to extensive clinical testing before receiving market approval to guarantee safety, efficacy, and quality. Still, their actual use in daily medical practice can, and often does, unveil unknown effects that were not detected during the clinical testing phases. **Chapter 4** contains four case studies illustrating how the fairly rational decisions of GPs to treat patients with newly marketed drugs may have unintentional and unwanted side effects in large populations. **Chapter 4.1** describes off-label prescribing of rofecoxib; the first representative of the new COX-2 inhibitors. Rofecoxib was registered in The Netherlands (November 1999) for a narrow clinical indication, namely the symptomatic treatment of arthritis. It was granted a label extension for the treatment of rheumatoid arthritis in adults (December 2001). However, while intended for the narrow indications, we observed that 82.6% of the patients starting on rofecoxib in 2001 received the drug to treat off-label indications. Off-label prescribing was not restricted to a subpopulation of GPs with distinct characteristics. So all GPs together determined a much wider clinical application for rofecoxib.

Rofecoxib was withdrawn from the market due to an excess risk of myocardial infarction and stroke in September 2004. This reaffirmed the fact that prescribing of newly marketed drugs, irrespective of its volume of use, should be done with precaution to ensure the patient safety. Selective prescribing, or so-called 'channelling', of new drugs in high-risk patients is highlighted in **Chapter 4.2**. This chapter shows that rofecoxib was prescribed to a select group of patients with distinct characteristics. There has been ample public debate about the effectiveness and safety of rofecoxib. Concerns regarding cardiovascular safety in high-risk patients, in particular the elderly with poor health and other co-morbidity have evolved. However, our data showed that rofecoxib was preferentially prescribed to patients with

a high age (OR_{adj} 80 and older vs 25-44 8.7; 95% CI 6.7-11.2), poor self-perceived health (OR_{adj}=2.4; 95% CI 1.8-3.3), and previous paracetamol use (OR_{adj}=1.3; 95% CI 1.1-1.7).

In **Chapter 4.3**, we assessed differences in cardiovascular risk between starters of rofecoxib versus starters of other NSAIDs. We noted pre-existing cardiovascular co-morbidity in 40.4% of patients starting on rofecoxib. Patients starting on rofecoxib were twice as likely to have a history of gastrointestinal morbidity, compared to patients starting on other NSAIDs (OR_{adj}=2.09; 95% CI 1.652.66). The patients were also more likely to have cardiovascular co-morbidity (OR_{adj}=1.90; 95% CI 1.60-2.24) compared to recipients of rofecoxib with no gastrointestinal co-morbidity. Cardiovascular morbidity was present in over 61% of carriers of a composite risk profile including age 60 years or older, gastrointestinal co-morbidity and diagnosis of rheumatoid arthritis and osteoarthritis.

Another drug surrounded by controversy regarding its safety profile, even before it received market approval, was rosuvastatin. In light of its safety controversy, we assessed in **Chapter 4.4** the attitude of clinical practice towards prescribing of rosuvastatin and identified the first users of this drug during the first nine months after market introduction. Similar to adoption of rofecoxib, we noted that both GPs and medical specialists were keen to prescribe the new drug in large groups of patients that often had no previous experience with lipid lowering drugs, and in many cases had predisposing risk factors for a potentially lethal side effect. In over one third of all decisions to initiate a (new) statin therapy, the choice for the latest drug on the market was made, not only for patients with lack of effect on previous lipid-lowering drugs, but over 40% for de novo patients.

In conclusion, the studies presented in this thesis show that rapid prescribing of new drugs during the early post-marketing period is credited to a small group of innovative GPs. However, the decision to prescribe is very much dependent on the new drug in question and not so much on the prescriber. Although medical specialists are commonly believed to be the real innovators in pharmacotherapy, our data show that this is not always the case for all new drugs. When it comes to rapid prescribing of new drugs, a substantial number of GPs do not need any conformation in the form of prescriptions from medical specialists to start prescribing new drugs. Overall, our data call for a re-evaluation of the 'diffusion of innovations' theory when new drugs are the innovations. Furthermore, our studies show that the individual and fairly rational decisions of GPs to prescribe new drugs may have unintentional and unexpected consequences on a population level, such as market driven prescribing and new drugs being channelled in to high-risk patients. Professional collaboration of GPs and community pharmacists in the form of PTAMs may be an approperiate way to ensure a sustainable adoption of new drugs in primary care.

Samenvatting

Het doel van dit proefschrift was het detecteren en verklaren van de wijze waarop nieuwe geneesmiddelen door huisartsen worden voorgeschreven en om de huisartsen te karakteriseren die nieuwe geneesmiddelen snel na marktintroductie voorschrijven. Bovendien is de invloed van medisch specialisten, openbaar apothekers en de farmaceutische industrie op de beslissingen van huisartsen om een nieuw geneesmiddel voor te schrijven onderzocht. Gedurende de laatste decennia heeft de innovatie op het gebied van de farmacotherapie voor grote veranderingen gezorgd in de mogelijkheid om vele ziekten te voorkomen, te diagnosticeren en te behandelen. De ontwikkeling en beschikbaarheid van nieuwe en innovatieve geneesmiddelen is daarom een hoeksteen van de hedendaagse medische praktijk. Echter, ondanks alle positieve aspecten van nieuwe geneesmiddelen bestaat er gegronde zorg over een disbalans tussen de mogelijke risico's en beoogde voordelen voor patiënten en stijgende kosten aan geneesmiddelen wanneer nieuwe geneesmiddelen op een onzorgvuldige wijze worden voorgeschreven. Onderzoek naar het voorschrijven van nieuwe geneesmiddelen draagt dan ook bij aan een beter inzicht in hoe patientveiligheid en een beheersbare kostenstijging in de gezondheidszorg kunnen worden gegarandeerd.

Hoofdstuk 2 beschrijft de gegevens die zijn gebruikt in de studies naar het voorschrijven van nieuwe geneesmiddelen. Zoals in de meeste gezondheidszorgsystemen wordt in Nederland medische informatie in toenemende mate in elektronische vorm opgeslagen en vervolgens voor wetenschappelijk onderzoek beschikbaar gesteld. Zo worden bijvoorbeeld voorschrijfgegevens van huisartsen en aflevergegevens van apotheken veelvuldig gebruikt voor farmaco-epidemiologisch onderzoek. Echter, afhankelijk van de herkomst van de gegevens hebben alle databases beperkingen die voor een belangrijk deel de bruikbaarheid voor wetenschappelijk onderzoek bepalen. Een mogelijke oplossing voor de individuele tekortkomingen is het samenvoegen van afzonderlijke gegevensbronnen. Dit zou zelfs mogelijkheden kunnen opleveren die nu nog niet beschikbaar zijn.

In **Hoofdstuk 2.1** is het succespercentage bepaald voor het koppelen van apotheek-aflevergegevens van de Stichting Farmaceutische Kengetallen (SFK) aan voorschrijfgegevens uit de tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk (NS-2), welke in 2001 is uitgevoerd door het NIVEL. In een verzorgingsgebied van 123 openbare apotheken, 90 huisartspraktijken en 170.000 patiënten, was het mogelijk om op basis van een deterministisch koppelingsalgoritme de gegevens van 110.102 (64,8%) patiënten te koppelen. De uiteindelijke database bevat zowel de complete voorschrijf- als afleverhistorie van een groot aantal patiënten, huisartsen en openbare apothekers, waarvan bovendien gedetailleerde informatie beschikbaar is.

Voor de farmaco-epidemiologie is de beschikbaarheid van gedetailleerde informatie over het geneesmiddelgebruik van patiënten van fundamenteel belang, aangezien misclassificatie van het gebruik kan leiden tot vertekende effectschattingen. Gebruikmakend van de gekoppelde database is in **Hoofdstuk 2.2** bepaald of de voorschrijfgegevens van huisartsen een goede informatiebron zijn om het werkelijke geneesmiddelgebruik van patiënten te meten. Het onderzoek wijst uit dat 92.4% van alle recepten die huisartsen uitschrijven ook daadwerkelijk door patiënten in de apotheek wordt ingeleverd. Echter, 20.0% van alle bij de apotheek ingeleverde recepten blijkt niet in de voorschrijfgegevens van de huisarts aanwezig te zijn. Deze recepten zijn van andere voorschrijvers dan hun eigen huisarts afkomstig (voornamelijk de medisch specialist). Het niet ophalen van recepten en het ontvangen van recepten van andere voorschrijvers was vooral zichtbaar bij patiënten met meerdere chronische aandoeningen. Onze resultaten zouden een aanwijzing kunnen zijn dat de validiteit van het gebruik van huisartsgegevens voor het meten van geneesmiddelgebruik onder patiënten beperkt is doordat patiënten niet al hun geneesmiddelen ophalen en doordat patiënten recepten krijgen van andere voorschrijvers dan hun eigen huisarts.

In **Hoofdstuk 3** worden vier studies gepresenteerd waarin de keuzes van huisartsen om nieuwe geneesmiddelen voor te schrijven en de context waarin deze beslissingen worden genomen worden bestudeerd. In **Hoofdstuk 3.1** staan de keuzes van huisartsen centraal om of een nieuw geneesmiddel of een bestaand middel voor te schrijven gedurende de eerste zes maanden nadat het nieuwe geneesmiddel is geïntroduceerd. Vijf nieuwe geneesmiddelen zijn bestudeerd, te weten esomeprazol, rofecoxib, rosuvastatine, tiotropium en de combinatie salmeterol/fluticason. De vijf nieuwe geneesmiddelen lieten elk een snelle marktpenetratie zien, maar ondanks de snelle adoptie bestonden er toch grote verschillen tussen huisartsen in het voorschrijven. Een kleine groep huisartsen was verantwoordelijk voor een onevenredig aandeel van alle vroege voorschriften. Opmerkelijk was dat het voorschrijven van nieuwe geneesmiddelen erg afhankelijk was van het geneesmiddel in kwestie en niet zo zeer van de voorschrijver zelf. Dit is in tegenspraak met de veronderstelling dat er een universele innovator bestaat. Het voorschrijven van nieuwe geneesmiddelen lijkt onderdeel uit te maken van de attitude van huisartsen ten aanzien van nieuwe geneesmiddelen en de farmaceutische industrie. Huisartsen met een positieve houding ten opzichte van nieuwe geneesmiddelen en degenen met een positieve houding ten opzichte van de farmaceutische industrie, schrijven vaker kort na marktintroductie nieuwe geneesmiddelen voor. Bovendien blijkt dat groepsdwang van collegae huisartsen en openbare apothekers resulteert in het minder voorschrijven van nieuwe geneesmiddelen.

Het raakvlak tussen de eerste- en tweedelijnsgezondheidszorg is een belangrijke determinant voor het scala aan geneesmiddelen dat door huisartsen wordt voorgeschreven. In het algemeen worden medisch specialisten als de echte eerste voorschrijvers van nieuwe geneesmiddelen

beschouwd, maar het wetenschappelijk bewijs dat aan deze veronderstelling ten grondslag ligt is beperkt. In **Hoofdstuk 3.2** hebben we de invloed van medische specialisten op het voorschrijven van de bovengenoemde vijf nieuwe geneesmiddelen in de eerste zes maanden na introductie bestudeerd. Het blijkt dat de invloed van medisch specialisten duidelijk zichtbaar is voor alle nieuwe geneesmiddelen en in de meeste gevallen groter dan bij de reeds bestaande geneesmiddelen uit dezelfde therapeutische groep. Echter, de invloed van de specialist verschilt aanmerkelijk tussen de verschillende nieuwe geneesmiddelen en het snel voorschrijven van nieuwe geneesmiddelen in de eerstelijns lijkt niet voor elk geneesmiddel door specialisten geïnduceerd te zijn. Huisartsen zijn verantwoordelijk voor een substantieel deel van alle vroege voorschriften en bovendien schrijft een aantal huisartsen, variërend van 21,1% voor esomeprazol tot 32,9% voor rofecoxib, nieuwe geneesmiddelen voor zonder dat zij enige bevestiging van medische specialisten in de vorm van een eerder voorschrijft nodig hebben. Verder blijkt dat de tijd totdat een huisarts start met voorschrijven niet wordt verkort wanneer specialisten het geneesmiddel eerder aan patiënten van de huisarts hebben voorgeschreven. Dit is in tegenstelling met het algemene idee dat de diffusie van nieuwe geneesmiddelen altijd een twee-staps model volgt met specialisten als de innovators en huisartsen als volgers.

In **Hoofdstuk 3.3 en 3.4** staat de invloed van openbare apothekers op de keuzes van huisartsen om nieuwe geneesmiddelen voor te schrijven centraal. De invloed van apothekers door middel van hun participatie in het farmacotherapeutisch overleg (FTO) is bestudeerd. De studies laten zien dat deze vorm van professionele samenwerking tussen huisartsen en apothekers een effectieve manier kan zijn om het voorschrijven van nieuwe geneesmiddelen te sturen. Hoofdstuk 3.3 toont aan dat huisartsen die FTO's op niveau 1 (laagste kwaliteitsniveau) (OR=2,24; 95% CI 1,04-4,81) of niveau 2 (OR=2,31; 95% CI 1.30-4,09) bijwonen meer nieuwe geneesmiddelen voorschrijven dan hun collegae die deelnemen aan FTO's van het hoogste niveau (niveau 4). Bovendien blijkt dat wanneer meer personen deelnemen aan het FTO, de huisartsen ook meer nieuwe geneesmiddelen voorschrijven (OR=1,06; 95% 1,02-1,10). Verder schrijven huisartsen minder nieuwe geneesmiddelen voor wanneer zij deelnemen aan FTO's waarin beslissingen worden genomen over wie buiten het FTO de artsenbezoekers ontvangen (OR=0,36; 95% CI 0,24-0,56). **Hoofdstuk 3.4** had tot doel om de apothekers die bijdragen aan kwalitatief hoogwaardige FTO's te identificeren. Vergeleken met apothekers die deelnamen aan FTO's op het laagste niveau, rapporteerden de apothekers die deelnamen aan FTO's op het hoogste niveau vaker initiatieven te ondernemen (OR=2,98; 95% CI 1,07-8,26). Opmerkelijk was het ontbreken van enig bewijs dat de actief zorgverlenende apotheker, namelijk met actieve eerste en tweede uitgifte begeleiding, eigen spreekkamer en actief uitnodigen van patiënten om hun medicatie te bespreken, ook de apotheker was die deelneemt aan kwalitatief hoogwaardige FTO's.

Om de kwaliteit, veiligheid en werkzaamheid van nieuwe geneesmiddelen te garanderen worden alle nieuwe geneesmiddelen uitvoerig getest in klinische onderzoeken voordat een handelsvergunning wordt afgegeven. Toch brengt het gebruik van deze middelen in de dagelijkse praktijk nieuwe effecten aan het licht. Het betreft vaak bijwerkingen die niet in het klinisch onderzoek niet kunnen worden gedetecteerd. In **Hoofdstuk 4** worden vier studies gepresenteerd die illustreren hoe individuele en redelijk rationele beslissingen van huisartsen om patiënten met nieuwe geneesmiddelen te behandelen op populatieniveau tot onbedoelde en ongewenste effecten kunnen leiden.

Hoofdstuk 4.1 beschrijft het buiten de registratie voorschrijven ('off-label') van rofecoxib; de eerste vertegenwoordiger van de nieuwe COX-2 remmers. Rofecoxib werd in Nederland geregistreerd (november 1999) voor een nauwe klinische indicatie, namelijk de symptomatische behandeling van artrose. Een uitbreiding van de indicatie werd afgegeven voor de behandeling van reumatoïde artritis bij volwassenen (december 2001). Echter, bedoeld voor een beperkt indicatiegebied uit ons onderzoek bleek dat bij 82.6% van de patiënten die rofecoxib voor het eerst kregen voorgeschreven het geneesmiddel voor een off-label indicatie was bedoeld. Het buiten de geregistreerde indicatie voorschrijven was niet beperkt tot een selecte groep huisartsen en daarmee bepaalden huisartsen een veel uitgebreider klinisch toepassinggebied voor rofecoxib.

Rofecoxib werd uiteindelijk in september 2004 vrijwillig van de markt gehaald vanwege een verhoogd risico op het krijgen van een hartaanval en hersenbloeding. Dit onderstreepte wederom het feit dat het voorschrijven van nieuwe geneesmiddelen, onafhankelijk van voorschrijfvolume, met gepaste terughoudendheid dient te gebeuren zodat veiligheid van patiënten tot op zekere hoogte kan worden gewaarborgd. Selectief voorschrijven, ook wel bekend als 'channelling', wordt in **Hoofdstuk 4.2** uitgelicht. In dit hoofdstuk worden de eerste gebruikers van de rofecoxib beschreven. Er is een uitvoerig debat gevoerd over de effectiviteit en veiligheid van rofecoxib, gezien de bezorgdheid omtrent de cardiovasculaire veiligheid onder hoogrisico patiënten, in het bijzonder ouderen met slechte gezondheid en andere co-morbiditeit. Echter, onze gegevens laten zien dat rofecoxib juist werd voorgeschreven aan patiënten met hoge leeftijd (OR_{adj} voor 80 jaar of ouder vs. 25-44=8.7; 95% CI 6.7-11.2), een zelf gerapporteerde slechte gezondheid (OR_{adj}=2.4; 95% CI 1.8-3.3) en eerder gebruik van paracetamol (OR_{adj}=1.3; 95% 1.1-1.7).

In **Hoofdstuk 4.3** zijn de verschillen in cardiovasculair risico bepaald tussen patiënten die startten met rofecoxib en patiënten die startten met andere NSAIDs. Cardiovasculaire co-morbiditeit was aanwezig in 40,4% van de patiënten die startten met rofecoxib. Een geschiedenis van gastrointestinale morbiditeit kwam tweemaal zo vaak voor bij patiënten die startten met rofecoxib dan bij patiënten die startten met een andere NSAID

(OR_{adj}=2,09; 95% 1,65-2,66). De patiënten hadden ook tweemaal zo veel kans om ook cardiovasculaire co-morbiditeit te hebben vergeleken met rofecoxib starters zonder gastrointestinale co-morbiditeit (OR_{adj}=1,90; 95% CI 1,60-2,24). Cardiovasculaire co-morbiditeit was aanwezig in meer dan 61% van de patiënten met een samengesteld risicoprofiel van een leeftijd van 60 jaar of ouder, gastrointestinale co-morbiditeit en met een diagnose reumatoïde artritis of artrose.

Een ander geneesmiddel dat omringd werd door controverse omtrent het veiligheidsprofiel, nog voordat het überhaupt was geïntroduceerd, was rosuvastatine. In het licht van de discussie over de veiligheid van het nieuwe middel hebben we in **Hoofdstuk 4.4** bepaald wat de houding van de klinische praktijk was ten aanzien van het voorschrijven van rosuvastatine en wie de eerste gebruikers waren tijdens de eerste negen maanden na marktintroductie. Overeenkomstig met de adoptie van rofecoxib bleek dat zowel huisartsen als medisch specialisten enthousiast waren om het nieuwe middel voor te schrijven aan grote groepen patiënten die vaak geen enkele ervaring hadden met het gebruik van lipide verlagende middelen en een verhoogd basis risico hadden voor mogelijke dodelijke bijwerkingen. In meer dan eenderde van alle beslissingen om (voor het eerst) te starten met statines viel de keuze op het nieuwste middel; en niet alleen voor die patiënten waarbij eerdere behandeling met lipide verlagende middelen onvoldoende effectief bleek, maar zelfs bij 40% van alle patiënten die nog nooit eerder lipide verlagende middelen hadden gebruikt.

Concluderend, de studies in dit proefschrift laten zien dat het voorschrijven van nieuwe geneesmiddelen die net op de markt zijn verschenen toe te schrijven is aan een kleine groep huisartsen. Echter, de beslissing om een nieuw geneesmiddel voor te schrijven is sterk afhankelijk van het middel in kwestie en minder van de voorschrijver. Hoewel medisch specialisten vaak worden gezien als de echte vernieuwers in de farmacotherapie, is dat niet het geval voor alle nieuwe geneesmiddelen. De studies in dit proefschrift roepen op tot een herevaluatie van de bruikbaarheid van de 'diffusion of innovation' theorie in het geval dat nieuwe geneesmiddelen de innovaties zijn. Bovendien laten de studies zien dat de individuele en redelijk rationele beslissingen van huisartsen onbewuste en onbedoelde effecten op populatieniveau kunnen hebben, zoals marketing gedreven voorschrijven en het voornamelijk voorschrijven van nieuwe geneesmiddelen aan hoogrisico patiënten. Professionele samenwerking tussen huisartsen en apothekers in de vorm van FTO's zou een geschikte manier kunnen zijn om een duurzame adoptie van nieuwe geneesmiddelen in de huisartspraktijk te garanderen.

ACKNOWLEDGEMENTS

Veel mensen hebben bijgedragen aan de totstandkoming van dit proefschrift. Ik wil dan ook iedereen bedanken die heeft bijgedragen aan mijn onderzoek en een aantal mensen wil ik hierbij graag in het bijzonder noemen.

Prof. Bert Leufkens, beste Bert, jij bent een innovator. Jouw vernieuwende ideeën over hoe met geneesmiddelen om te gaan zullen ook in de toekomst een inspiratie voor mij zijn.

Prof. Peter Groenewegen, beste Peter, in onderzoek wordt de werkelijkheid vaak vereenvoudigd in een model om vervolgens het verleden te verklaren of de toekomst te voorspellen. Velen zullen zeggen: "Keep it simple, s****d!". Toch is het vaak verstandig om de werkelijkheid niet te veel te versimpelen en multilevel analyses zijn daar dé oplossing voor.

Dr. Rob Heerdink, beste Rob, bedankt voor je pragmatische aanpak bij het toegankelijk maken van de enorme berg aan data die we onderweg hebben verzameld. Zonder jouw hulp had ik nooit uit die tientallen huisartsen en apothekers, honderdduizenden patiënten, miljoenen recepten en miljarden nullen en enen enige relevante informatie weten te distilleren.

Dr. ir. Liset van Dijk, beste Liset, een goed begin is het halve werk. Door het IGZ-rapport kon ik meteen in de trein springen en was ik onderweg. Ook halverwege heb je met veel succes mijn manuscripten verdedigd in de WO-vergaderingen. Bedankt voor alle inzet.

Dr. Rolf van Hulten, beste Rolf, *"New drugs - Why not?"* vind ik nog steeds een goede titel voor mijn proefschrift. Dr. Lyda Blom, beste Lyda, jouw vragen over hoe het met mijn 'onderzoek' ging heb ik altijd erg gewaardeerd.

Door het gezellige team in de top van het Went gebouw is de tijd voorbijgevlogen. Ik wil dan ook alle Epithera's hierbij bedanken voor de goede tijd. Speciale dank gaat uit naar Pieter Stolk, dr. Michiel Storimans en Boris van Wijk: De heren van N813. Zittend in een kring en de voeten op tafel deden wij echte Science.

N813 alumnus, dr. Patrick Souverein, beste Patrick, jij bent UNICA! Zonder jouw hulp was mijn data expeditie nooit geslaagd. Begrippen als phareg, nawnr, patnum, en roze ruis doen je wankelen op je voeten.

Het UNICA onderzoek is een samenwerking tussen de Universiteit Utrecht; Betawetenschappen; Departement Farmaco-epidemiologie en Farmacotherapie en het NIVEL (Nederlands instituut voor onderzoek van de gezondheidszorg). In het bijzonder wil ik dr. Dinny de Bakker en drs. Peter Spreeuwenberg noemen.

Eigenlijk had ik mijn onderzoek UNICA*S* moeten noemen. Zonder de vruchtbare samenwerking met de Stichting Farmaceutische Kengetallen (SFK) was mijn onderzoek nooit een dergelijk succes geworden. Drs. Fabiënne Griens, bedankt voor het kritisch lezen van mijn manuscripten en de prettige samenwerking.

Dank gaat ook uit naar het Wetenschappelijk Instituut Nederlandse Apothekers (WINAp) voor het financieren van het onderzoek.

De huisartsen en apothekers die bereid waren om hun medewerking te geven aan het UNICA onderzoek ben ik zeer erkentelijk.

De leden van de leescommissie ben ik zeer erkentelijk voor het beoordelen van mijn proefschrift.

Lieve Werner, Claudine en Sam, bedankt voor jullie steun. Werner, het was voor mij een natuurlijke keuze om je te vragen als paranimf. Clau, doe het proefschrift eens dicht. Het ziet er schitterend uit. Lieve Paula en Mellany, jullie volharding is voor mij een inspiratie geweest om ook in mindere tijden door te gaan. Lieve koude kant, bedankt voor de warme gesprekken. Gert en Mieke, jullie oprechte interesse in mijn onderzoek heb ik altijd zeer gewaardeerd. Lieve pap en mam, bedankt voor jullie onvoorwaardelijke steun. Ik hoop jullie ook in de toekomst als spiegel te mogen gebruiken. Lieve Jo, samen zijn we hiervoor gegaan en samen ronden we het nu af. We gaan een leuke tijd tegemoet!

LIST OF PUBLICATIONS

1. Stefan R. Florentinus, Liset van Dijk, Annemarie de Jong, Eibert R. Heerdink. *Relaties tussen farmaceutische industrie en artsen/apothekers. Invloed? Welke invloed?* Pharm Weekbl, 2004.**139**:p.180-185
2. Liset van Dijk, Annemarie de Jong, Stefan R. Florentinus, Robert Verheij. *Off-label voorschrijven in de huisartspraktijk. Therapeutisch probleem of academisch probleem?* Pharm Weekbl. 2004.**139**:p.902-905
3. Stefan R. Florentinus, Eibert R. Heerdink, Olaf H. Klungel, Antonius de Boer. *Should rosuvastatin be withdrawn from the market?* Lancet, 2004.**364**(9445):p.1577.
4. Stefan R. Florentinus, Merete W. Nielsen, Liset van Dijk, Hubert G.M. Leukens, Eibert R. Heerdink. *Patient characteristics associated with prescribing of a newly marketed drug: the case of rofecoxib.* Eur J Clin Pharmacol, 2005.**61**(2):p.157-159.
5. Stefan R. Florentinus, Eibert R. Heerdink, Antonius de Boer, Liset van Dijk, Hubert G.M. Leufkens. *The trade-off between cardiovascular and gastrointestinal effects of rofecoxib.* Pharmacoepidemiol Drug Safety, 2005.**14**(7):p.437-441.
6. Stefan R. Florentinus, Rolf van Hulten. *Huisarts wil feedback van apotheker. FTO wel invloed op voorschrijven nieuwe geneesmiddelen.* Pharm Weekbl, 2005:p.140:1176
7. Stefan R. Florentinus, Patrick C. Souverein, A.M.G. Fabiënne Griens, Peter P. Groenewegen, Hubert G.M. Leufkens, Eibert E. Heerdink. *Linking pharmacy dispensing data to prescribing data of general practitioners.* BMC Med Inform Decis Mak. (in press)

REFERENCES

Chapter 1
INTRODUCTION

1. Rosenthal, N., *Tools of the trade--recombinant DNA*. N Engl J Med, 1994. **331**(5): p. 315-7.
2. Drews, J. and S. Ryser, *The role of innovation in drug development*. Nat Biotechnol, 1997. **15**(13): p. 1318-9.
3. Le Fanu, J., *The Rise and Fall of Modern Medicine*. 1999, London: Abacus.
4. Lichtenberg, F.R., *The impact of new drug launches on longevity: evidence from longitudinal disease-level data from 52 countries, 1982-2001*. 2003, National Bureau of Economic Research: Cambridge.
5. Avorn, J., *Powerful Medicines*. 2004, New York: Alfred A. Knopf.
6. McBride, W., *Thalidomide and congenital abnormalities*. Lancet, 1961. **ii**: p. 1358.
7. Herbst, A.L., H. Ulfelder, and D.C. Poskanzer, *Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women*. N Engl J Med, 1971. **284**(15): p. 878-81.
8. Abraham, J., *Regulating the drugs industry transparently*. BMJ, 2005. **331**(7516): p. 528-529.
9. Ray, W.A. and C.M. Stein, *Reform of drug regulation--beyond an independent drug-safety board*. N Engl J Med, 2006. **354**(2): p. 194-201.
10. DiMasi, J.A., N.R. Bryant, and L. Lasagna, *New drug development in the United States from 1963 to 1990*. Clin Pharmacol Ther, 1991. **50**(5 Pt 1): p. 471-86.
11. DiMasi, J.A., M.A. Seibring, and L. Lasagna, *New drug development in the United States from 1963 to 1992*. Clin Pharmacol Ther, 1994. **55**(6): p. 609-22.
12. *Changing Patterns of Pharmaceutical Innovation*. 2002 (http://www.nihcm.org/innovations.pdf), The National Institute for Health Care Management Research and Educational Foundation (NIHCM): Washington DC (accessed Apr 3, 2006).
13. Kaitin, K.I. and C. Cairns, *The new drug approvals of 1999, 2002, and 2001: Drug development trends a decade after passage of the prescription drug user free act of 1992*. Drug Info Journal, 2003. **37**(4): p. 357-371.
14. Charles River Associates, *Innovation in the pharmaceutical sector: a study undertaken for the European Commission*. 2004: http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2004/nov/EU%20Pharma%20Innovation_25-11-04.pdf (accessed Apr 3, 2006).
15. EMEA. (European Medicines Agency) http://www.emea.eu.int/pdfs/general/direct/emeaar/000204en.pdf.
16. Hensley, S., *Prescription costs become harder to swallow. Providers and payers get a big dose of reality with explosive spending and patient demand for new drugs*. Mod Healthc, 1999. **29**(34): p. 30-4.
17. DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, *The price of innovation: new estimates of drug development costs*. J Health Econ, 2003. **22**(2): p. 151-85.
18. Smith MC, Kolassa EM, Perkins G, and Siecker B, *Pharmaceutical Marketing. Principles, Environment, and Practice*. 2002, Binghampton, NY: Pharmaceutical Products Press.
19. IMS, IMS *Reports 8 Percent Constant Dollar Growth in 2002 Audited Global Pharmaceutical Sales to $400.6 Billion*. 2003, http://www.imshealth.com/ims/portal/front/articleC/0,2777,6599_3665_41336931,00.html.

20. DiMasi, J.A., *Rising research and development costs for new drugs in a cost containment environment*. Pharmacoeconomics, 1992. **1**(Suppl 1): p. 13-20.
21. Ess, S.M., S. Schneeweiss, and T.D. Szucs, *European healthcare policies for controlling drug expenditure*. Pharmacoeconomics, 2003. **21**(2): p. 89-103.
22. Strom, B.L., O.S. Miettinen, and K.L. Melmon, *Postmarketing studies of drug efficacy: when must they be randomized?* Clin Pharmacol Ther, 1983. **34**(1): p. 1-7.
23. Leufkens, H.G. and J. Urquhart, *Variability in patterns of drug usage*. J Pharm Pharmacol, 1994. **46 Suppl 1**: p. 433-7.
24. Ferner, R.E., *Newly licensed drugs*. BMJ, 1996. **313**(7066): p. 1157-8.
25. Friedman, M.A., J. Woodcock, M.M. Lumpkin, J.E. Shuren, A.E. Hass, and L.J. Thompson, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?* JAMA, 1999. **281**(18): p. 1728-1734.
26. Stricker, B.H. and B.M. Psaty, *Detection, verification, and quantification of adverse drug reactions*. BMJ, 2004. **329**(7456): p. 44-47.
27. Assal, F., L. Spahr, A. Hadengue, L. Rubbia-Brandt, and P.R. Burkhard, *Tolcapone and fulminant hepatitis*. Lancet, 1998. **352**(9132): p. 958.
28. Po, A.L. and W.Y. Zhang, *What lessons can be learnt from withdrawal of mibefradil from the market?* Lancet, 1998. **351**(9119): p. 1829-30.
29. Weber, W., *Drug firm withdraws statin from the market*. Lancet, 2001. **358**: p. 568.
30. Merck, *Merck announces voluntary worldwide withdrawal of VIOXX®*. Available at: http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf (accessed Sep 30, 2004). 2004.
31. Wood, A.J.J., *The Safety of New Medicines: The Importance of Asking the Right Questions*. JAMA, 1999. **281**(18): p. 1753-1754.
32. Lasser, K.E., P.D. Allen, S.J. Woolhandler, D.U. Himmelstein, S.M. Wolfe, and D.H. Bor, *Timing of new black box warnings and withdrawals for prescription medications*. JAMA, 2002. **287**(17): p. 2215-20.
33. Denig, P., F.M. Haaijer-Ruskamp, and D.H. Zijsling, *How physicians choose drugs*. Soc Sci Med, 1988. **27**(12): p. 1381-1386.
34. Denig, P. and F.M. Haaijer-Ruskamp, *Therapeutic decision making of physicians*. Pharm Weekbl Sci, 1992. **14**(1): p. 9-15.
35. Denig, P., C.L. Witteman, and H.W. Schouten, *Scope and nature of prescribing decisions made by general practitioners*. Qual Saf Health Care, 2002. **11**(2): p. 137-43.
36. Berkeley, J.S. and I.M. Richardson, *Drug usage in general practice. An analysis of the drugs prescribed by a sample of the doctors participating in the 1969-70 North-east Scotland work-load study*. J R Coll Gen Pract, 1973. **23**(128): p. 155-61.
37. Williamson, P.M., *The adoption of new drugs by doctors practising in group and solo practice*. Soc Sci Med, 1975. **9**(4-5): p. 233-236.
38. Carthy, P., I. Harvey, R. Brawn, and C. Watkins, *A study of factors associated with cost and variation in prescribing among GPs*. Fam Pract, 2000. **17**(1): p. 36-41.
39. Taylor, R.J. and C.M. Bond, *Change in the established prescribing habits of general practitioners: an analysis of initial prescriptions in general practice*. Br J Gen Pract, 1991. **41**(347): p. 244-8.

40. Mapes, R.E., *Physicians' drug innovation and relinquishment*. Soc Sci Med, 1977. **11**(11-13): p. 619-24.
41. Prosser, H. and T. Walley, *New drug uptake: qualitative comparison of high and low prescribing GPs' attitudes and approach*. Fam Pract, 2003. **20**(5): p. 583-591.
42. Rogers, E., *Diffusion of Innovations*. Fifth edition ed. 2003, New York: Free Press.
43. Dybdahl, T., M. Andersen, J. Kragstrup, I.S. Kristiansen, and J. Sondergaard, *General practitioners' adoption of new drugs and previous prescribing of drugs belonging to the same therapeutic class: a pharmacoepidemiological study*. Br J Clin Pharmacol, 2005. **I60**(5): p. 526-33.
44. Jacoby, A., M. Smith, and M. Eccles, *A qualitative study to explore influences on general practitioners' decisions to prescribe new drugs*. Br J Gen Pract, 2003. **53**(2): p. 120-5.
45. Winick, C., *The Diffusion of an Innovation Among Physicians in a Large City*. Sociometry, 1961. **24**(4): p. 384-396.
46. Coleman, J.S., E. Katz, and H. Menzel, *Medical Innovation: A Diffusion Study*. 1966, The Bobbs-Merril Company, Inc.: New York.
47. Strickland-Hodge, B. and M.H. Jepson, *Identification and characterization of early and late prescribers in general practice*. J R Soc Med, 1982. **75**(5): p. 341-5.
48. Inman, W. and G. Pearce, *Prescriber profile and post-marketing surveillance*. Lancet, 1993. **342**(8872): p. 658-661.
49. Steffensen, F.H., H.T. Sorensen, and F. Olesen, *Diffusion of new drugs in Danish general practice*. Fam Pract, 1999. **16**(4): p. 407-413.
50. Jones, M.I., M. Greenfield, and C.P. Bradley, *Prescribing new drugs: qualitative study of influences on consultants and general practitioners*. BMJ, 2001. **323**(7309): p. 378-85.
51. Jones, M.I., S.M. Greenfield, S. Jowett, C.P. Bradley, and R. Seal, *Proton pump inhibitors: a study of GPs' prescribing*. Fam Pract, 2001. **18**(3): p. 333-338.
52. Tamblyn, R., P. McLeod, J.A. Hanley, N. Girard, and J. Hurley, *Physician and practice characteristics associated with the early utilization of new prescription drugs*. Med Care, 2003. **41**(8): p. 895-908.
53. Dybdahl, T., M. Andersen, J. Sondergaard, J. Kragstrup, and I.S. Kristiansen, *Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs*. Eur J Clin Pharmacol, 2004.60(9):p.667-72.
54. de Jong, J.D., P.P. Groenewegen, and G.P. Westert, *Mutual influences of general practitioners in partnerships*. Soc Sci Med, 2003. **57**(8): p. 1515-24.
55. Prosser, H., S. Almond, and T. Walley, *Influences on GPs' decision to prescribe new drugs - the importance of who says what*. Fam Pract, 2003. **20**(1): p. 61-68.
56. Bradley, C.P., *Uncomfortable prescribing decisions: a critical incident study*. BMJ, 1992. **304**(6822): p. 294-6.
57. Cockburn, J. and S. Pit, *Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations--a questionnaire study*. BMJ, 1997. **315**(7107): p. 520-3.
58. Watkins, C., I. Harvey, P. Carthy, L. Moore, E. Robinson, and R. Brawn, *Attitudes and behaviour of general practitioners and their prescribing costs: a national cross sectional survey*. Qual Saf Health Care, 2003. **12**(1): p. 29-34.
59. McGavock, H., C.H. Webb, G.D. Johnston, and E. Milligan, *Market penetration of new drugs in one United Kingdom region: implications for general practitioners and administrators*. BMJ, 1993. **307**(6912): p. 1118-20.
60. Strickland-Hodge, B. and M.H. Jepson, *The role of the hospital consultant in general practitioner prescribing*. J R Soc Med, 1988. **81**(4): p. 207-9.

61. de Vries, C.S., N.M. van Diepen, T.F. Tromp, and L.T. de Jong-van den Berg, *Auditing GPs' prescribing habits: cardiovascular prescribing frequently continues medication initiated by specialists*. Eur J Clin Pharmacol, 1996. **50**(5): p. 349-52.

62. Bijl, D., E. Van Sonderen, and F.M. Haaijer-Ruskamp, *Prescription changes and drug costs at the interface between primary and specialist care*. Eur J Clin Pharmacol, 1998. **54**(4): p. 333-6.

63. Robertson, J., J.L. Fryer, D.L. O'Connell, A. Sprogis, and D.A. Henry, *The impact of specialists on prescribing by general practitioners*. Med J Aust, 2001. **175**(8): p. 407-11.

64. Kasje, W.N., P. Denig, and F.M. Haaijer-Ruskamp, *Specialists' expectations regarding joint treatment guidelines for primary and secondary care*. Int J Qual Health Care, 2002. **14**(6): p. 509-18.

65. Robertson, J., C.J. Treloar, A. Sprogis, and D.A. Henry, *The influence of specialists on prescribing by GPs. A qualitative study*. Aust Fam Physician, 2003. **32**(7): p. 573-6.

66. Kasje, W.N., P. Denig, P.A. De Graeff, and F.M. Haaijer-Ruskamp, *Physicians' views on joint treatment guidelines for primary and secondary care*. Int J Qual Health Care, 2004. **16**(3): p. 229-36.

67. Strickland-Hodge, B. and M.H. Jeqson, *Usage of information sources by general practitioners*. J R Soc Med, 1980. **73**(12): p. 857-62.

68. Strickland-Hodge, B. and M.H. Jepson, *Hospital consultants--an influence on GP prescribing? A pilot study*. J Clin Hosp Pharm, 1982. **7**(2): p. 131-6.

69. Peay, M.Y. and E.R. Peay, *Differences among practitioners in patterns of preference for information sources in the adoption of new drugs*. Soc Sci Med, 1984. **18**(12): p. 1019-1025.

70. Avery, A.J., S. Rodgers, T. Heron, R. Crombie, D. Whynes, M. Pringle, D. Baines, and R. Petchey, *A prescription for improvement? An observational study to identify how general practices vary in their growth in prescribing costs*. BMJ, 2000. **321**(7256): p. 276-81.

71. Schroder-Bernhardi, D. and G. Dietlein, *Lipid-lowering therapy: do hospitals influence the prescribing behavior of general practitioners?* Int J Clin Pharmacol Ther, 2002. **40**(7): p. 317-21.

72. Cochrane, R.A., A.R. Mandal, M. Ledger-Scott, and R. Walker, *Changes in drug treatment after discharge from hospital in geriatric patients*. BMJ, 1992. **305**(6855): p. 694-6.

73. Himmel, W., M. Tabache, and M.M. Kochen, *What happens to long-term medication when general practice patients are referred to hospital?* Eur J Clin Pharmacol, 1996. **50**(4): p. 253-7.

74. Feely, J., R. Chan, J. McManus, and B. O'Shea, *The influence of hospital-based prescribers on prescribing in general practice*. Pharmacoeconomics, 1999. **16**(2): p. 175-81.

75. van den Bulte, C. and G. Lilien, *Medical Innovation Revisited: Social Contagion versus Marketing Effort*. Am J Soc, 2001. **106**(5): p. 1409-1435.

76. Peay, M.Y. and E.R. Peay, *The role of commercial sources in the adoption of a new drug*. Soc Sci Med, 1988. **26**(12): p. 1183-1189.

77. Somerset, M., M. Weiss, and T. Fahey, *Dramaturgical study of meetings between general practitioners and representatives of pharmaceutical companies; Commentary: dramaturgical model gives valuable insight*. BMJ, 2001. **323**(7327): p. 1481-4.

78. Prosser, H. and T. Walley, *Understanding why GPs see pharmaceutical representatives: a qualitative interview study*. Br J Gen Pract, 2003. **53**(489): p. 305-11.

79. Watkins, C., L. Moore, I. Harvey, P. Carthy, E. Robinson, and R. Brawn, *Characteristics of general practitioners who frequently see drug industry representatives: national cross sectional study*. BMJ, 2003. **326**(7400): p. 1178-9.

80. Peay, M.Y. and E.R. Peay, *Patterns of preference for informationn sources in the adoption of new drugs by specialists*. Soc Sci Med, 1990. **31**(4): p. 467-476.

81. McGettigan, P., J. Golden, J. Fryer, R. Chan, and J. Feely, *Prescribers prefer people: The sources of information used by doctors for prescribing suggest that the medium is more important than the message*. Br J Clin Pharmacol, 2001. **51**(2): p. 184-9.

82. Jones, M., S. Greenfield, and C. Bradley, *A survey of the advertising of nine new drugs in the general practice literature*. J Clin Pharm Ther, 1999. **24**(6): p. 451-60.

83. Hepler, C.D. and L.M. Strand, *Opportunities and responsibilities in pharmaceutical care*. Am J Hosp Pharm, 1990. **47**(3): p. 533-43.

84. de Vries, C.S., *Collaboration in healthcare; the tango to drug safety, in Department of Social Pharmacy & Pharmacoepidemiology, University Centre for Pharmacy, Groningen Institute for Drug Studies*. 1998, State University Groningen: Groningen.

85. Edmunds, J. and M.W. Calnan, *The reprofessionalisation of community pharmacy? An exploration of attitudes to extended roles for community pharmacists amongst pharmacists and General Practioners in the United Kingdom*. Soc Sci Med, 2001. **53**(7): p. 943-55.

86. Muijrers, P.E., J.A. Knottnerus, J. Sijbrandij, R. Janknegt, and R.P. Grol, *Changing relationships: attitudes and opinions of general practitioners and pharmacists regarding the role of the community pharmacist*. Pharm World Sci, 2003. **25**(5): p. 235-41.

87. van Mil, J.W.F., M. Schulz, and T.F.J.D. Tromp, *Pharmaceutical care, European developments in concepts, implementation, teaching, and research: a review*. Pharm World Sci, 2004. **26**(6): p. 303-311.

88. Zillich, A.J., R.P. McDonough, B.L. Carter, and W.R. Doucette, *Influential characteristics of physician/pharmacist collaborative relationships*. Ann Pharmacother, 2004. **38**(5): p. 764-70.

89. Buurma, H., P.A. de Smet, O.P. van den Hoff, and A.C. Egberts, *Nature, frequency and determinants of prescription modifications in Dutch community pharmacies*. Br J Clin Pharmacol, 2001. **52**(1): p. 85-91.

90. Buurma, H., P.A. De Smet, H.G. Leufkens, and A.C. Egberts, *Evaluation of the clinical value of pharmacists' modifications of prescription errors*. Br J Clin Pharmacol, 2004. **58**(5): p. 503-11.

91. van Wijk, B.L., O.H. Klungel, E.R. Heerdink, and A. de Boer, *Effectiveness of interventions by community pharmacists to improve patient adherence to chronic medication: a systematic review*. Ann Pharmacother, 2005. **39**(2): p. 319-28.

92. Carroll, N.V., *Do community pharmacists influence prescribing?* J Am Pharm Assoc (Wash DC), 2003. **43**(5): p. 612-21.

93. Hawksworth, G.M., A.J. Corlett, D.J. Wright, and H. Chrystyn, *Clinical pharmacy interventions by community pharmacists during the dispensing process*. Br J Clin Pharmacol, 1999. **47**(6): p. 695-700.

94. SFK, *Succesvolle introducties [In Dutch]*. Pharm Weekbl, 2002. **137**(37): p. 1291

95. SFK, *Minder uit de pijplijn [In Dutch]*. Pharm Weekbl, 2005. **140**(18): p. 586

96. Angell, M., *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*. 2004, New York: The Random House Publishing Group.

97. Hughes, D.A., K. Bodger, P. Bytzer, D. de Herdt, and D. Dubois, *Economic analysis of on-demand maintenance therapy with proton pump inhibitors in patients with non-erosive reflux disease*. Pharmacoeconomics, 2005. **23**(10): p. 1031-41.

98. Meyboom, R.H. and I.R. Edwards, *Rosuvastatin and the statin wars--the way to peace*. Lancet. **364**(9450): p. 1997-1999.

99. *The statin wars: why AstraZeneca must retreat*. Lancet, 2003. **362**(9393): p. 1341.

100. Davidson, M.H., *Rosuvastatin safety: lessons from the FDA review and post-approval surveillance*. Expert Opin Drug Saf, 2004. **3**(6): p. 547-57.

101. Florentinus, S.R., E.R. Heerdink, O.H. Klungel, and A. de Boer, *Should rosuvastatin be withdrawn from the market?* Lancet, 2004. **364**(9445):p.1577.

102. *Changes to the product information for Crestor.* 2004 http://www.cbg-meb.nl/uk/spc/ib-crestor.pdf. (accessed Apr 3, 2006).

103. Wolfe, S.M., *Dangers of rosuvastatin identified before and after FDA approval*. Lancet, 2004. **363**(9427): p. 2189-2190.

104. Bombardier, C., L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davis, R. Day, M.B. Ferraz, C.J. Hawkey, M.C. Hochberg, T.K. Kvien, and T.J. Schnitzer, *Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group*. N Engl J Med, 2000. **343**(21): p. 1520-8, 2 p following 1528.

105. Hawkey, C.J., *COX-2 inhibitors*. Lancet, 1999. **353**(9149): p. 307-14.

106. Josefson, D., *FDA warns Merck over its promotion of rofecoxib*. BMJ, 2001. **323**(7316): p. 767a-.

107. Juni, P., L. Nartey, S. Reichenbach, R. Sterchi, P.A. Dieppe, and M. Egger, *Risk of cardiovascular events and rofecoxib: cumulative meta-analysis*. Lancet, 2004. **364**(9450): p. 2021-9.

108. Florentinus, S.R., E.R. Heerdink, A. de Boer, L. van Dijk, and H.G.M. Leufkens, *The trade-off between cardiovascular and gastrointestinal effects of rofecoxib*. Pharmacoepidemiol Drug Saf, 2005. **14**(7): p. 437-441.

109. Florentinus, S.R., M.W. Nielsen, L. van Dijk, H.G. Leufkens, E.H. Hansen, and E.R. Heerdink, *Patient characteristics associated with prescribing of a newly introduced drug: the case of rofecoxib*. Eur J Clin Pharmacol, 2005. **62**(2): p. 157-159.

110. Nefarma, *Stapsgewijze innovatie [In Dutch]*. FarmaFeiten, 2003. **3**(4) (http://www.nefarma.nl/gfx/content/RMADW2003-02778-factsheet%20Stapsgewijze%20Innovatie1.pdf) (accessed Apr 3, 2006).

Chapter 2

DATA USED IN THE UNICA PROJECT

2.1 *Linking pharmacy dispensing data to prescribing data of general practitioners.*

1. Herings, R.M.C., J. Urquhart, and H.G.M. Leufkens, *Venous thromboembolism among new users of different oral contraceptives*. Lancet, 1999. **354**(9173): p. 127-128.
2. Herings, R.M. and J.A. Erkens, *Increased suicide attempt rate among patients interrupting use of atypical antipsychotics*. Pharmacoepidemiol Drug Saf, 2003. **12**(5): p. 423-4.
3. Herings, R.M.C., A. Bakker, B.H. Stricker, and G. Nap, *Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts*. J Epidemiol Community Health, 1992. **46**(2): p. 136-40.
4. Wood, L. and C. Martinez, *The general practice research database: role in pharmacovigilance*. Drug Saf, 2004. **27**(12): p. 871-81.
5. Carroll, N.V., *Do community pharmacists influence prescribing?* J Am Pharm Assoc (Wash DC), 2003. **43**(5): p. 612-21.
6. www.LINH.nl, (accessed June 17, 2005).
7. www.NIVEL.nl, (accessed June 17, 2005).
8. Tinke, J. and A. Griens, *Facts and Figures 2004*. 2004, Foundation for Pharmaceutical Statistics: The Hague; The Netherlands.
9. Jones, R., F. Schellevis, and G. Westert, *The changing face of primary care: the second Dutch national survey*. Fam Pract, 2004. **21**(6): p. 597-598.
10. Westert, G.P., F.G. Schellevis, D.H. de Bakker, P.P. Groenewegen, J.M. Bensing, and J. van der Zee, *Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice*. Eur J Public Health, 2005. **15**(1): p. 59-65.
11. WHO, *Guidelines for ATC Classification and DDD assignment*. 1999, WHO Collaborating Centre for Drug Statistics Methodology - Nordic Council on Medicines: Oslo.
12. Lamberts, H., M. Woods, and I. Hofmans-Okkes, *The international classification of primary care in the European Community*. 1993, Oxford: Oxford University Press.
13. Beardon, P.H., M.M. McGilchrist, A.D. McKendrick, D.G. McDevitt, and T.M. MacDonald, *Primary non-compliance with prescribed medication in primary care*. BMJ, 1993. **307**(6908): p. 846-8.
14. Buurma, H., P.A. De Smet, H.G. Leufkens, and A.C. Egberts, *Evaluation of the clinical value of pharmacists' modifications of prescription errors*. Br J Clin Pharmacol, 2004. **58**(5): p. 503-11.
15. Tobi, H., N.J. van den Heuvel, and L.T. de Jong-van den Berg, *Does uncollected medication reduce the validity of pharmacy dispensing data?* Pharmacoepidemiol Drug Saf, 2004. **13**(7): p. 497-500.
16. http://www.whocc.no/ATCddd, (accessed Dec 19, 2005).
17. de Smet, P.A. and M. Dautzenberg, *Repeat prescribing: scale, problems and quality management in ambulatory care patients*. Drugs, 2004. **64**(16): p. 1779-800.
18. Buurma, H., P.A. de Smet, O.P. van den Hoff, and A.C. Egberts, *Nature, frequency and determinants of prescription modifications in Dutch community pharmacies*. Br J Clin Pharmacol, 2001. **52**(1): p. 85-91.

19. Bright, R.A., J. Avorn, and D.E. Everitt, *Medicaid data as a resource for epidemiologic studies: strengths and limitations*. J Clin Epidemiol, 1989. **42**(10): p. 937-45.
20. Stergachis, A., *Evaluating the quality of linked automated databases for use in pharmacoepidemiology,* in *Hartzema. AG. Porta, MS. Tilson, HH. eds Pharmacoepidemiology: an introduction 2nd ed*. 1991, Harvey Withney: Cincinnati. p. 222-35.
21. Simel, D.L., G.P. Samsa, and D.B. Matchar, *Likelihood ratios with confidence: sample size estimation for diagnostic test studies*. J Clin Epidemiol, 1991. **44**(8): p. 763-70.

2.2 *Discrepancies between prescribing and dispensing of medicines in general practice.*

1. Heerdink, E.R., H.G. Leufkens, C. Koppedraaijer, and A. Bakker, *Information on drug use in the elderly: a comparison of pharmacy, general-practitioner and patient data*. Pharm World Sci, 1995. **17**(1): p. 20-4.
2. Rothman, K.J., *Modern Epidemiology. 2nd edition*. 1998, Philadelphia: Lippincott Williams & Wilkins.
3. Walley, T. and A. Mantgani, *The UK General Practice Research Database*. Lancet, 1997. **350**(9084): p. 1097-1099.
4. van Staa, T.P., S. Wegman, F. de Vries, B. Leufkens, and C. Cooper, *Use of statins and risk of fractures*. JAMA, 2001. **285**(14): p. 1850-5.
5. van der Lei, J., J.S. Duisterhout, H.P. Westerhof, E. van der Does, P.V.M. Cromme, W.M. Boon, and J.H. van Bemmel, *The Introduction of Computer-based Patient Records in The Netherlands*. Ann Intern Med, 1993. **119**(10): p. 1036-1041.
6. Verhamme, K.M., J.P. Dieleman, M.A. Van Wijk, J. van der Lei, J.L. Bosch, B.H. Stricker, and M.C. Sturkenboom, *Nonsteroidal anti-inflammatory drugs and increased risk of acute urinary retention*. Arch Intern Med, 2005. **165**(13): p. 1547-51.
7. Evans, J.M.M. and T.M. MacDonald, *Record-linkage for pharmacovigilance in Scotland*. Br J Clin Pharmacol, 1999. **47**(1): p. 105-110.
8. Herings, R.M.C., J. Urquhart, and H.G.M. Leufkens, *Venous thromboembolism among new users of different oral contraceptives*. Lancet, 1999. **354**(9173): p. 127-128.
9. Jones, R., F. Schellevis, and G. Westert, *The changing face of primary care: the second Dutch national survey*. Fam Pract, 2004. **21**(6): p. 597-598.
10. Westert, G.P., F.G. Schellevis, D.H. de Bakker, P.P. Groenewegen, J.M. Bensing, and J. van der Zee, *Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice*. Eur J Public Health, 2005. **15**(1): p. 59-65.
11. Tinke, J. and A. Griens, Facts and Figures 2004. 2004, Foundation for Pharmaceutical Statistics: The Hague; The Netherlands.
12. WHO, *Guidelines for ATC Classification and DDD assignment*. 1999, WHO Collaborating Centre for Drug Statistics Methodology - Nordic Council on Medicines: Oslo.

13. Buurma, H., P.A. de Smet, O.P. van den Hoff, and A.C. Egberts, *Nature, frequency and determinants of prescription modifications in Dutch community pharmacies*. Br J Clin Pharmacol, 2001. **52**(1): p. 85-91.
14. Buurma, H., P.A. De Smet, H.G. Leufkens, and A.C. Egberts, *Evaluation of the clinical value of pharmacists' modifications of prescription errors*. Br J Clin Pharmacol, 2004. **58**(5): p. 503-11.
15. von Korff, M., E.H. Wagner, and K. Saunders, *A chronic disease score from automated pharmacy data*. J Clin Epidemiol, 1992. **45**(2): p. 197-203.
16. Rashid, A., *Do patients cash prescriptions?* Br Med J (Clin Res Ed), 1982. **284**(6308): p. 24-6.
17. Begg, D., *Do patients cash prescriptions? An audit in one practice*. J R Coll Gen Pract, 1984. **34**(262): p. 272-4.
18. Conrad, P., *The meaning of medications: another look at compliance*. Soc Sci Med, 1985. **20**(1): p. 29-37.
19. Beardon, P.H., M.M. McGilchrist, A.D. McKendrick, D.G. McDevitt, and T.M. MacDonald, *Primary non-compliance with prescribed medication in primary care*. BMJ, 1993. **307**(6908): p. 846-8.
20. Gardner, T.L., S.M. Dovey, M.W. Tilyard, and E. Gurr, *Differences between prescribed and dispensed medications*. N Z Med J, 1996. **109**(1017): p. 69-72.
21. Hagstrom, B., B. Mattsson, I.-M. Rost, and R.K. Gunnarsson, *What happened to the prescriptions?: A single, short, standardized telephone call may increase compliance*. Fam Pract, 2004. **21**(1): p. 46-50.
22. Trostle, J.A., *Medical compliance as an ideology*. Soc Sci Med, 1988. **27**(12): p. 1299-308.
23. Jones, I. and N. Britten, *Why do some patients not cash their prescriptions?* Br J Gen Pract, 1998. **48**(426): p. 903-5.
24. Clinard, F., C. Sgro, M. Bardou, M. Dumas, P. Hillon, and C. Bonithon-Kopp, *Nonsteroidal anti-inflammatory drug prescribing patterns in general practice: comparison of a general practitioner-based survey and a pharmacy-based survey in France*. Pharmacoepidemiol Drug Saf, 2001. **10**(4): p. 329-38.
25. Maselli, J.H. and R. Gonzales, *Measuring antibiotic prescribing practices among ambulatory physicians: Accuracy of administrative claims data*. J Clin Epidemiol, 2001. **54**(2): p. 196-201.
26. Florentinus, S.R., E.R. Heerdink, O.H. Klungel, and A. de Boer, *Should rosuvastatin be withdrawn from the market?* Lancet, 2004. **364**(9445):p.1577.

Chapter 3
NEW DRUGS IN GENERAL PRACTICE

3.1 *Who are the early prescribers of new drugs? Five cases of rapid market introductions.*

1. EMEA. (European Medicines Agency) http://www.emea.eu.int/pdfs/general/direct/emeaar/000204en.pdf (accessed Apr 3, 2006).
2. McGavock, H., C.H. Webb, G.D. Johnston, and E. Milligan, *Market penetration of new drugs in one United Kingdom region: implications for general practitioners and administrators*. BMJ, 1993. **307**(6912): p. 1118-20.
3. Friedman, M.A., J. Woodcock, M.M. Lumpkin, J.E. Shuren, A.E. Hass, and L.J. Thompson, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?* JAMA, 1999. **281**(18): p. 1728-1734.

4. Wood, A.J.J., *The Safety of New Medicines: The Importance of Asking the Right Questions*. JAMA, 1999. **281**(18): p. 1753-1754.
5. Lasser, K.E., P.D. Allen, S.J. Woolhandler, D.U. Himmelstein, S.M. Wolfe, and D.H. Bor, *Timing of new black box warnings and withdrawals for prescription medications*. JAMA, 2002. **287**(17): p. 2215-20.
6. Florentinus, S.R., E.R. Heerdink, O.H. Klungel, and A. de Boer, *Should rosuvastatin be withdrawn from the market?* Lancet, 2004. **364**(9445): p. 1577.
7. Florentinus, S.R., E.R. Heerdink, A. de Boer, L. van Dijk, and H.G.M. Leufkens, *The trade-off between cardiovascular and gastrointestinal effects of rofecoxib*. Pharmacoepidemiol Drug Saf, 2005. **14**(7): p. 437-441.
8. Inman, W. and G. Pearce, *Prescriber profile and post-marketing surveillance*. Lancet, 1993. **342**(8872): p. 658-661.
9. Leufkens, H.G. and J. Urquhart, *Prescriber profile and postmarketing surveillance*. Lancet, 1993. **342**(8880): p. 1178.
10. Tamblyn, R., P. McLeod, J.A. Hanley, N. Girard, and J. Hurley, *Physician and practice characteristics associated with the early utilization of new prescription drugs*. Med Care, 2003. **41**(8): p. 895-908.
11. Prosser, H. and T. Walley, *New drug uptake: qualitative comparison of high and low prescribing GPs' attitudes and approach*. Fam Pract, 2003. **20**(5): p. 583-591.
12. Jones, M.I., M. Greenfield, and C.P. Bradley, *Prescribing new drugs: qualitative study of influences on consultants and general practitioners*. BMJ, 2001. **323**(7309): p. 378-85.
13. Jacoby, A., M. Smith, and M. Eccles, *A qualitative study to explore influences on general practitioners' decisions to prescribe new drugs*. Br J Gen Pract, 2003. **53**(2): p. 120-5.
14. Prosser, H. and T. Walley, *Understanding why GPs see pharmaceutical representatives: a qualitative interview study*. Br J Gen Pract, 2003. **53**(489): p. 305-11.
15. Cardol, M., P.P. Groenewegen, D.H. de Bakker, P. Spreeuwenberg, L. van Dijk, and W. van den Bosch, *Shared help seeking behaviour within families: a retrospective cohort study*. BMJ, 2005. **330**(7496): p. 882.
16. Westert, G.P., F.G. Schellevis, D.H. de Bakker, P.P. Groenewegen, J.M. Bensing, and J. van der Zee, *Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice*. Eur J Public Health, 2005. **15**(1): p. 59-65.
17. Tinke, J. and A. Griens, *Facts and Figures 2001*. 2001, Foundation for Pharmaceutical Statistics: The Hague; The Netherlands.
18. Herings, R.M.C., A. Bakker, B.H. Stricker, and G. Nap, *Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts*. J Epidemiol Community Health, 1992. **46**(2): p. 136-40.
19. van Dijk, L., H. Barnhoorn, and D.H. De Bakker, *Het Farmaco Therapie Overleg in 1999; stand van zaken en effecten op voorschrijven [In Dutch: Pharmacotherapy audit meetings in 1999: the state of affairs]*. 2001, NIVEL: Utrecht.
20. Leyland, A.H. and H. Goldstein, *Multilevel Modelling of Health Statistics*. 2001, Chichester: John Wiley & Sons, Ltd.
21. Leyland, A.H. and P.P. Groenewegen, *Multilevel modelling and public health policy*. Scand J Public Health, 2003. **31**(4): p. 267-74.
22. von Korff, M., E.H. Wagner, and K. Saunders, *A chronic disease score from automated pharmacy data*. J Clin Epidemiol, 1992. **45**(2): p. 197-203.
23. Dybdahl, T., M. Andersen, J. Sondergaard, J. Kragstrup, and I.S. Kristiansen, *Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs*. Eur J Clin Pharmacol, 2004.

24. Prosser, H., S. Almond, and T. Walley, *Influences on GPs' decision to prescribe new drugs - the importance of who says what*. Fam Pract, 2003. **20**(1): p. 61-68.
25. Williamson, P.M., *The adoption of new drugs by doctors practising in group and solo practice*. Soc Sci Med, 1975. **9**(4-5): p. 233-236.
26. Steffensen, F.H., H.T. Sorensen, and F. Olesen, *Diffusion of new drugs in Danish general practice*. Fam Pract, 1999. **16**(4): p. 407-413.
27. de Jong, J.D., P.P. Groenewegen, and G.P. Westert, *Mutual influences of general practitioners in partnerships*. Soc Sci Med, 2003. **57**(8): p. 1515-24.
28. McGettigan, P., J. Golden, J. Fryer, R. Chan, and J. Feely, *Prescribers prefer people: The sources of information used by doctors for prescribing suggest that the medium is more important than the message*. Br J Clin Pharmacol, 2001. **51**(2): p. 184-9.
29. Prosser, H. and T. Walley, *A qualitative study of GPs' and PCO stakeholders' views on the importance and influence of cost on prescribing*. Soc Sci Med, 2005. **60**(6): p. 1335-1346.

3.2 *Is new drug prescribing specialist induced?*

1. Inman, W. and G. Pearce, *Prescriber profile and post-marketing surveillance*. Lancet, 1993. **342**(8872): p. 658-661.
2. Leufkens, H.G. and J. Urquhart, *Prescriber profile and postmarketing surveillance*. Lancet, 1993. **342**(8880): p. 1178.
3. Tamblyn, R., P. McLeod, J.A. Hanley, N. Girard, and J. Hurley, *Physician and practice characteristics associated with the early utilization of new prescription drugs*. Med Care, 2003. **41**(8): p. 895-908.
4. Pryce, A.J., H.F. Heatlie, and S.R. Chapman, *Buccaling under the pressure: influence of secondary care establishments on the prescribing of glyceryl trinitrate buccal tablets in primary care*. BMJ, 1996. **313**(7072): p. 1621-1624.
5. Cochrane, R.A., A.R. Mandal, M. Ledger-Scott, and R. Walker, *Changes in drug treatment after discharge from hospital in geriatric patients*. BMJ, 1992. **305**(6855): p. 694-6.
6. Avery, A.J., S. Rodgers, T. Heron, R. Crombie, D. Whynes, M. Pringle, D. Baines, and R. Petchey, *A prescription for improvement? An observational study to identify how general practices vary in their growth in prescribing costs*. BMJ, 2000. **321**(7256): p. 276-81.
7. de Vries, C.S., N.M. van Diepen, T.F. Tromp, and L.T. de Jong-van den Berg, *Auditing GPs' prescribing habits: cardiovascular prescribing frequently continues medication initiated by specialists*. Eur J Clin Pharmacol, 1996. **50**(5): p. 349-52.
8. Feely, J., R. Chan, J. McManus, and B. O'Shea, *The influence of hospital-based prescribers on prescribing in general practice*. Pharmacoeconomics, 1999. **16**(2): p. 175-81.
9. Robertson, J., J.L. Fryer, D.L. O'Connell, A. Sprogis, and D.A. Henry, *The impact of specialists on prescribing by general practitioners*. Med J Aust, 2001. **175**(8): p. 407-11.
10. Friedman, M.A., J. Woodcock, M.M. Lumpkin, J.E. Shuren, A.E. Hass, and L.J. Thompson, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?* JAMA, 1999. **281**(18): p. 1728-1734.

11. Wood, A.J.J., *The Safety of New Medicines: The Importance of Asking the Right Questions*. JAMA, 1999. **281**(18): p. 1753-1754.
12. Cardol, M., P.P. Groenewegen, D.H. de Bakker, P. Spreeuwenberg, L. van Dijk, and W. van den Bosch, *Shared help seeking behaviour within families: a retrospective cohort study*. BMJ, 2005. **330**(7496): p. 882.
13. Westert, G.P., F.G. Schellevis, D.H. de Bakker, P.P. Groenewegen, J.M. Bensing, and J. van der Zee, *Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice*. Eur J Public Health, 2005. **15**(1): p. 59-65.
14. Tinke, J. and A. Griens, *Facts and Figures 2001*. 2001, Foundation for Pharmaceutical Statistics: The Hague; The Netherlands.
15. Herings, R.M.C., A. Bakker, B.H. Stricker, and G. Nap, *Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts*. J Epidemiol Community Health, 1992. **46**(2): p. 136-40.
16. Coleman, J.S., E. Katz, and H. Menzel, *Medical Innovation: A Diffusion Study*. 1966, The Bobbs-Merril Company, Inc.: New York.
17. Rogers, E., *Diffusion of Innovations*. 1995, New York: Free Press.
18. Jones, M.I., M. Greenfield, and C.P. Bradley, *Prescribing new drugs: qualitative study of influences on consultants and general practitioners*. BMJ, 2001. **323**(7309): p. 378-85.
19. Jacoby, A., M. Smith, and M. Eccles, *A qualitative study to explore influences on general practitioners' decisions to prescribe new drugs*. Br J Gen Pract, 2003. **53**(2): p. 120-5.
20. Himmel, W., M. Tabache, and M.M. Kochen, *What happens to long-term medication when general practice patients are referred to hospital?* Eur J Clin Pharmacol, 1996. **50**(4): p. 253-7.
21. Robertson, J., C.J. Treloar, A. Sprogis, and D.A. Henry, *The influence of specialists on prescribing by GPs. A qualitative study*. Aust Fam Physician, 2003. **32**(7): p. 573-6.
22. Josefson, D., *FDA warns Merck over its promotion of rofecoxib*. BMJ, 2001. **323**(7316): p. 767a-.
23. Burton, B., *AstraZeneca digs in over advertising criticisms*. BMJ, 2004. **328**(7447): p. 1035-a-.
24. Florentinus, S.R., E.R. Heerdink, O.H. Klungel, and A. de Boer, *Should rosuvastatin be withdrawn from the market?* Lancet, 2004. **364**(9445):p.1577.
25. Florentinus, S.R., E.R. Heerdink, A. de Boer, L. van Dijk, and H.G.M. Leufkens, *The trade-off between cardiovascular and gastrointestinal effects of rofecoxib*. Pharmacoepidemiol Drug Saf, 2005. **14**(7): p. 437-441.
26. Florentinus, S.R., M.W. Nielsen, L. van Dijk, H.G. Leufkens, E.H. Hansen, and E.R. Heerdink, *Patient characteristics associated with prescribing of a newly introduced drug: the case of rofecoxib*. Eur J Clin Pharmacol, 2005. **62**(2): p. 157-159.
27. Leufkens, H.G., J. Urquhart, B.H. Stricker, A. Bakker, and H. Petri, *Channelling of controlled release formulation of ketoprofen (Oscorel) in patients with history of gastrointestinal problems*. J Epidemiol Community Health, 1992. 46(4): p. 428-32.

3.3 The effect of pharmacotherapy audit meetings on new drug prescribing by general practitioners.

1. Inman, W. and G. Pearce, *Prescriber profile and post-marketing surveillance*. Lancet, 1993. **342**(8872): p. 658-661.
2. Tamblyn, R., P. McLeod, J.A. Hanley, N. Girard, and J. Hurley, *Physician and practice characteristics associated with the early utilization of new prescription drugs*. Med Care, 2003. **41**(8): p. 895-908.
3. Dybdahl, T., M. Andersen, J. Sondergaard, J. Kragstrup, and I.S. Kristiansen, *Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs*. Eur J Clin Pharmacol, 2004.60(9):p.667-72.
4. Friedman, M.A., J. Woodcock, M.M. Lumpkin, J.E. Shuren, A.E. Hass, and L.J. Thompson, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?* JAMA, 1999. **281**(18): p. 1728-1734.
5. Florentinus, S.R., E.R. Heerdink, O.H. Klungel, and A. de Boer, *Should rosuvastatin be withdrawn from the market?* Lancet, 2004. **364**(9445):p.1577.
6. Florentinus, S.R., E.R. Heerdink, A. de Boer, L. van Dijk, and H.G.M. Leufkens, *The trade-off between cardiovascular and gastrointestinal effects of rofecoxib*. Pharmacoepidemiol Drug Saf, 2005. **14**(7): p. 437-441.
7. Jones, M.I., M. Greenfield, and C.P. Bradley, *Prescribing new drugs: qualitative study of influences on consultants and general practitioners*. BMJ, 2001. **323**(7309): p. 378-85.
8. Jacoby, A., M. Smith, and M. Eccles, *A qualitative study to explore influences on general practitioners' decisions to prescribe new drugs*. Br J Gen Pract, 2003. **53**(2): p. 120-5.
9. Prosser, H., S. Almond, and T. Walley, *Influences on GPs' decision to prescribe new drugs - the importance of who says what*. Fam Pract, 2003. **20**(1): p. 61-68.
10. Hughes, C.M. and S. McCann, *Perceived interprofessional barriers between community pharmacists and general practitioners: a qualitative assessment*. Br J Gen Pract, 2003. **53**(493): p. 600-6.
11. Zillich, A.J., R.P. McDonough, B.L. Carter, and W.R. Doucette, *Influential characteristics of physician/pharmacist collaborative relationships*. Ann Pharmacother, 2004. **38**(5): p. 764-70.
12. Blom, A.T., A.H. Paes, A. Bakker, C.J. Koopman, and C. van der Meer, *Pharmacist-physician co-operation at a regional level*. Pharm World Sci, 1994. **16**(1): p. 13-7.
13. van Dijk, L., H. Barnhoorn, and D.H. De Bakker, Het Farmaco *Therapie Overleg in 1999; stand van zaken en effecten op voorschrijven [In Dutch: Pharmacotherapy audit meetings in 1999: the state of affairs]*. 2001, NIVEL: Utrecht.
14. DGV, *FTO-peiling 2003 [In Dutch]*. 2003, Dutch Institute for Effective Use of Medication: Utrecht http://www.medicijngebruik.nl/content/17_vind_op_thema/17-7-1.htm (accessed august 10, 2005).
15. Muijrers, P.E.M., R.P.T.M. Grol, J. Sijbrandij, R. Janknegt, and J.A. Knottnerus, *Differences in prescribing between GPs. Impact of the cooperation with pharmacists and impact of visits from pharmaceutical industry representatives*. Fam Pract, 2005: p. cmi074.
16. Westert, G.P., F.G. Schellevis, D.H. de Bakker, P.P. Groenewegen, J.M. Bensing, and J. van der Zee, *Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice*. Eur J Public Health, 2005. **15**(1): p. 59-65.
17. Tinke, J. and A. Griens, Facts and Figures 2003. 2003, *Foundation for Pharmaceutical Statistics: The Hague; The Netherlands*.

18. Herings, R.M.C., A. Bakker, B.H. Stricker, and G. Nap, *Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts*. J Epidemiol Community Health, 1992. **46**(2): p. 136-40.
19. Leyland, A.H. and P.P. Groenewegen, *Multilevel modelling and public health policy*. Scand J Public Health, 2003. **31**(4): p. 267-74.
20. von Korff, M., E.H. Wagner, and K. Saunders, *A chronic disease score from automated pharmacy data*. J Clin Epidemiol, 1992. **45**(2): p. 197-203.
21. Prosser, H. and T. Walley, *New drug uptake: qualitative comparison of high and low prescribing GPs' attitudes and approach*. Fam Pract, 2003. **20**(5): p. 583-591.
22. de Jong, J.D., P.P. Groenewegen, and G.P. Westert, *Mutual influences of general practitioners in partnerships*. Soc Sci Med, 2003. **57**(8): p. 1515-24.
23. Veninga, C.C.M., P. Denig, R. Zwaagstra, and F.M. Haaijer-Ruskamp, *Improving drug treatment in general practice*. Journal of Clinical Epidemiology, 2000. **53**(7): p. 762-772.
24. Watkins, C., L. Moore, I. Harvey, P. Carthy, E. Robinson, and R. Brawn, *Characteristics of general practitioners who frequently see drug industry representatives: national cross sectional study*. BMJ, 2003. **326**(7400): p. 1178-9.
25. Blumenthal, D., *Doctors and drug companies*. N Engl J Med, 2004. **351**(18): p. 1885-90.
26. Muijrers, P.E., J.A. Knottnerus, J. Sijbrandij, R. Janknegt, and R.P. Grol, *Changing relationships: attitudes and opinions of general practitioners and pharmacists regarding the role of the community pharmacist*. Pharm World Sci, 2003. **25**(5): p. 235-41.

3.4 *Which pharmacists contribute to high-level pharmacotherapy audit meetings with GPs?*

1. Guzman, J., R. Esmail, K. Karjalainen, A. Malmivaara, E. Irvin, and C. Bombardier, *Multidisciplinary rehabilitation for chronic low back pain: systematic review*. BMJ, 2001. **322**(7301): p. 1511-1516.
2. Hughes, C.M. and S. McCann, *Perceived interprofessional barriers between community pharmacists and general practitioners: a qualitative assessment*. Br J Gen Pract, 2003. **53**(493): p. 600-6.
3. Zillich, A.J., R.P. McDonough, B.L. Carter, and W.R. Doucette, *Influential characteristics of physician/pharmacist collaborative relationships*. Ann Pharmacother, 2004. **38**(5): p. 764-70.
4. Avery, A.J. and M. Pringle, *Extended prescribing by UK nurses and pharmacists*. BMJ, 2005. **331**(7526): p. 1154-1155.
5. Medicines and Healthcare *Products Regulatory Agency (MHRA), D.o.H. Consultation on proposals to introduce independent prescribing by pharmacists*. www.dh.gov.uk/assetRoot/04/10/48/81/04104881.pdf (accessed Nov 14, 2005).
6. van Mil, J.W.F., M. Schulz, and T.F.J.D. Tromp, *Pharmaceutical care, European developments in concepts, implementation, teaching, and research: a review*. Pharm World Sci, 2004. **26**(6): p. 303-311.
7. CoAst-Senior, E.A., B.A. Kroner, C.L. Kelley, and L.E. Trilli, *Management of patients with type 2 diabetes by pharmacists in primary care clinics*. Ann Pharmacother, 1998. **32**(6): p. 636-41.

8. Leape, L.L., D.J. Cullen, M.D. Clapp, E. Burdick, H.J. Demonaco, J.I. Erickson, and D.W. Bates, *Pharmacist participation on physician rounds and adverse drug events in the intensive care unit*. JAMA, 1999. **282**(3): p. 267-70.
9. Borenstein, J.E., G. Graber, E. Saltiel, J. Wallace, S. Ryu, J. Archi, S. Deutsch, and S.R. Weingarten, *Physician-pharmacist comanagement of hypertension: a randomized, comparative trial*. Pharmacotherapy, 2003. **23**(2): p. 209-16.
10. Bradley, C.P., R.J. Taylor, and A. Blenkinsopp, *Primary care--opportunities and threats. Developing prescribing in primary care*. BMJ, 1997. **314**(7082): p. 744-7.
11. Kocken, G.A., *Medication discussion groups in The Netherlands: five years of experience*. Med Educ, 1999. **33**(5): p. 390-3.
12. Blom, A.T., A.H. Paes, A. Bakker, C.J. Koopman, and C. van der Meer, *Pharmacist-physician co-operation at a regional level*. Pharm World Sci, 1994. **16**(1): p. 13-7.
13. DGV, *FTO-peiling 2003 [In Dutch]*. 2003, Dutch Institute for Effective Use of Medication: Utrecht http://www.medicijngebruik.nl/content/17_vind_op_thema/17-7-1.htm (accessed august 10, 2005).
14. de Vries, C.S., *Collaboration in healthcare; the tango to drug safety, in Department of Social Pharmacy & Pharmacoepidemiology, University Centre for Pharmacy, Groningen Institute for Drug Studies*. 1998, State University Groningen: Groningen.
15. Schellevis, F.G., G.P. Westert, D.H. De Bakker, P.P. Groenewegen, J. Van der Zee, and J.M. Bensing, *De tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: aanleiding en methoden [In Dutch]*. Huisarts Wet, 2003. **46**(1): p. 7-12.
16. Westert, G.P., F.G. Schellevis, D.H. de Bakker, P.P. Groenewegen, J.M. Bensing, and J. van der Zee, *Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice*. Eur J Public Health, 2005. **15**(1): p. 59-65.
17. van Dijk, L., H. Barnhoorn, and D.H. De Bakker, *Het Farmaco Therapie Overleg in 1999; stand van zaken en effecten op voorschrijven [In Dutch: Pharmacotherapy audit meetings in 1999: the state of affairs]*. 2001, NIVEL: Utrecht.
18. Schwarzer, R., Self-efficacy: *Thought control of action*. 1992, Washington, DC: Hemisphere.
19. Muijrers, P.E., J.A. Knottnerus, J. Sijbrandij, R. Janknegt, and R.P. Grol, *Changing relationships: attitudes and opinions of general practitioners and pharmacists regarding the role of the community pharmacist*. Pharm World Sci, 2003. **25**(5): p. 235-41.
20. Storimans, M.J., O.H. Klungel, H. Talsma, M.L. Bouvy, and C.J. de Blaey, *Collaborative services among community pharmacies for patients with diabetes*. Ann Pharmacother, 2005. **39**(10): p. 1647-52.
21. Pronk, M.C., L.T. Blom, R. Jonkers, E.M. Rogers, A. Bakker, and K.J. de Blaey, *Patient oriented activities in Dutch community pharmacy: diffusion of innovations*. Pharm World Sci, 2002. **24**(4): p. 154-61.

Chapter 4

CASE STUDIES ON NEW DRUG PRESCRIBING

4.1 *Off-label use of the new drug rofecoxib.*

1. Jones, M.I., M. Greenfield, and C.P. Bradley, P*rescribing new drugs: qualitative study of influences on consultants and general practitioners*. BMJ, 2001. **323**(7309): p. 378-85.
2. Jacoby, A., M. Smith, and M. Eccles, *A qualitative study to explore influences on general practitioners' decisions to prescribe new drugs*. Br J Gen Pract, 2003. **53**(2): p. 120-5.
3. Prosser, H., S. Almond, and T. Walley, *Influences on GPs' decision to prescribe new drugs - the importance of who says what*. Fam Pract, 2003. **20**(1): p. 61-68.
4. Prosser, H. and T. Walley, *New drug uptake: qualitative comparison of high and low prescribing GPs' attitudes and approach*. Fam Pract, 2003. **20**(5): p. 583-591.
5. Inman, W. and G. Pearce, *Prescriber profile and post-marketing surveillance*. Lancet, 1993. **342**(8872): p. 658-661.
6. Steffensen, F.H., H.T. Sorensen, and F. Olesen, *Diffusion of new drugs in Danish general practice*. Fam Pract, 1999. **16**(4): p. 407-413.
7. Tamblyn, R., P. McLeod, J.A. Hanley, N. Girard, and J. *Hurley, Physician and practice characteristics associated with the early utilization of new prescription drugs*. Med Care, 2003. **41**(8): p. 895-908.
8. Dybdahl, T., M. Andersen, J. Sondergaard, J. Kragstrup, and I.S. Kristiansen, *Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs*. Eur J Clin Pharmacol, 2004.
9. Cutts, C., A. LaCaze, and S. Tett, *A clinical audit of the prescribing of celecoxib and rofecoxib in Australian rural general practice*. Br J Clin Pharmacol, 2002. **54**(5): p. 522-7.
10. Schellevis, F.G., G.P. Westert, D.H. De Bakker, P.P. Groenewegen, J. Van der Zee, and J.M. *Bensing, De tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: aanleiding en methoden [In Dutch]*. Huisarts Wet, 2003. **46**(1): p. 7-12.
11. Westert, G.P., F.G. Schellevis, D.H. de Bakker, P.P. Groenewegen, J.M. Bensing, and J. van der Zee, *Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice*. Eur J Public Health, 2005. **15**(1): p. 59-65.
12. Schnitzer, T.J., K. Truitt, R. Fleischmann, P. Dalgin, J. Block, Q. Zeng, J. Bolognese, B. Seidenberg, and E.W. Ehrich, *The safety profile, tolerability, and effective dose range of rofecoxib in the treatment of rheumatoid arthritis*. Phase II Rofecoxib Rheumatoid Arthritis Study Group. Clin Ther, 1999. **21**(10): p. 1688-702.
13. Bombardier, C., L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davis, R. Day, M.B. Ferraz, C.J. Hawkey, M.C. Hochberg, T.K. Kvien, and T.J. Schnitzer, *Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis*. VIGOR Study Group. N Engl J Med, 2000. **343**(21): p. 1520-8, 2 p following 1528.
14. Konstam, M.A., M.R. Weir, A. Reicin, D. Shapiro, R.S. Sperling, E. Barr, and B.J. Gertz, *Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib*. Circulation, 2001. **104**(19): p. 2280-8.
15. Layton, D., J. Riley, L.V. Wilton, and S.A. Shakir, *Safety profile of rofecoxib as used in general practice in England: results of a prescription-event monitoring study*. Br J Clin Pharmacol, 2003. **55**(2): p. 166-74.

16. Juni, P., L. Nartey, S. Reichenbach, R. Sterchi, P.A. Dieppe, and M. Egger, *Risk of cardiovascular events and rofecoxib: cumulative meta-analysis*. Lancet, 2004. **364**(9450): p. 2021-9.
17. Boers, M., *NSAIDs and selective COX-2 inhibitors: competition between gastroprotection and cardioprotection*. Lancet, 2001. **357**(9264): p. 1222-3.
18. Leufkens, H.G., J. Urquhart, B.H. Stricker, A. Bakker, and H. Petri, *Channelling of controlled release formulation of ketoprofen (Oscorel) in patients with history of gastrointestinal problems*. J Epidemiol Community Health, 1992. **46**(4): p. 428-32.

4.2 *Patient characteristics associated with prescribing of a newly introduced drug: the case of rofecoxib.*

1. Merck, *Merck announces voluntary worldwide withdrawal of VIOXX®.* Available at: http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf (accessed Sep 30, 2004). 2004.
2. Topol, E.J., *Failing the public health--rofecoxib,* Merck, and the FDA. N Engl J Med, 2004. **351**(17): p. 1707-9.
3. FDA Issues Public Health Advisory on Vioxx as its Manufacturer Voluntarily Withdraws the Product. 09/30/2004. http://www.fda.gov/bbs/topics/news/2004/NEW01122.html. (accessed Apr 3, 2006).
4. Jabaaij, L.J. and D.H. De Bakker, *Artrosemiddel in de lift [In Dutch].* Medisch Contact, 2001. **56**(42).
5. Jong, t., G.W., I.A. Eland, M.C.J.M. Sturkenboom, v.d. Anker, J.N., and B.H.C. Stricker, *Unlicensed and off label prescription of drug to children: population based cohort study*. BMJ, 2002. **324**: p. 1313-1314.
6. Schirm, E., H. Tobi, and L.T. de Jong-van den Berg, *Risk factors for unlicensed and off-label drug use in children outside the hospital*. Pediatrics, 2003. **111**(2): p. 291-5.
7. Turner, S., A. Gill, T. Nunn, B. Hewitt, and I. Choonara, *Use of "off-label" and unlicensed drugs in paediatric intensive care unit*. Lancet, 1996. **347**(9000): p. 549-50.
8. www.FDA.com, http://www.fda.gov/cder/foi/nda/99/021042_52_vioxx_appltr.pdf. 1999 (accessed Apr 3, 2006).
9. Malmstrom, K., S. Daniels, P. Kotey, B.C. Seidenberg, and P.J. Desjardins, *Comparison of rofecoxib and celecoxib, two cyclo-oxygenase-2 inhibitors, in postoperative dental pain: a randomized, placebo- and active-comparator-controlled clinical trial*. Clin Ther, 1999. **21**(10): p. 1653-63.
10. Schnitzer, T.J., K. Truitt, R. Fleischmann, P. Dalgin, J. Block, Q. Zeng, J. Bolognese, B. Seidenberg, and E.W. Ehrich, *The safety profile, tolerability, and effective dose range of rofecoxib in the treatment of rheumatoid arthritis*. Phase II Rofecoxib Rheumatoid Arthritis Study Group. Clin Ther, 1999. **21**(10): p. 1688-702.
11. Schellevis, F.G., G.P. Westert, D.H. De Bakker, P.P. Groenewegen, J. Van der Zee, and J.M. Bensing, *De tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: aanleiding en methoden [In Dutch].* Huisarts Wet, 2003. **46**(1): p. 7-12.
12. Westert, G.P., F.G. Schellevis, D.H. de Bakker, P.P. Groenewegen, J.M. Bensing, and J. van der Zee, *Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice*. Eur J Public Health, 2005. **15**(1): p. 59-65.

13. Lamberts, H. and M. Wood, *International Classification of Primary Care*. 1984, Oxford: Oxford University Press. 201.
14. Leyland, A.H. and H. Goldstein, *Multilevel Modelling of Health Statistics*. 2001, Chichester: John Wiley & Sons, Ltd.
15. Leyland, A.H. and P.P. Groenewegen, *Multilevel modelling and public health policy*. Scand J Public Health, 2003. **31**(4): p. 267-74.
16. Leufkens, H.G., J. Urquhart, B.H. Stricker, A. Bakker, and H. Petri, *Channelling of controlled release formulation of ketoprofen (Oscorel) in patients with history of gastrointestinal problems*. J Epidemiol Community Health, 1992. **46**(4): p. 428-32.
17. Florentinus, S.R., E.R. Heerdink, O.H. Klungel, and A. de Boer, *Should rosuvastatin be withdrawn from the market?* Lancet, 2004. **364**(9445):p.1577.
18. Florentinus, S., E.R. Heerdink, A. de Boer, L. van Dijk, and H.G.M. Leufkens, *The trade-off between cardiovascular and gastrointestinal effects of rofecoxib*. Pharmacoepidemiol Drug Saf, 2005. **14**(7): p. 437-441.
19. Florentinus, S.R., M.W. Nielsen, L. van Dijk, H.G. Leufkens, E.H. Hansen, and E.R. Heerdink, *Patient characteristics associated with prescribing of a newly introduced drug: the case of rofecoxib*. Eur J Clin Pharmacol, 2005. **62**(2): p. 157-159.
20. Cutts, C., A. LaCaze, and S. Tett, *A clinical audit of the prescribing of celecoxib and rofecoxib in Australian rural general practice*. Br J Clin Pharmacol, 2002. **54**(5): p. 522-7.
21. Kerr, S.J., A. Mant, F.E. Horn, K. McGeechan, and G.P. Sayer, *Lessons from early large-scale adoption of celecoxib and rofecoxib by Australian general practitioners*. Med J Aust, 2003. **179**(8): p. 403-7.
22. Banta, H.D., *Social science research on medical technology: utility and limitations*. Soc Sci Med, 1983. **17**(18): p. 1363-9.
23. Banta, H.D. and H. Vondeling, *Diffusion of minimally invasive therapy in Europe*. Health Policy, 1993. **23**(1-2): p. 125-33.
24. Tamblyn, R., P. McLeod, J.A. Hanley, N. Girard, and J. Hurley, *Physician and practice characteristics associated with the early utilization of new prescription drugs*. Med Care, 2003. **41**(8): p. 895-908.
25. Bombardier, C., L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davis, R. Day, M.B. Ferraz, C.J. Hawkey, M.C. Hochberg, T.K. Kvien, and T.J. Schnitzer, *Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis*. VIGOR Study Group. N Engl J Med, 2000. **343**(21): p. 1520-8, 2 p following 1528.
26. Silverstein, F.E., G. Faich, J.L. Goldstein, L.S. Simon, T. Pincus, A. Whelton, R. Makuch, G. Eisen, N.M. Agrawal, W.F. Stenson, A.M. Burr, W.W. Zhao, J.D. Kent, J.B. Lefkowith, K.M. Verburg, and G.S. Geis, *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**(10): p. 1247-55.
27. Langman, M.J., D.M. Jensen, D.J. Watson, S.E. Harper, P.L. Zhao, H. Quan, J.A. Bolognese, and T.J. Simon, *Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs*. JAMA, 1999. **282**(20): p. 1929-33.
28. Layton, D., J. Riley, L.V. Wilton, and S.A. Shakir, *Safety profile of rofecoxib as used in general practice in England: results of a prescription-event monitoring study*. Br J Clin Pharmacol, 2003. **55**(2): p. 166-74.

29. Kvien, T.K., *Epidemiology and burden of illness of rheumatoid arthritis*. Pharmacoeconomics, 2004. **22**(2 Suppl): p. 1-12.
30. Josefson, D., *FDA warns Merck over its promotion of rofecoxib*. BMJ, 2001. **323**(7316): p. 767a.

4.3 *Trade-off between cardiovascular and gastrointestinal effects of rofecoxib in 2001.*

1. Hawkey, C.J., *COX-2 inhibitors*. Lancet, 1999. **353**(9149): p. 307-14.
2. Weir, M.R., R.S. Sperling, A. Reicin, and B.J. Gertz, *Selective COX-2 inhibition and cardiovascular effects: a review of the rofecoxib development program*. American Heart Journal, 2003. **146**(4): p. 591-604.
3. Bombardier, C., L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davis, R. Day, M.B. Ferraz, C.J. Hawkey, M.C. Hochberg, T.K. Kvien, and T.J. Schnitzer, *Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis*. VIGOR Study Group. N Engl J Med, 2000. **343**(21): p. 1520-8, 2 p following 1528.
4. Boers, M., *NSAIDs and selective COX-2 inhibitors: competition between gastroprotection and cardioprotection*. Lancet, 2001. **357**(9264): p. 1222-3.
5. Boers, M., *Discontinuation of Vioxx*. Lancet, 2004. **365**: p. 25-26.
6. Juni, P., L. Nartey, S. Reichenbach, R. Sterchi, P.A. Dieppe, and M. Egger, *Risk of cardiovascular events and rofecoxib cumulative meta-analysis*. Lancet, 2004. **364**(9450): p. 2021-9.
7. Topol, E.J., Failing the public health--rofecoxib, *Merck, and the FDA*. N Engl J Med, 2004. **351**(17): p. 1707-9.
8. Merck, *Merck announces voluntary worldwide withdrawal of VIOXX®*. Available at: http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf (accessed Sep 30, 2004). 2004.
9. Schellevis, F.G., G.P. Westert, D.H. De Bakker, P.P. Groenewegen, J. Van der Zee, and J.M. Bensing, *De tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: aanleiding en methoden [In Dutch]*. Huisarts Wet, 2003. **46**(1): p. 7-12.
10. Westert, G.P., F.G. Schellevis, D.H. de Bakker, P.P. Groenewegen, J.M. Bensing, and J. van der Zee, *Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice*. Eur J Public Health, 2005. **15**(1): p. 59-65.
11. Lamberts, H., M. Woods, and I. Hofmans-Okkes, *The international classification of primary care in the European Community*. 1993, Oxford: Oxford University Press.
12. Rogers, E., *Diffusion of Innovations*. Fifth edition ed. 2003, New York: Free Press.
13. Cutts, C., A. LaCaze, and S. Tett, *A clinical audit of the prescribing of celecoxib and rofecoxib in Australian rural general practice*. Br J Clin Pharmacol, 2002. **54**(5): p. 522-7.
14. Kerr, S.J., A. Mant, F.E. Horn, K. McGeechan, and G.P. Sayer, *Lessons from early large-scale adoption of celecoxib and rofecoxib by Australian general practitioners*. Med J Aust, 2003. **179**(8): p. 403-7.
15. Layton, D., J. Riley, L.V. Wilton, and S.A. *Shakir, Safety profile of rofecoxib as used in general practice in England: results of a prescription-event monitoring study*. Br J Clin Pharmacol, 2003. **55**(2): p. 166-74.

16. Konstam, M.A., M.R. Weir, A. Reicin, D. Shapiro, R.S. Sperling, E. Barr, and B.J. Gertz, *Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib*. Circulation, 2001. **104**(19): p. 2280-8.
17. Mukherjee, D., S.E. Nissen, and E.J. Topol, *Risk of cardiovascular events associated with selective COX-2 inhibitors*. JAMA, 2001. **286**(8): p. 954-9.
18. Mamdani, M., P.A. Rochon, D.N. Juurlink, A. Kopp, G.M. Anderson, G. Naglie, P.C. Austin, and A. Laupacis, *Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo-oxygenase-2 inhibitors or conventional nonsteroidal anti-inflammatory drugs*. BMJ, 2002. **325**(7365): p. 624.
19. MacDonald, T.M., S.V. Morant, J.L. Goldstein, T.A. Burke, and D. Pettitt, *Channelling bias and the incidence of gastrointestinal haemorrhage in users of meloxicam, coxibs, and older, non-specific nonsteroidal anti-inflammatory drugs*. Gut, 2003. **52**(9): p. 1265-1270.
20. Mamdani, M., D.N. Juurlink, D.S. Lee, P.A. Rochon, A. Kopp, G. Naglie, P.C. Austin, A. Laupacis, and P.T.A. Stukel, *Cyclo-oxygenase-2 inhibitors versus non-selective nonsteroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study*. Lancet, 2004. **363**(9423): p. 1751-1756.
21. GIP, *GIP-databank at www.cvz.nl* The Dutch Health Care Insurance Board (accessed Apr 3, 2006).

4.4 *The use of rosuvastatin shortly after marketing.*

1. Friedman, M.A., J. Woodcock, M.M. Lumpkin, J.E. Shuren, A.E. Hass, and L.J. Thompson, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?* JAMA, 1999. **281**(18): p. 1728-1734.
2. Wood, A.J.J., *The Safety of New Medicines: The Importance of Asking the Right Questions*. JAMA, 1999. **281**(18): p. 1753-1754.
3. Lasser, K.E., P.D. Allen, S.J. Woolhandler, D.U. Himmelstein, S.M. Wolfe, and D.H. Bor, *Timing of new black box warnings and withdrawals for prescription medications*. JAMA, 2002. **287**(17): p. 2215-20.
4. Boers, M., *NSAIDs and selective COX-2 inhibitors: competition between gastroprotection and cardioprotection*. Lancet, 2001. **357**(9264): p. 1222-3.
5. Josefson, D., *FDA warns Merck over its promotion of rofecoxib*. BMJ, 2001. **323**(7316): p. 767a.
6. Mukherjee, D., S.E. Nissen, and E.J. Topol, *Risk of cardiovascular events associated with selective COX-2 inhibitors*. JAMA, 2001. **286**(8): p. 954-9.
7. *The statin wars: why AstraZeneca must retreat*. Lancet, 2003. **362**(9393): p. 1341.
8. Wolfe, S.M., *Dangers of rosuvastatin identified before and after FDA approval*. Lancet, 2004. **363**(9427): p. 2189-2190.
9. *Changes to the product information for Crestor.* 2004 http://www.cbg-meb.nl/uk/spc/ib-crestor.pdf. (accessed Apr 3, 2006).
10. Ault, A., *Pressure group urges rosuvastatin recall*. Lancet, 2004. **363**(9412): p. 871.
11. Inman, W. and G. Pearce, P*rescriber profile and post-marketing surveillance*. Lancet, 1993. **342**(8872): p. 658-661.
12. Leufkens, H.G. and J. Urquhart, *Prescriber profile and postmarketing surveillance*. Lancet, 1993. **342**(8880): p. 1178.

13. Tamblyn, R., P. McLeod, J.A. Hanley, N. Girard, and J. Hurley, *Physician and practice characteristics associated with the early utilization of new prescription drugs*. Med Care, 2003. **41**(8): p. 895-908.
14. Jones, R., F. Schellevis, and G. Westert, *The changing face of primary care: the second Dutch national survey*. Fam Pract, 2004. **21**(6): p. 597-598.
15. Cardol, M., P.P. Groenewegen, D.H. de Bakker, P. Spreeuwenberg, L. van Dijk, and W. van den Bosch, *Shared help seeking behaviour within families: a retrospective cohort study*. BMJ, 2005. **330**(7496): p. 882.
16. Westert, G.P., F.G. Schellevis, D.H. de Bakker, P.P. Groenewegen, J.M. Bensing, and J. van der Zee, *Monitoring health inequalities through general practice: the Second Dutch National Survey of General Practice*. Eur J Public Health, 2005. **15**(1): p. 59-65.
17. Schellevis, F.G., G.P. Westert, D.H. De Bakker, P.P. Groenewegen, J. Van der Zee, and J.M. Bensing, *De tweede nationale studie naar ziekten en verrichtingen in de huisartspraktijk: aanleiding en methoden [In Dutch]*. Huisarts Wet, 2003. **46**(1): p. 7-12.
18. Tinke, J. and A. Griens, *Facts and Figures 2002*. 2002, Foundation for Pharmaceutical Statistics: The Hague; The Netherlands.
19. Herings, R.M.C., *PHARMO; a record linkage system for postmarketing surveillance of prescription drugs in The Netherlands, in Utrecht Institute for Pharmaceutical Sciences*. 1993, Utrecht University: Utrecht.
20. Weber, W., *Drug firm withdraws statin from the market*. Lancet, 2001. **358**: p. 568.
21. Pirmohamed, M., S. James, S. Meakin, C. Green, A.K. Scott, T.J. Walley, K. Farrar, B.K. Park, and A.M. Breckenridge, *Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients*. BMJ, 2004. **329**(7456): p. 15-9.
22. Bombardier, C., L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davis, R. Day, M.B. Ferraz, C.J. Hawkey, M.C. Hochberg, T.K. Kvien, and T.J. Schnitzer, *Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group*. N Engl J Med, 2000. 343(21): p. 1520-8, 2 p following 1528.
23. Konstam, M.A., M.R. Weir, A. Reicin, D. Shapiro, R.S. Sperling, E. Barr, and B.J. Gertz, *Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib*. Circulation, 2001. **104**(19): p. 2280-8.
24. Layton, D., E. Heeley, K. Hughes, and S.A. Shakir, *Comparison of the incidence rates of thromboembolic events reported for patients prescribed rofecoxib and meloxicam in general practice in England using prescription-event monitoring (PEM) data*. Rheumatology (Oxford), 2003. **42**(11): p. 1342-53.
25. Mamdani, M., P. Rochon, D.N. Juurlink, G.M. Anderson, A. Kopp, G. Naglie, P.C. Austin, and A. Laupacis, *Effect of selective cyclo-oxygenase 2 inhibitors and naproxen on short-term risk of acute myocardial infarction in the elderly*. Arch Intern Med, 2003. **163**(4): p. 481-6.
26. Weir, M.R., R.S. Sperling, A. Reicin, and B.J. Gertz, *Selective COX-2 inhibition and cardiovascular effects: a review of the rofecoxib development program*. American Heart Journal, 2003. **146**(4): p. 591-604.
27. SFK, *Méér gebruikers cholesterolverlagers [In Dutch]*. Pharm Weekblad, 2003. **138**(38).

Chapter 5
GENERAL DISCUSSION

1. Lichtenberg, F.R., *The impact of new drug launches on longevity: evidence from longitudinal disease-level data from 52 countries,* 1982-2001. 2003, National Bureau of Economic Research: Cambridge.
2. Strom, B.L., O.S. Miettinen, and K.L. Melmon, *Postmarketing studies of drug efficacy: when must they be randomized?* Clin Pharmacol Ther, 1983. **34**(1): p. 1-7.
3. Stricker, B.H. and B.M. Psaty, *Detection, verification, and quantification of adverse drug reactions*. BMJ, 2004. **329**(7456): p. 44-47.
4. DiMasi, J.A., R.W. Hansen, and H.G. Grabowski, *The price of innovation: new estimates of drug development costs*. J Health Econ, 2003. **22**(2): p. 151-85.
5. *Changing Patterns of Pharmaceutical Innovation*. 2002 (http://www.nihcm.org/innovations.pdf), The National Institute for Health Care Management Research and Educational Foundation (NIHCM): Washington DC (accessed Apr 3, 2006).
6. Friedman, M.A., J. Woodcock, M.M. Lumpkin, J.E. Shuren, A.E. Hass, and L.J. Thompson, *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There Is a Problem?* JAMA, 1999. **281**(18): p. 1728-1734.
7. Ferner, R.E., Newly licensed drugs. BMJ, 1996. **313**(7066): p. 1157-8.
8. Wood, A.J.J., *The Safety of New Medicines: The Importance of Asking the Right Questions*. JAMA, 1999. **281**(18): p. 1753-1754.
9. Rogers, E., *Diffusion of Innovations*. Fifth edition ed. 2003, New York: Free Press.
10. EMEA. (European Medicines Agency) http://www.emea.eu.int/pdfs/general/direct/emeaar/000204en.pdf (accessed Apr 3, 2006).
11. DiMasi, J.A., *Success rates for new drugs entering clinical testing in the United States*. Clin Pharmacol Ther, 1995. **58**(1): p. 1-14.
12. Coleman, J.S., E. Katz, and H. Menzel, *Medical Innovation: A Diffusion Study*. 1966, The Bobbs-Merril Company, Inc.: New York.
13. Coleman, J.S., H. Menzel, and E. Katz, *The diffusion of an innovation among physicians*. Sociometry, 1957. **20**: p. 253-270.
14. Steffensen, F.H., H.T. Sorensen, and F. Olesen, *Diffusion of new drugs in Danish general practice*. Fam Pract, 1999. **16**(4): p. 407-413.
15. Zwart-van Rijkom, J.E., N.S. Breekveldt-Postma, H.G. Leufkens, and A.C. Egberts, *Diffusion of new medicines into hospital practice*. Eur J Clin Pharmacol, 2003. **59**(5-6): p. 495-6.
16. Berndt, E.R., A. Bhattacharjya, D.N. Mishol, A. Arcelus, and T. Lasky, *An analysis of the diffusion of new antidepressants: variety, quality, and marketing efforts*. J Ment Health Policy Econ, 2002. **5**(1): p. 3-19.
17. Dybdahl, T., M. Andersen, J. Kragstrup, I.S. Kristiansen, and J. Sondergaard, *General practitioners' adoption of new drugs and previous prescribing of drugs belonging to the same therapeutic class: a pharmacoepidemiological study*. Br J Clin Pharmacol, 2005. **160**(5): p. 526-33.
18. van den Bulte, C. and G. Lilien, *Medical Innovation Revisited: Social Contagion versus Marketing Effort*. Am J Soc, 2001. **106**(5): p. 1409-1435.

19. Dybdahl, T., M. Andersen, J. Sondergaard, J. Kragstrup, and I.S. Kristiansen, *Does the early adopter of drugs exist? A population-based study of general practitioners' prescribing of new drugs*. Eur J Clin Pharmacol, 2004.

20. Vondeling, H., E. Haerkens, A. de Wit, M. Bos, and H.D. Banta, *Diffusion of minimally invasive therapy in The Netherlands*. Health Policy, 1993. **23**(1-2): p. 67-81.

21. de Wit, A. and D. Banta, *Diffusion of in-vitro fertilization in The Netherlands and England: an exploratory study*. Int J Technol Aging, 1991. **7**(4): p. 574-84.

22. Banta, H.D. and H. Vondeling, *Diffusion of minimally invasive therapy in Europe*. Health Policy, 1993. **23**(1-2): p. 125-33.

23. Jones, M.I., M. Greenfield, and C.P. Bradley, *Prescribing new drugs: qualitative study of influences on consultants and general practitioners*. BMJ, 2001. **323**(7309): p. 378-85.

24. Tamblyn, R., P. McLeod, J.A. Hanley, N. Girard, and J. Hurley, *Physician and practice characteristics associated with the early utilization of new prescription drugs*. Med Care, 2003. **41**(8): p. 895-908.

25. McGettigan, P., J. Golden, J. Fryer, R. Chan, and J. Feely, *Prescribers prefer people: The sources of information used by doctors for prescribing suggest that the medium is more important than the message*. Br J Clin Pharmacol, 2001. **51**(2): p. 184-9.

26. Prosser, H. and T. Walley, *New drug uptake: qualitative comparison of high and low prescribing GPs' attitudes and approach*. Fam Pract, 2003. **20**(5): p. 583-591.

27. Prosser, H., S. Almond, and T. Walley, *Influences on GPs' decision to prescribe new drugs - the importance of who says what*. Fam Pract, 2003. **20**(1): p. 61-68.

28. Peay, M.Y. and E.R. Peay, *Innovation in high risk drug therapy*. Soc Sci Med, 1994. **39**(1): p. 39-52.

29. Peay, M.Y. and E.R. Peay, *Patterns of preference for informationn sources in the adoption of new drugs by specialists*. Soc Sci Med, 1990. **31**(4): p. 467-476.

30. Wieringa, N.F., P. Denig, P.A. de Graeff, and R. Vos, *Assessment of new cardiovascular drugs. Relationships between considerations, professional characteristics, and prescribing*. Int J Technol Assess Health Care, 2001. **17**(4): p. 559-70.

31. Denig, P., F.M. Haaijer-Ruskamp, H. Wesseling, and A. Versluis, *Impact of clinical trials on the adoption of new drugs within a university hospital*. Eur J Clin Pharmacol, 1991. 41(4): p. 325-8.

32. de Vries, C.S., N.M. van Diepen, T.F. Tromp, and L.T. de Jong-van den Berg, *Auditing GPs' prescribing habits: cardiovascular prescribing frequently continues medication initiated by specialists*. Eur J Clin Pharmacol, 1996. 50(5): p. 349-52.

33. Bijl, D., E. Van Sonderen, and F.M. Haaijer-Ruskamp, *Prescription changes and drug costs at the interface between primary and specialist care*. Eur J Clin Pharmacol, 1998. **54**(4): p. 333-6.

34. Feely, J., R. Chan, J. McManus, and B. O'Shea, *The influence of hospital-based prescribers on prescribing in general practice*. Pharmacoeconomics, 1999. **16**(2): p. 175-81.

35. Avery, A.J., S. Rodgers, T. Heron, R. Crombie, D. Whynes, M. Pringle, D. Baines, and R. Petchey, *A prescription for improvement? An observational study to identify how general practices vary in their growth in prescribing costs*. BMJ, 2000. **321**(7256): p. 276-81.

36. Robertson, J., J.L. Fryer, D.L. O'Connell, A. Sprogis, and D.A. Henry, *The impact of specialists on prescribing by general practitioners*. Med J Aust, 2001. **175**(8): p. 407-11.

37. Robertson, J., C.J. Treloar, A. Sprogis, and D.A. Henry, *The influence of specialists on prescribing by GPs. A qualitative study*. Aust Fam Physician, 2003. **32**(7): p. 573-6.
38. de Smet, P.A. and M. Dautzenberg, *Repeat prescribing: scale, problems and quality management in ambulatory care patients*. Drugs, 2004. **64**(16): p. 1779-800.
39. Winick, C., *The Diffusion of an Innovation Among Physicians in a Large City*. Sociometry, 1961. **24**(4): p. 384-396.
40. ANP, *Farmacie verlaagt korting van ziekenhuisapotheken. [In Dutch],* in Het Financieele Dagblad. 2000.
41. Mat, J., *'Medicijnen keiharde business' ; Vraaggesprek met ziekenhuisapotheker Arnold Vulto. [In Dutch],* in NRC Handelsblad. 1999: Rotterdam.
42. Pryce, A.J., H.F. Heatlie, and S.R. Chapman, *Buccaling under the pressure: influence of secondary care establishments on the prescribing of glyceryl trinitrate buccal tablets in primary care*. BMJ, 1996. **313**(7072): p. 1621-1624.
43. Banta, H.D., *Social science research on medical technology: utility and limitations*. Soc Sci Med, 1983. **17**(18): p. 1363-9.
44. Weatherby, L.B., B.L. Nordstrom, D. Fife, and A.M. Walker, *The impact of wording in "Dear doctor" letters and in black box labels*. Clin Pharmacol Therap, 2002. **72**(6): p. 735-742.
45. Wilkinson JJ, Force RW, and Cady PS, *Impact of safety warnings on drug utilization: marketplace life span of cisapride and troglitazone*. Pharmacotherapy, 2004. **24**(8): p. 978-86.
46. de Bruin, M., M. Panneman, H. Leufkens, A. Hoes, and R. Herings, *Use of cisapride with contraindicated drugs in The Netherlands*. Ann Pharmacother, 2002. **36**(2): p. 338-343.
47. Smith MC, Kolassa EM, Perkins G, and Siecker B, Pharmaceutical Marketing. Principles, *Environment, and Practice*. 2002, Binghampton, NY: Pharmaceutical Products Press.
48. Kerr, S.J., A. Mant, F.E. Horn, K. McGeechan, and G.P. Sayer, *Lessons from early large-scale adoption of celecoxib and rofecoxib by Australian general practitioners*. Med J Aust, 2003. **179**(8): p. 403-7.
49. Helin-Salmivaara, A., R. Huupponen, A. Virtanen, and T. Klaukka, *Adoption of celecoxib and rofecoxib: a nationwide database study*. Journal of Clinical Pharmacy and Therapeutics, 2005. **30**(2): p. 145-152.
50. Hughes, D.A., K. Bodger, P. Bytzer, D. de Herdt, and D. Dubois, *Economic analysis of on-demand maintenance therapy with proton pump inhibitors in patients with non-erosive reflux disease*. Pharmacoeconomics, 2005. **23**(10): p. 1031-41.
51. Meyboom, R.H. and I.R. *Edwards, Rosuvastatin and the statin wars--the way to peace*. Lancet. **364**(9450): p. 1997-1999.
52. Florentinus, S.R., E.R. Heerdink, O.H. Klungel, and A. de Boer, *Should rosuvastatin be withdrawn from the market?* Lancet, 2004. **364**(9445): p. 1577.
53. Shepherd, J., D.B. Hunninghake, E.A. Stein, J.J.P. Kastelein, S. Harris, J. Pears, and H.G. Hutchinson, *Safety of rosuvastatin*. Am J Cardiol, 2004. **94**(7): p. 882-888.
54. Alsheikh-Ali, A.A., M.S. Ambrose, J.T. Kuvin, and R.H. Karas, *The Safety of Rosuvastatin as Used in Common Clinical Practice: A Postmarketing Analysis*. Circulation, 2005**. 111**(23): p. 3051-3057.
55. Claxton, A.J., J. Cramer, and C. Pierce, *A systematic review of the associations between dose regimens and medication compliance*. Clin Ther, 2001. **23**(8): p. 1296-310.

56. Leufkens, H.G., J. Urquhart, B.H. Stricker, A. Bakker, and H. Petri, *Channelling of controlled release formulation of ketoprofen (Oscorel) in patients with history of gastrointestinal problems*. J Epidemiol Community Health, 1992. **46**(4): p. 428-32.

57. Ray, W.A. and C.M. Stein, *Reform of drug regulation--beyond an independent drug-safety board*. N Engl J Med, 2006. **354**(2): p. 194-201.

58. Abraham, J., *Regulating the drugs industry transparently*. BMJ, 2005. **331**(7516): p. 528-529.

59. Strom, B.L., *Pharmacoepidemiology*. 3rd ed. 2000, New York: John Wiley & Sons.

60. Leufkens, H.G. and J. Urquhart, *Prescriber profile and postmarketing surveillance*. Lancet, 1993. **342**(8880): p. 1178.

61. DGV, *FTO-peiling 2002 Farmacotherapieoverleg in 2001/2002 [In Dutch]*. 2003, DGV Nederlands Instituut voor verantwoord medicijngebruik: Utrecht.

62. Davidse, W., D. Somai, R. Perenboom, R. Verheij, D. de Bakker, and L. *Van Dijk, Doelmatig voorschrijven van nieuwe geneesmiddelen; off label voorschrijven van COX-2 remmers als casus [In Dutch]*. 2006, TNO Kwaliteit van Leven: Leiden. p. 160.

63. van Eijk, M.E., J. Avorn, A.J. Porsius, and A. de Boer, *Reducing prescribing of highly anticholinergic antidepressants for elderly people: randomised trial of group versus individual academic detailing*. BMJ, 2001. **322**(7287): p. 654-7.

64. Carboneau, C., *Using diffusion of innovations and academic detailing to spread evidence-based practices*. J Healthc Qual, 2005. **27**(2): p. 48-52.

65. Blom, A.T., A.H. Paes, A. Bakker, C.J. Koopman, and C. van der Meer, *Pharmacist-physician co-operation at a regional level*. Pharm World Sci, 1994. **16**(1): p. 13-7.

66. van Dijk, L., H. Barnhoorn, and D.H. De Bakker, *Het Farmaco Therapie Overleg in 1999; stand van zaken en effecten op voorschrijven [In Dutch: Pharmacotherapy audit meetings in 1999: the state of affairs]*. 2001, NIVEL: Utrecht.

67. *FTO-peiling 2003 [In Dutch]*. 2005, Dutch Institute for Effective Use of Medication (DGV): Utrecht; The Netherlands (accessed Jan 2006: http://www.medicijngebruik.nl/content/17_vind_op_thema/17-7-1.htm).

68. Avorn, J., M. Chen, and R. Hartley, *Scientific versus commercial sources of influence on the prescribing behavior of physicians*. Am J Med, 1982. **73**(1): p. 4-8.

69. Florentinus, S.R., L. Van Dijk, A. de Jong, and E.R. Heerdink, *Relaties tussen farmaceutische industrie en artsen/apothekers. Invloed? Welke invloed? [in Dutch]*. Pharm Weekblad, 2004. **139**(6): p. 181-85.

70. de Laat E, Windmeijer F, and Douven R, *How does pharmaceutical marketing influence doctors' prescribing behaviour?* 2002 (http://www.cpb.nl/nl/pub/cpbreeksen/bijzonder/38/bijz38.pdf), CPB Netherlands' Bureau for Economic Policy Analysis: The Hague (accessed Apr 3, 2006).

71. Timmer H, Vrije S, Zwanepol E, and Brand H, Interacties Zonder Bijwerkingen. *Een inventarisatie van de interacties tussen de innoverende farmaceutische industrie en de voorschrijvende arts [In Dutch]*. 2001 (http://www.minvws.nl/images/2191036B_tcm10-19640.pdf), Dutch Ministry of Health, Welfare and Sports: The Hague (accessed Apr 3, 2006).

72. Prosser, H. and T. Walley, *A qualitative study of GPs' and PCO stakeholders' views on the importance and influence of cost on prescribing*. Soc Sci Med, 2005. **60**(6): p. 1335-1346.

73. Lee, T.H., *"Me-Too" Products -- Friend or Foe?* N Engl J Med, 2004. **350**(3): p. 211-212.

74. Frothingham, R., A.S. Relman, and T.H. Lee, *"Me-Too" Products -- Friend or Foe?* N Engl J Med, 2004. **350**(20): p. 2100-2101.

75. Hollis, A., *Me-too drugs: Is there a problem?* 2004 http://www.who.int/intellectualproperty/topics/ip/Me-tooDrugs_Hollis1.pdf (accessed Jan 2006).

76. Kant A, Palm I, and van Raak R, *Medisch-wetenschappelijk onderzoek en de farmaceutische industrie. Ongemakkelijke minnaars [In Dutch].* 2001 (http://www.sp.nl/nieuws/nwsoverz/div/ongemakkelijkeminnaars.pdf), Dutch Socialist Party (SP): The Hague.

77. Angell, M., *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*. 2004, New York: The Random House Publishing Group.

78. Nefarma, *Stapsgewijze innovatie [In Dutch].* FarmaFeiten, 2003. 3(4) (http://www.nefarma.nl/gfx/content/RMADW2003-02778-factsheet%20Stapsgewijze%20Innovatie1.pdf) (accessed Apr 3, 2006).

79. Dimasi, J.A., *Risks in new drug development: approval success rates for investigational drugs*. Clin Pharmacol Ther, 2001. **69**(5): p. 297-307.

80. McIntyre, J., S. Conroy, A. Avery, H. Corns, and I. Choonara, *Unlicensed and off label prescribing of drugs in general practice*. Arch Dis Child, 2000. **83**(6): p. 498-501.

81. Jong, t., G.W., I.A. Eland, M.C.J.M. Sturkenboom, v.d. Anker, J.N., and B.H.C. Stricker, *Unlicensed and off label prescription of drug to children: population based cohort study*. BMJ, 2002. **324**: p. 1313-1314.

82. Ufer, M., A. Rane, A. Karlsson, E. Kimland, and U. Bergman, *Widespread off-label prescribing of topical but not systemic drugs for 350,000 paediatric outpatients in Stockholm*. Eur J Clin Pharmacol, 2003. **58**(11): p. 779-83.

83. Schirm, E., H. Tobi, and L.T. de Jong-van den Berg, *Risk factors for unlicensed and off-label drug use in children outside the hospital*. Pediatrics, 2003. **111**(2): p. 291-5.

84. Knoester, P., *Assessment of the value of lamotrigine in daily practice, in Department of Clinical Pharmacy*. 2005, University Medical Centre Nijmegen: Nijmegen.

85. de Boer, A., *Hoe nu verder met de COX-2-remmers? [In Dutch].* Geneesmiddelenbulletin, 2005. **39**: p. 121-129.

86. Jabaaij, L., D.H. Stokx, and D.H. De Bakker, *Artrosemiddel in de lift: huisartsen schrijven rofecoxib breder voor dan geïndiceerd is. [In Dutch].* Medisch Contact, 2001. **56**: p. 1493-6.

87. Josefson, D., *FDA warns Merck over its promotion of rofecoxib*. BMJ, 2001. **323**(7316): p. 767a-.

88. Bombardier, C., L. Laine, A. Reicin, D. Shapiro, R. Burgos-Vargas, B. Davis, R. Day, M.B. Ferraz, C.J. Hawkey, M.C. Hochberg, T.K. Kvien, and T.J. Schnitzer, *Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group*. N Engl J Med, 2000. **343**(21): p. 1520-8, 2 p following 1528.

89. Abbasi, K., *Is drug regulation failing?* BMJ, 2004. **329**(7477): p. 0-g-.

90. Juni, P., L. Nartey, S. Reichenbach, R. Sterchi, P.A. Dieppe, and M. Egger, *Risk of cardiovascular events and rofecoxib: cumulative meta-analysis*. Lancet, 2004. **364**(9450): p. 2021-9.

91. Merck, *Merck announces voluntary worldwide withdrawal of VIOXX®.* Available at: http://www.vioxx.com/vioxx/documents/english/vioxx_press_release.pdf (accessed Sep 30, 2004). 2004.

92. Layton, D., J. Riley, L.V. Wilton, and S.A. Shakir, *Safety profile of rofecoxib as used in general practice in England: results of a prescription-event monitoring study*. Br J Clin Pharmacol, 2003. **55**(2): p. 166-74.

93. *Vioxx: an unequal partnership between safety and efficacy*. Lancet, 2004. **364**(9442): p. 1287-1288.

94. Boers, M., *NSAIDs and selective COX-2 inhibitors: competition between gastroprotection and cardioprotection*. Lancet, 2001. **357**(9264): p. 1222-3.

95. Konstam, M.A., M.R. Weir, A. Reicin, D. Shapiro, R.S. Sperling, E. Barr, and B.J. Gertz, *Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib*. Circulation, 2001. **104**(19): p. 2280-8.

96. *The statin wars: why AstraZeneca must retreat*. Lancet, 2003. **362**(9393): p. 1341.

97. Bouma, J., 'Dokters betaald voor recept' ; *Farmaceut AstraZeneca zou artsen geld bieden voor voorschrijven van eigen pil [In Dutch],* in Trouw. 2004.

98. Ault, A., *Pressure group urges rosuvastatin recall*. Lancet, 2004. **363**(9412): p. 871.

99. Brewer, J., H. Bryan, *benefit-risk assessment of Rosuvastatin 10 to 40 milligrams*. Am J Cardiol, 2003. **92**(4, Supplement 2): p. 23-29.

100. Davidson, M.H., *Rosuvastatin safety: lessons from the FDA review and post-approval surveillance*. Expert Opin Drug Saf, 2004. **3**(6): p. 547-57.

101. *Changes to the product information for Crestor.* 2004. http://www.cbg-meb.nl/uk/spc/ib-crestor.pdf. (accessed Apr 3, 2006).

102. Wolfe, S.M., *Dangers of rosuvastatin identified before and after FDA approval*. Lancet, 2004. **363**(9427): p. 2189-2190.

103. Schirm, E., H. Tobi, and L.T. de Jong-van den Berg, *Unlicensed and off label drug use by children in the community: cross sectional study*. BMJ, 2002. **324**(7349): p. 1312-3.

104. 't Jong, G.W., P.D. van der Linden, E.M. Bakker, N. van der Lely, I.A. Eland, B.H. Stricker, and J.N. van den Anker, *Unlicensed and off-label drug use in a paediatric ward of a general hospital in The Netherlands*. Eur J Clin Pharmacol, 2002. **58**(4): p. 293-7.

105. Layton, D., E. Heeley, K. Hughes, and S.A. Shakir, *Comparison of the incidence rates of thromboembolic events reported for patients prescribed rofecoxib and meloxicam in general practice in England using prescription-event monitoring (PEM) data*. Rheumatology (Oxford), 2003. **42**(11): p. 1342-53.

106. Cutts, C., A. LaCaze, and S. Tett, A *clinical audit of the prescribing of celecoxib and rofecoxib in Australian rural general practice*. Br J Clin Pharmacol, 2002. **54**(5): p. 522-7.

107. Jacoby, A., M. Smith, and M. Eccles, *A qualitative study to explore influences on general practitioners' decisions to prescribe new drugs*. Br J Gen Pract, 2003. **53**(2): p. 120-5.

108. Denig, P., F.M. Haaijer-Ruskamp, H. Wesseling, and A. Versluis, *[On which criteria are drug choices by hospital physicians based?].* Ned Tijdschr Geneeskd, 1993. **137**(9): p. 448-51.

109. Denig, P., F.M. Haaijer-Ruskamp, and D.H. Zijsling, *Impact of a drug bulletin on the knowledge, perception of drug utility, and prescribing behavior of physicians*. Dicp, 1990. **24**(1): p. 87-93.

110. Denig, P. and F.M. Haaijer-Ruskamp, *[The decision process of the family physician in the choice of a drug].* Ned Tijdschr Geneeskd, 1989. **133**(12): p. 632-3.

111. Bradley, C.P., *Uncomfortable prescribing decisions: a critical incident study*. BMJ, 1992. **304**(6822): p. 294-6.

112. Peay, M.Y. and E.R. Peay, *Differences among practitioners in patterns of preference for information sources in the adoption of new drugs*. Soc Sci Med, 1984. **18**(12): p. 1019-1025.

113. Kasje, W.N., P. Denig, P.A. de Graeff, and F.M. Haaijer-Ruskamp, *Perceived barriers for treatment of chronic heart failure in general practice; are they affecting performance?* BMC Fam Pract, 2005. **6**(1): p. 19.

114. Haines, A. and A. Donald, *Looking forward: Getting research findings into practice: Making better use of research findings*. BMJ, 1998. **317**(7150): p. 72-75.

115. Smith, M.C., E.M. Kolassa, G. Perkins, and B. Siecker, Pharmaceutical Marketing. *Principles, Environment, and Practice*. 2002, Binghampton, NY: Pharmaceutical Products Press.

116. van Dijk, L. and D.H. de Bakker, *Professionalization of Dutch PRGs and volume and costs of frequently prescribed drugs*. *Zeitschrift für Gesundheitswissenschaften,* 2002. **10**(4): p. 292-304.

117. DGV, *FTO-peiling 2003 [In Dutch]*. 2004, http://www.dgvinfo.nl/content/5_persberichten/5-4.htm#5 (Accessed Febr 2006).

118. DGV, *FTO-peiling 2004 [In Dutch]*. 2005, http://www.dgvinfo.nl/content/5_persberichten/5-4.htm#5 (Accessed Febr 2006).

CURRICULUM VITAE

Stefan Florentinus was born on January 22, 1977 in Amstelveen, The Netherlands. He completed secondary school (Gymnasium) at the 'Hermann Wesselink College' in Amstelveen. In 1995, he studied Pharmaceutical Sciences at Groningen University and he obtained his BSc in Pharmacy at Utrecht University in 2000 and in 2002 his master's degree. In the same year, he accepted a position as a PhD-student at the Division of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences.