CLINICAL RISK MANAGEMENT IN COMMUNITY PHARMACY

HENK BUURMA

Cover illustration:	Heleen Swart
Cover design:	Martijn Pieck (DGV, Department of Pharmaceutical Sciences, Utrecht University
Lay-out inside work:	Francis te Nijenhuis
Printed by:	Optima Grafische Communicatie, Rotterdam

The work presented in this thesis was performed at the Division of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences (UIPS), in collaboration with the SIR Institute for Pharmacy Practice and Policy (Leiden) and the Department of Clinical Pharmacy of the Radboud University Nijmegen Medical Centre.

CIP-gegevens Koninklijke Bibliotheek, Den Haag

Buurma, H.
Clinical risk management in community pharmacy
Thesis University Utrecht – with ref. – with summary in Dutch

ISBN-10: 90-393-4318-7
ISBN-13: 978-90-393-4318-0

CLINICAL RISK MANAGEMENT IN COMMUNITY PHARMACY

RISICOMANAGEMENT IN DE ZORGPRAKTIJK VAN DE OPENBARE APOTHEEK

(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 woensdag 4 oktober 2006 des middags te 2.30 uur

door

HINDRIK BUURMA

geboren op 3 november 1950 te Groningen

PROMOTOREN:

Prof.dr. A.C.G. Egberts
Prof.dr. P.A.G.M. de Smet (Radboud University Nijmegen)

Financial support of several institutions and organizations for conducting parts of the presented studies as well as for the publication of this thesis are gratefully acknowledged: Scientific Institute of Dutch Pharmacists (WINAp); Health Base Foundation (SHB); PRISMA foundation; the Ministry of Health, Welfare and Sport; and the 'Stichting KNMP fondsen'.

Voor Heleen, Marleen, Jorien

Als je doet wat je leuk vindt,
hoef je nooit te werken.
Mahatma Gandhi

CONTENTS

Chapter 1

INTRODUCTION

INTRODUCTION

Medicines constitute a crucial backbone of both prevention and therapy of disease in modern health care. However, pharmaceutical agents only provide efficacious and safe care to patients when they are applied in a sustained, monitored and safeguarded usage environment. Like in many countries, Dutch (community) pharmacists have contributed to the development and implementation of patient-oriented systems to boost up the balance sheet of the benefits and risks of drug therapy. These efforts to improve the outcomes of drug therapy for the individual patient have been fuelled by a paramount transition in pharmacy practice and policy itself during recent years. Scientists, pharmacists and others have redefined modern pharmacy practice in definitions, descriptions and concepts: as a line of action for pharmacy practice itself and, among others things, to be accountable for the outer world. According to Barber "the mountain in its entirety is far too complex to be defined from one viewpoint".[1] The description of a mountain will be different depending on the direction one is nearing the mountain. Like the mountain, concepts mostly describe reality from one viewpoint. Because of inadequacies and limitations these concepts tend to evolve and new concepts will emerge. Depending on the starting point upon which the concept will be used (e.g. rational use of medicines, cost containment, risk management, patient centred care) or the setting or party by whom the concept will be applied (regulators, pharmacists, other health professionals, patients or consumers) one finds concepts underlying pharmacy practice that are in essence patient oriented or system oriented. The pharmaceutical professions in different countries embraced the patient centred concept of pharmaceutical care emerging from the concept of clinical pharmacy and mainly based upon the definition put forward by Hepler and Strand in 1990.[2-4] The more recently introduced concordance concept aims at a more active role of the patient himself in both the medical and pharmaceutical decision making process and the execution of the treatment.[5-7] Other more organizational concepts were developed as well, such as the strategy of medicines management (by the NHS in the United Kingdom), the concept of health or medical technology assessment and more recently the clinical risk management strategy.[1,4,8,9] While on the one hand these concepts intend to describe pharmacy practice focusing on the pharmacy profession either as part of a (health care) system or standing on its own, there is on the other hand a need for evidence-based pharmaceutical practice, from a scientific as well as from a societal and strategic perspective.[10]

What is the scientific basis of all these changes in pharmacies since the 1970s and therefore for all these definitions?[11]
In this thesis, an array of studies will be presented with the objective to increase our knowledge and understanding of pharmacists' contribution to patient care in the modern healthcare system. Although there are basically no differences between community and hospital pharmacy concerning the main responsibilities and although several developments that will be described below are applicable to both professions,[12] we will confine ourselves to community pharmacy. As an introduction to the presented studies we will elaborate on the role of community pharmacists using the concept of 'pharmaceutical care', meaning patient oriented pharmacy practice, and the rather recently introduced concept of clinical risk management.

RECENT HISTORY OF COMMUNITY PHARMACY PRACTICE

Until the 1950s pharmacists' tasks consisted mainly of compounding (including quality control) and of distributing medicines, which were prescribed by physicians. The image of a pharmacy as presented in the thesis of Rypkema from 1954, that can be specified as an early pharmacy practice research study, is completely different and opposite from that of the modern pharmacy and its prescriptions nowadays.[13] Along with the rise of modern medicine in general and the discovery, development and introduction of several important and effective drugs in particular, the number of compounded medicines in pharmacies decreased significantly until it stabilized between 1970 and 1990 to about 7% of all dispensed prescriptions.[14]
Since the beginning of the 1970s the role of the community pharmacist changed rapidly, particularly in the Netherlands. There are three mutually linked developments, described by Leufkens, by which the transition of the profession can be described: reprofessionalization in pharmacy, drug use in a 'risk society' and medical information systems.[15] The reprofessionalization in pharmacy, expressed by the adoption of three new tasks, namely patient information, consulting with physicians, and medication surveillance, led from a product oriented (compounding and quality control) to a more drug therapy (i.e. patient) oriented attitude of pharmacists.[16] A key report in the Netherlands was the concrete description of the tasks of the community pharmacist by a multidisciplinary commission, the so-called Commissie 2000, in 1979, by which

this new role was formally sanctioned by professional organizations, the government and the health insurance system.[15,17] There were several developments in society and healthcare that were in favour of this reprofessionalization. Worth mentioning is the tendency to cooperate more in primary healthcare (also reflected by democratization of health care, patient empowerment and societal accountability) which has led to structured pharmacotherapy consultation groups of physicians and pharmacists.[16] The other two above-mentioned notions, however, were important as well. Since the thalidomide crisis in the beginning of the 1960s, the perception of risk and the benefit-risk ratio due to the use of health care provisions and the use of medicines in particular, grew tremendously. Already in the sixties and seventies in the last century there were scientific as well as lay articles issued about the extent of hospitalisations, basically not different from those nowadays, and other adverse events due to the use of drugs.[18] Dutch studies in the 1970s showed the need for good medication surveillance of, for instance, drug-drug interactions.[16] The introduction of medical information systems based upon new computer technologies was very stimulating in favour of the development of the new tasks of pharmacies. Contrary to general practice (about 5%), approximately 80% of Dutch community pharmacies were using advanced computer systems in 1987 for prescription recording, medication surveillance, labelling and administrative functions.[15]

One may conclude that the reprofessionalization of community pharmacy has been in essence related to the more general recognition that minimizing the risks of drug therapy goes beyond the molecular effects of the medicine itself and can be attributed to the prescribing and usage process as well. The strong development of medical information systems was very helpful to that reprofessionalization. Since decennia information technology has been used in Dutch community pharmacies to support professional practice enabling the pharmacist to check the drug prescription for several potential drug therapy related problems, especially dosing problems, drug-drug interactions and duplicate medications. In this respect, the rise of knowledge about pharmacokinetics and pharmacodynamics was very supportive. By incorporating clinical data like diseases and intolerabilities in the medication surveillance systems it became also possible to check for drug-disease interactions (contraindications) and drug-intolerabilities (including allergies). Moreover, Dutch pharmacies fulfil until today a very important prerequisite, namely a low degree of fragmented prescription filling due to a high pharmacy compliance of

the patient.[15,19,20] Later on, patient orientation in pharmacies resulted in new forms of interference with the prescribing and use of drugs, such as individualized patient information leaflets, protocols for patient information to be presented in case of first use or second use of medicines, sophisticated protocols to be used in cooperation with general practitioners and free text possibilities in the electronic patient record. Pharmacies, increasingly in close cooperation with doctors, created new opportunities individually as well as locally or regionally directed at certain groups of patients, such as chronic users (specific counselling, medication analysis based upon indicators as to certain drug therapy related problem, interference with refilling), and patients admitted or discharged from hospital.[3,14] This transition in pharmacy practice is also receptive to other innovations in health care (e.g. genetic testing, biomarkers).[21]

Another driver for these developments in pharmacy practice has been the concept that actions, processes and systems in health care should be 'evidence based' in order to assess their efficacy, efficiency and value for money.[10] In this era, society is increasingly requesting evidence concerning a profession's role in health care, not only as to pharmacists, but also concerning others such as general practitioners and physiotherapists. This means evidence based decision-making, but also another way of professional acting leading to more communication and recording of actions. For sure, this driver has also contributed in a visible fashion to the development of practice research, which in the field of pharmacy developed along with the development of the concept of pharmaceutical care, but relatively late and rather limited compared to practice research in general medical practice.

DRUG THERAPY RELATED PROBLEMS, PHARMACEUTICAL CARE AND COMMUNITY PHARMACISTS

The management of patient health care can be compromised by drug therapy related morbidity and mortality, which in their turn can be the result of drug therapy related problems.[a] Current practice of drug therapy is highly susceptible to drug therapy related problems in the population. In the US it is estimated that more than 25% of all people are taking at least 5 medications in one week,

[a] In this introduction we use the broader term 'drug therapy related problem'. By using this, certain problems are additionally included, such as no drug therapy where it was indicated or a drug therapy where an alternative therapy would have been indicated.[11]

including over the counter drugs, herbals and vitamins.[22] The actual occurrence of drug therapy related problems has been subject of several studies.[23-26] The widespread interest, scientifically as well as socially, in the frequency and nature of problems related to prescribing and use of medicines has had its repercussions in for instance the existence of high standard (pharmaco)epidemiological institutes, post-marketing surveillance, and a multiplicity of scientific articles as well as lay-articles. With the turn of the century the subject of patient safety and medical errors got a strong boost of attention with the publication of a research report by the Institute of Medicine in the United States, called "To err is human. Building a safer health care",[27] followed by reports in the UK ("A Spoonful of sugar")[28] and the Netherlands.[29] In the Netherlands the issue of drug therapy related problems was exposed to professional, regulatory and policy responses and mirrored by a series of activities by various stakeholders.[30,31]

Drug therapy related problems can be divided into three main groups. The first one concerns the availability of a medicine or a specific dosage form that is needed by an individual patient but that is not commercially available. This problem probably occurs especially in children, and is also related to off-label use.[32,33] The second and third group of drug therapy related problems, which are more common, concern effectiveness and safety. Effectiveness problems occur for instance when a medicine is prescribed with a too low dosage or for a too short period of time. With respect to safety one can discriminate for instance between side effects, drug-drug interactions, drug-disease interactions, and drug toxicity/poisoning. With respect to drug therapy related problems, especially those concerning effectiveness and safety, one also finds other descriptions. Van den Bemt discriminates between intrinsic and extrinsic problems.[34] The latter involve errors somewhere in the process from prescribing the drug up to the administration of it. These extrinsic problems are basically preventable, where in most instances the intrinsic are not. The intrinsic problems are called adverse drug reactions, which are related to the pharmacological or immunological properties of the drug and which will result in discomfort or harm to the patient. Preventable problems are related to (parts of) the health care system and can be described as medication errors, such as dosing problems, duplicate medications, drug-drug interactions, drug-disease interactions and to some extent intolerabilities. For research purposes several drug therapy related problem classification systems have been developed, partly consisting of intervention classifications as well.[35-37]

Several medication related problems originate during the prescribing process, such as dosing problems, drug-drug interactions and drug-disease interactions. Automation plays an important role in preventing these. A part of the problems arise during daily use of medicines, such as therapy adherence and overuse. Certain surveillance software can discover the latter, while others, like uncertainty or lack of knowledge about the aim or function of the drug, need communication between the pharmacist and the patient.[38] Although a part of the drug therapy related problems cannot be prevented because of their nature, community pharmacies can play a role in helping and solving them.[38,39] The fact that the contribution of pharmacists to the Dutch spontaneous reporting system is substantial as to numbers and quality, indicates the involvement of pharmacists in this respect.[39] The introduction of specific protocols for the provision of information and guidance of first time and second time dispensing, may help the pharmacist and his co-workers to communicate with the patient about this type of problems. The growing awareness of drug therapy related problems has initiated research on pharmacists' strategies for dealing with these problems. Several, mainly observational, studies describe and, to some extent, support the positive contribution of pharmacists in detecting and reducing the impact of drug therapy related problems.[40-46] Other studies, however, focusing on the implementation of pharmaceutical care activities conclude that 'new' tasks, such as patient education, medication surveillance and guidance, and drug therapy meetings are performed in practice, but not always on a routine basis.[47-50]

CLINICAL RISK MANAGEMENT, A COMPLEMENTARY APPROACH

The question is whether the concept of pharmaceutical care gives a good answer to the systematic problem of medication errors and drug therapy related adverse events. Although Hepler and Strand[2] and other authors afterwards have presented a broad definition of the concept of pharmaceutical care and of the operationalization of it as well, in daily practice the pharmaceutical care concept has reengineered the pharmacist's role with the individual patient as primary focus point. Pharmacy practice has changed as well as the education leading to this practice.[3] Competencies have changed to act on the basis of evidence and with skills that are profitable in the relation with patients (and prescribers). But in the meanwhile, society is still confronted with a relatively high grade of errors, adverse events and other problems concerning health care and medicines.[27,51]

Some suggest that there is even an increase in the number of medication errors.[52] In this respect one is searching for other concepts to deal with these problems. Based upon research in safety critical industries, such as aviation and oil and gas industry, the concept of risk management is gradually being introduced into the healthcare system (clinical or medical risk management). Especially aviation is used as an example, where accidents are usually highly visible. As a result aviation has developed standardized methods of investigating, documenting and disseminating errors and their lessons.[51] This concept implies a systems approach acknowledging the limitations of technological solutions.[53] In other words, the starting point is that medical errors do not occur from individual recklessness, but rather from basic (systematic) flaws in the organization of the health care system.[54] Clinical risk management aims to change the organization from organizational vulnerability towards organizational integrity. It accepts the inevitability of errors and urges reliable data on errors in the beginning of the process, but also during the process by incident reports.[51]

> "The automatic teller machine that dispenses cash and other banking transactions has become ubiquitous in many parts of the world. Most machines follow one of the sequences to complete a transaction. Some dispense the money first and then return the card. Others reverse these two steps. Since the aim of the transaction is to obtain money, common sense and research in human factors predict that the person using the machine is more likely to forget the card if it is returned after the money is dispensed. The order is designed into the system and produces a predictable risk of error."
>
> *From: Nolan TW.*[55]

Nolan poses that health care systems, that are often complex in nature, should be designed in such a way, that errors are prevented, that errors when made become visible and, that errors are mitigated in case they are not intercepted.[55] For these three strategies he describes five overall tactics: reduce complexity, optimize information processing, automate wisely, use constraints and mitigate side effects of change.

The clinical risk management process can be described as consisting of mainly three steps, i.e. risk assessment, risk management and evaluation of the total risk management process. During the risk assessment phase potential hazards are identified and stratified in terms of evidence, probability and significance. The second step concerning risk management tries to define the operational strategies needed to minimize hazards, the identification of resources and the execution of those strategies. The latter one includes the identification, analysis and treatment

of (potential) health hazards in daily clinical practice. The final and crucial part of clinical risk management is the performance evaluation of risk treatment strategies, i.e. have these actually been effective and efficient. In the meanwhile, the concept of risk management has been introduced in several parts of health care and by several stakeholders (e.g. hospital departments, EMEA, FDA, ISPE, hospital pharmacy sector and other).[9,56-58]

CLINICAL RISK MANAGEMENT AND MEDICINES

Based upon current literature, it may appear that risk management concerning medicines is primarily limited to hospital settings, especially hospital pharmacy.[31,56,59] However, in various community (pharmacy) setting, also in the Netherlands, the risk management concept has already been applied for many years, although it was not coined like that. Several steps of the clinical risk management process can be observed in the prevention, identification and treatment of drug therapy related problems concerning prescribing, dispensing and use of medicines or related products.[9,56] In this process several health care providers are involved, such as physicians, physician assistants, pharmacists, pharmacy technicians and patients and their relatives. All act in the risk management phase of identification, analysis and treatment of (potential) hazards of drugs in daily clinical practice.

Concerning the assessment phase, drug regulators at agencies as EMEA (EU), CBG (the Netherlands) and FDA (USA) are most notably involved. During recent years the concept of risk management has been explicitly and proactively adopted by these agencies, and drug companies are now obliged to add Risk Management Plans including specific and targeted postmarketing surveillance activities to their registration files.[58,60] Also certain institutions within pharmaceutical industries are engaged in the assessment of risk and the balance of risk and efficacy. The practice of risk management is also described as to the different phases of a drug's life cycle within pharmaceutical industries.[60]

Concerning specific drugs, a risk management plan can be drawn up in which for instance specific post-marketing surveillance activities, observational studies or restricted distribution can be set up based upon pre-clinical data. The role of pharmacoepidemiology is evident in such risk management plans.

In the Netherlands there are two, to some extent, different resources containing information about drug therapy related problems, such as dosing, drug-drug

interactions, drug-disease interactions, duplicate medications and patient adherence. This information is translated into drug therapy related problems signalling software by the five electronic pharmacy information systems that in turn are used by Dutch community pharmacies (and several general practitioners). Two assessment committees (the 'Werkgroep Farmacotherapie en Geneesmiddeleninformatie' of the scientific Institute of Dutch pharmacists (WINAp) and the 'Commissie Medicatiebewaking Medicom Pharmacom' of the Health Base Foundation) are responsible for the content of these two resources.

Management of alerts is to some extent supported by management plans, presented on the pharmacy computer screen or in written forms, especially regarding drug-drug interactions and drug-disease interactions.[61] Depending on the patient's situation and based upon certain internal procedures, general practitioners and pharmacists will 'manage' these alerts. Pharmacists' actions can be considered as an essential way of double-checking.[55]

In order to manage or to minimize risks much importance is given to risk communication or, more precisely, communication about the balance between safety and efficacy. Discussions about recently introduced medicines, operative standards in pharmacotherapy and prescription data, all taking place in consultation groups with general practitioners, are important examples of actions in the process of risk communication and management.[3,14] In this way, communication with patients is targeted at minimizing risks. The provided information will enable patients or medicine users to understand possible risks and, when needed, to take measures to minimize these, for instance, by contacting the prescriber or pharmacist.[60]

Recent efforts of community pharmacists to deliver special care for certain specific groups of patients, such as patients with repeat prescriptions or polypharmacy, patients discharged from hospital, patients with memory loss or ambulatory psychiatric patients, are aimed at minimizing special risks. One may find protocols for identification and management of these in individual pharmacy practices, but also on a broader scale.

The process within pharmacies is part of the described process as well. The introduction of a bar-coding system and recently robotization, but also the application of standardized protocols as to compounding medicines and of a certified Quality System as well as a system of mandatory retraining can be considered as methods to minimize the risk in the distribution phase.

Evaluation of the system or parts of it is a key element of the described risk management model. Pharmacy practice research, defining pharmacy practice as

the study object, fits well in this process. It is necessary to analyse and to improve pharmacy practice as a tool in the whole process of ameliorating the benefit-risk ratio by minimizing risks.

PHARMACEUTICAL CARE AND CLINICAL RISK MANAGEMENT

The concept of pharmaceutical care has changed the way of thinking and acting of pharmacists. The essence of pharmacists' care has shifted from the drug to its user. Pharmaceutical care has become a prime issue in the education of pharmacists, so that the competencies of pharmacists have been altered dramatically compared to those thirty years ago. The recent introduction of the concept of concordance has underlined the central position of the patient even more. However, the question is whether these concepts give the most appropriate response to the systematic problem of medication errors and drug therapy related problems in general. Although the concept of pharmaceutical care focuses pharmacists' care at preventing, identifying and managing drug therapy related problems, it makes sense to involve the concept of risk management in the description and evaluation of pharmacy practice. It adds several essential items that are underexposed in the current pharmaceutical care concept. Firstly, there is the problem orientation, the accurate identification and assessment of risks of medicines. Prioritising for and focusing on essential problems in this respect is important.[62] So, for instance, which drug-drug interactions need to be put into the drug surveillance systems of community pharmacies? Secondly, there is the system orientation with on the one hand the whole system of drug distribution from drug innovation to drug use and on the other hand the care chain from prescriber via pharmacy to the user of medicines. Which management tools will be deployed on what moments in these processes to prevent or identify problems? It means the application of the so-called 'Swiss cheese' model for these systems, meaning the setting up of several layers or barriers (naturally, all with their own specific 'Swiss cheese holes'). And what barriers do we need? In such a system the legitimate place for community pharmacy can be defined. Thirdly, in this concept evaluation is very important. In this way, pharmacy practice research is challenged to provide scientific proof and evidence to the sense and nonsense of professional transitions.

OBJECTIVE AND OUTLINE OF THE THESIS

Society is requesting evidence concerning a profession's role in health care, and pharmacists have to comply as well to this societal contract. Evidence based practice demands data from practice research, which in the field of pharmacy practice developed along with the development of the concepts of clinical pharmacy and pharmaceutical care.[11,63,64] Research data are needed in order to make pharmacists eligible and accountable for an evidence based and justifiable position. In this thesis, a series of studies are presented aiming to answer the question whether there is, or may be, an added value of community pharmacists concerning their interventions of several drug therapy related problems. Practice research is needed to evaluate the (clinical) risk management process and the position of pharmacies in it, as it has been developed during the last three decades and as described above. Apart from the focus on the pharmacist and his contribution and quality to the 'solution' of drug therapy related problems, this thesis will provide data about the frequency, nature, preconditions, and clinical relevance of drug therapy related problems as they occur in daily pharmaceutical practice.

In this thesis, an array of studies will be presented with the objective to increase our knowledge and understanding of pharmacists' contribution to patient care in the modern healthcare system. The thesis consists of three parts. The first part focuses on the frequency and nature of drug therapy related problems encountered in Dutch community pharmacies, in other words the outcomes of the daily pharmaceutical, primary processes in community pharmacy.

- In a sample of community pharmacies the nature and frequency of compounded medicines as well as several determinants thereof were assessed. In addition, some organizational characteristics, like compounding site and use of protocols, were investigated. The value of compounded medicines in terms of necessity, as perceived by the participating pharmacists, was evaluated (Chapter 2.1);
- In a large sample of community pharmacies the frequency and nature of various drug therapy related problems were investigated using modified prescriptions as the study set (Chapter 2.2);
- In a specific sample of community pharmacies a specific drug therapy related problem was investigated in more detail, namely drug-drug interactions. The

frequency and nature of drug-drug interaction alerts as well as their management by pharmacies were studied (Chapter 2.3).

In the second part, we were interested in some preconditions for the quality of risk management by pharmacies.

- An important precondition for managing drug-disease interactions and drug-intolerability interactions is the documentation of diseases and intolerabilities. In this chapter a study on the prevalence and quality of this documentation in electronic patient records in a specific sample of Dutch community pharmacies is presented (Chapter 3.1);
- In a large sample of community pharmacies the adherence of these pharmacies to a Dutch guideline for the management of drug-drug interactions was measured as well as patient- and prescriber-related determinants for non-adherence (Chapter 3.2).

In the third part, we focused more on patient outcomes of clinical risk management by community pharmacies.

- Based upon the second study of this thesis (Chapter 2.2), a random sample of prescription modifications was evaluated by a large panel of reviewers. After generally rating each modification as positive, negative, or neutral, the reviewers assessed its outcome (prevention of an adverse drug reaction, improvement in effectiveness or other), the probability and importance of improvements in effectiveness and/or the probability and seriousness of an adverse drug reaction in case of a non-intervention (Chapter 4.1);
- Based upon data obtained from a large pharmacy claims database we investigated the prevalence and determinants of pharmacy shopping behaviour. In addition, we were interested in the association between pharmacy shopping behaviour and heavy use of anxiolytics and hypnotics, antidepressants, antipsychotics, and opioids respectively (Chapter 4.2).

Finally, the results of these studies are summarized and put into a broader perspective in Chapter 5. In that general discussion we also focus on the implications of our research for Dutch community pharmacy and pharmacy practice research in particular.

REFERENCES

1. Barber N. Pharmaceutical care and medicines management - is there a difference? Pharm World Sci 2001;23:210-1.

2. Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. Am J Hosp Pharm 1990;47:533-43.
3. Van Mil JF. Pharmaceutical care in community pharmacy: practice and research in the Netherlands. Ann Pharmacother 2005;39:1720-5.
4. Almarsdottir AB, Traulsen JM. Rational use of medicines--an important issue in pharmaceutical policy. Pharm World Sci 2005;27:76-80.
5. Elwyn G, Edwards A, Britten N. What information do patients need about medicines? 'Doing prescribing': how doctors can be more effective. BMJ 2003;327:864-7.
6. Marinker M, Shaw J. Not to be taken as directed. BMJ 2003;326(7385):348-9.
7. Elwyn G, Edwards A, Wensing M, Hood K, Atwell C, Grol R. Shared decision making: developing the OPTION scale for measuring patient involvement. Qual Saf Health Care 2003;12:93-9.
8. Simoens S, Laekeman G. Applying health technology assessment to pharmaceutical care: pitfalls and future directions. Pharm World Sci 2005;27:73-5.
9. Hudson PT, Guchelaar HJ. Risk assessment in clinical pharmacy. Pharm World Sci 2003;25:98-103.
10. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362:1225-30.
11. De Smet PAGM. Kwaliteit van de Farmaceutische Patiëntenzorg: 'Je kunt het niet alleen' [dissertation]. Nijmegen: Katholieke Universiteit Nijmegen; 2001.
12. Schobben AFAM. De apotheker: uw therapeut [dissertation]. Utrecht: Utrecht University; 2002.
13. Rypkema BH. Het onderzoek naar het geneesmiddelgebruik in Nederland. 's Gravenhage; 1954.
14. Buurma H, de Gier JJ, Egberts ACG. De apotheek als zorgpraktijk. In: Buurma H, Beudeker HJ, de Jong-van den Berg LTW, Leufkens HGM, redacteurs. Het Geneesmiddel. 4e editie. Maarssen, the Netherlands: Elsevier Gezondheidszorg; 2005. p. 144-67
15. Leufkens HGM. Pharmacy records in pharmacoepidemiology. Studies on anti-inflammatory and antirheumatic drugs [dissertation]. Utrecht: Utrecht University; 1990.
16. Paes AHP. Apothekers en artsen in overleg [dissertation]. Utrecht: Utrecht University; 1989.
17. Commissie 2000. De apotheker, nu en straks. The Hague, the Netherlands: KNMP; 1979.
18. Silverman M, Lee PR. Pills, Profits, and Politics. Berkeley and Los Angeles, USA: University of California Press; 1974.

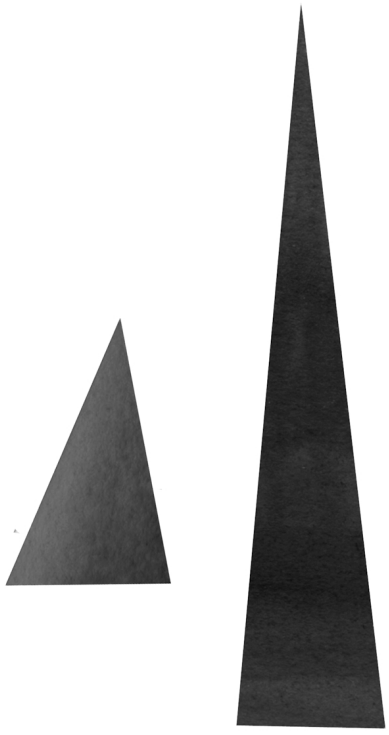
19. Monster TB, Janssen WM, de Jong PE, de Jong-van den Berg LT. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. Pharmacoepidemiol Drug Saf 2002;11:379-84.
20. Klungel OH, de Boer A, Paes AH, Herings RM, Seidell JC, Bakker A. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in The Netherlands. Pharm World Sci 1999;21:217-20.
21. Koert W. Genotypering spaart kosten. Pharm Weekbl 2005;41:1283.
22. Kaufman D, Kelly J, Rosenberg L, Anderson T, Mitchell A. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA 2002;287:337-44.
23. Van den Bemt PM, Egberts TC, de Jong-van den Berg LT, Brouwers JR. Drug-related problems in hospitalised patients. Drug Saf 2000;22:321-33.
24. Green CF, Mottram DR, Rowe PH, Pirmohamed M. Adverse drug reactions as a cause of admission to an acute medical assessment unit: a pilot study. J Clin Pharm Ther 2000;25:355-61.
25. Gandhi TK, Seger DL, Bates DW. Identifying drug safety issues: from research to practice. Int J Qual Health Care 2000;12:69-76.
26. Gandhi TK, Burstin HR, Cook EF, Puopolo AL, Haas JS, Brennan TA, et al. Drug complications in outpatients. J Gen Intern Med 2000;15:149-54.
27. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human. Building a safer health system. Washington, DC: National Academy Press; 1999.
28. Anonymous. A spoonful of sugar. London: Audit Commission for Local Authorities and the National Health Services in England and Wales; 2001.
29. Egberts ACG, Leufkens HGM. Ongewenste, onbedoelde en sub-optimale effecten van geneesmiddelen. In: van den Berg Jeths A, editor. Volksgezondheid Toekomst Verkenning 2002, geneesmiddelen nu en in de toekomst. Houten, the Netherlands: Bohn Stafleu Van Loghum; 2002. p. 521-33
30. Schouten LMT, Graatsma BH, Janssen S, Smulders CMF, Tijink H. Van fouten kun je leren. Samen werken aan een goede medicatieveiligheid. Medisch Contact 2002;57:402-5.
31. Willems R. Hier werk je veilig, of je werkt hier niet. Sneller beter - De veiligheid in de zorg: Shell Nederland; 2004.
32. Nahata MC. Pediatric drug formulations: challenges and potential solutions. Ann Pharmacother 1999;33:247-9.
33. Schirm E, Tobi H, de Jong-van den Berg LT. Unlicensed and off label drug use by children in the community: cross sectional study. BMJ 2002;324:1312-3.
34. Van den Bemt PM. Drug safety in hospitalised patients [dissertation]. Groningen: University of Groningen; 2002.

35. Westerlund T, Almarsdottir AB, Melander A. Factors influencing the detection rate of drug-related problems in community pharmacy. Pharm World Sci 1999;21:245-50.
36. Schaefer M. Discussing basic principles for a coding system of drug-related problems: the case of PI-Doc. Pharm World Sci 2002;24:120-7.
37. Yuen YS. Classificatie van geneesmiddelgerelateerde problemen. Utrecht: Faculteit Farmacie - Universiteit Utrecht; 2001.
38. Paulino EI, Bouvy ML, Gastelurrutia MA, Guerreiro M, Buurma H. Drug related problems identified by European community pharmacists in patients discharged from hospital. Pharm World Sci 2004;26:353-60.
39. Van Grootheest AC, van Puijenbroek EP, de Jong-van den Berg LT. Contribution of pharmacists to the reporting of adverse drug reactions. Pharmacoepidemiol Drug Saf 2002;11:205-10.
40. Westerlund LT, Marklund BR, Handl WH, Thunberg ME, Allebeck P. Nonprescription drug-related problems and pharmacy interventions. Ann Pharmacother 2001;35:1343-9.
41. Boyko WL, Jr., Yurkowski PJ, Ivey MF, Armitstead JA, Roberts BL. Pharmacist influence on economic and morbidity outcomes in a tertiary care teaching hospital. Am J Health Syst Pharm 1997;54:1591-5.
42. Bouvy ML, Buurma H, Egberts TC. Laxative prescribing in relation to opioid use and the influence of pharmacy-based intervention. J Clin Pharm Ther 2002;27:107-10.
43. Beney J, Bero LA, Bond C. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes. Cochrane Database Syst Rev 2000(3):CD000336.
44. Singhal PK, Raisch DW, Gupchup GV. The impact of pharmaceutical services in community and ambulatory care settings: evidence and recommendations for future research. Ann Pharmacother 1999;33:1336-55.
45. Tully MP, Seston EM. Impact of pharmacists providing a prescription review and monitoring service in ambulatory care or community practice. Ann Pharmacother 2000;34:1320-31.
46. Bouvy ML, Heerdink ER, Urquhart J, Grobbee DE, Hoe AW, Leufkens HG. Effect of a pharmacist-led intervention on diuretic compliance in heart failure patients: A randomized controlled study. J Card Fail 2003;9:404-411.
47. Pronk M, Blom L, Jonkers R, Bakker A. Community pharmacy and patient-oriented activities: the Dutch case. Patient Educ Couns 2002;46:39-45.
48. Pronk MC, Blom LT, Jonkers R, Rogers EM, Bakker A, de Blaey KJ. Patient oriented activities in Dutch community pharmacy: diffusion of innovations. Pharm World Sci 2002;24:154-61.

49. Rossing C, Hansen EH, Krass I. The provision of pharmaceutical care in Denmark: a cross-sectional survey. J Clin Pharm Ther 2003;28:311-8.
50. Rossing C, Hansen EH, Krass I, Traulsen JM. Pharmaceutical care in Denmark: perceived importance of medicine-related problems and participation in postgraduate training. Pharm World Sci 2003;25:73-8.
51. Helmreich RL. On error management: lessons from aviation. BMJ 2000;320:781-5.
52. Phillips DP, Christenfeld N, Glynn LM. Increase in US medication-error deaths between 1983 and 1993. Lancet 1998;351:643-4.
53. Sexton JB, Thomas EJ, Helmreich RL. Error, stress, and teamwork in medicine and aviation: cross sectional surveys. BMJ 2000;320:745-9.
54. Misson JC. A review of clinical risk management. J Qual Clin Pract 2001;21:131-4.
55. Nolan TW. System changes to improve patient safety. BMJ 2000;320(7237):771-3.
56. Guchelaar HJ, Colen HB, Kalmeijer MD, Hudson PT, Teepe-Twiss IM. Medication errors: hospital pharmacist perspective. Drugs 2005;65:1735-46.
57. Madar J. Clinical risk management in newborn and neonatal resuscitation. Semin Fetal Neonatal Med 2005;10:45-61.
58. Lilienfeld DE. Pharmacoepidemiology 101: data monitoring committees in the post-marketing approval setting. Pharmacoepidemiol Drug Saf 2004;13:381-5.
59. Croonen H. Medicatiefouten 'gestrikt'. Pharm Weekbl. 2005;140:1178-81.
60. Bush JK, Dai WS, Dieck GS, Hostelley LS, Hassall T. The art and science of risk management: a US research-based industry perspective. Drug Saf 2005;28:1-18.
61. Commentaren Medicatiebewaking 2004-2005 (Commentaries Medication Surveillance). Houten, the Netherlands: Health Base; 2004.
62. Kuhn AM, Youngberg BJ. The need for risk management to evolve to assure a culture of safety. Qual Saf Health Care 2002;11:158-62.
63. Leufkens HGM. Praktijkonderzoek in de apotheek: stand van zaken en perspectief. Pharm Weekbl 1992;127:288-90.
64. Leufkens HG, Buurma H, Bakker A. 'Pharmacy practice research': na tien jaar nog steeds prominent op de agenda. Pharm Weekbl 1996;131:730-2.

Chapter 2

THE PROCESS



2.1

Frequency, nature and determinants of pharmacy compounded medicines in Dutch community pharmacies

Henk Buurma, Peter AGM de Smet, Olga P van den Hoff,
Henrieke Sysling-van Unen, Michiel Storimans, Antoine CG Egberts

Pharm World Sci 2003;25:280-7

ABSTRACT

Aims

To examine the frequency, nature and determinants of pharmacy compounded medicines in Dutch community pharmacies.

Methods

A prospective nested case-control study comparing prescriptions for pharmacy compounded medicines (cases) with non-pharmacy compounded medicines (controls) was carried out in 79 Dutch community pharmacies. 991 Prescriptions for compounded medicines, dispensed by the pharmacy on a predetermined day in a specific period (29 March until 11 April 2001), and 993 prescriptions for non-compounded medicines randomly selected on the same day, were studied. The nature and frequency of compounded medicines as well as patient, drug and prescriber related determinants were assessed. In addition, some organizational characteristics, like compounding site and use of protocols, were investigated. Also, the value of compounded medicines in terms of the availability of an industrially compounded equivalent and patient specific reasons, as perceived by the participating pharmacists, was evaluated.

Results

The overall frequency of prescriptions for pharmacy compounded medicines in relation to the total number of prescriptions was 3.4%. This means 12.5 compounded medicines per pharmacy per day on average, but there was a large variation between pharmacies. Excluding the products purchased from specialized compounding companies (28.4%) and the small part of medicines coming from other pharmacies (5.2%), we found an overall frequency of 2.3% of actual compounding in the pharmacy itself.

On average, approximately one employee was needed for compounding activities with a large variation between pharmacies. More than 13% of the pharmacists stated that they delivered more than 25% of their compounded medicines to other pharmacies. In two pharmacies (2.6%) no actual compounding took place. For 58% of the products manufactured in the pharmacy itself or coming from other pharmacies a (semi-)standardized protocol was used.

Compared to non-compounded medicines we found a huge share of dermatological dosage forms among compounded medicines (62.1% versus 5.3%). Oral solutions and ear-nose-throat products were also found relatively often. While no ATC (Anatomical Therapeutic Chemical) class was very

pronounced in the control group, the group of dermatologicals was prominently present in the case group (57%) followed by central nervous system (CNS) agents (8.4%). The dermatologist was a very strong determinant of compounded medicines compared to general practitioners (GPs) (OR_{adj} 12.2 [6.3-23.6]). Patients of 12 years or younger received a significantly higher rate of compounded medicines than persons older than 12 years of age (OR_{adj} 3.4 [2.5-4.8]). Compounding occurred almost twice as often when a medicine was prescribed for the first time compared to a repeat prescription (OR_{adj} 1.8 [1.5-2.2]).

In about 63% of the cases the pharmacist judged that an industrially produced medicine could not substitute for the compounded medicine. In about 33% of the compounded products they indicated a patient specific reason. In about 10% this reason concerned a strictly defined pharmaceutical care issue.

Conclusions

Based upon our research, all Dutch community pharmacies compound more than 13 000 medicines per day (2.3% of all prescriptions). They consist mainly of dermatological preparations. Younger children (<12 yr) receive a significantly higher rate of compounded medicines than other people. At least 1.2 compounded prescriptions per pharmacy per day have a specific pharmaceutical care reason according to the pharmacists.

INTRODUCTION

For centuries compounding was an elementary task of the pharmacist: the pharmacist as an artisan. Since World War II the situation has gradually changed. As more industrialized preparations became available the importance of compounding decreased and the profession shifted towards a more patient oriented role in the optimal choice and use of medicines. In several Western countries compounding by individual pharmacies even ceased to exist or was dramatically minimized. In the Netherlands, however, it remained substantially until today. At the beginning of the nineties the share of pharmacy compounded products in the Netherlands was still estimated at 10 to 15% of all dispensed drugs.[1] According to the Dutch National Health Insurance it declined from 5.5% in 1994 to 3.7% in 2000.[2] Data from the Foundation for Pharmaceutical Statistics (SFK; Stichting Farmaceutische Kengetallen, The Hague) confirm that there is a decline during these years, but not as strong: from 6.6% in 1995 to 5.5% in 2000.[3,4]

Since the middle of the 1980s, every now and then there has been a national debate about compounding in Dutch pharmacies. The arguments against are mainly related to the quality of compounded products. It has been suggested that the quality of compounded products can only be guaranteed by adherence to GMP (good manufacturing practice) rules, including the use of standardized protocols, in process controls, validation and laboratory controls.[5-9] Co-operation between pharmacies as to compounding of specific products and more consultation between pharmacists and prescribers about (ir)rational extemporaneous prescribing have been proposed as measures to ameliorate conditions to reach higher compounding quality.[8-11] In addition, pharmacy compounded medicines are far less studied and documented than their industrial equivalents with respect to biopharmaceutical aspects and safety, but in particular with respect to efficacy. While for standardized pharmacy compounded products (bio)pharmaceutical issues are to some extent sufficient and for safety a certain amount of experience can be build up, the real problem is with the efficacy issue. Formal clinical trials are hardly executed mainly due to costs. The arguments in favour of today's pharmacy compounding are primarily found in the realm of pharmaceutical care. It has been suggested that compounded products are needed in certain patient specific situations and can contribute to patient tailored pharmacotherapy, e.g. a product is needed but not commercially available (e.g. 'orphan drug' situations), or a special dosage form or strength is required, for

instance, for children. In some instances this means 'off-label use', which can also occur when a drug is used experimentally. This 'off-label use' can also be considered a reason against pharmacy compounding. Other pharmaceutical care arguments in favour are improved patient compliance and an existing contraindication or allergy for an ingredient of the speciality.[9,11,12] Another argument in favour of pharmacy compounding is that these medicines are often cheaper.[1,9,12] Some of the pros and cons are also found in international literature.[13-16]

We carried out this study into the frequency, nature and determinants of compounded medicines in Dutch community pharmacies, because of conflicting data about the frequency of compounding and the lack of detailed information about its nature and aspects related to their pros (e.g. patient tailoring) and cons (e.g. less stringent quality assurance).

METHODS

Setting and design

In 1999 we received a positive response from 470 Dutch community pharmacies to our invitation to participate in a previous study about prescription modifications.[17] Of the 60% of pharmacies (n=282) that did not participate in that study, we asked 50% (n=141) to join this prospective nested case-control study about pharmacy compounding. 84 Pharmacies were enrolled in the study, but five had to be excluded because they did not adhere to the study protocol, leaving 79 pharmacies (almost 5% of all Dutch pharmacies) for evaluation. Each participating pharmacy had to collect all dispensed prescriptions for pharmacy compounded medicines (cases) during one predetermined study day between 29 March and 11 April 2001. They had to sample at random an equal number of prescriptions for non-pharmacy compounded medicines (controls) that were dispensed on the study day. All participating pharmacies received a pre-tested study protocol and three types of registration forms: one for the documentation of each dispensed prescription for a pharmacy compounded medicine, one for each non-pharmacy compounded medicine and one general form concerning basic characteristics of the pharmacy on the study day. The protocol advised to contact a telephone help desk in case of any uncertainty.

Selection of cases

All prescriptions for medicines that were compounded and dispensed in the pharmacy on the study day, had to be included. A broad definition of a pharmacy compounded product was employed to measure the full magnitude of compounding. Following the Dutch national prices list, our definition comprised not only medicines compounded by the pharmacy itself, but also products compounded by other (hospital) pharmacies or by specialized compounding companies. The latter produce and deliver medicines to pharmacies in a finished or almost finished state without any assessment by the Dutch regulatory authorities. A protocol and an 'inclusion scheme' with eight examples were sent to help the pharmacists to select cases.

Selection of controls

The pharmacists had to provide an equal number of non-pharmacy compounded medicines by selecting this number at random from all prescriptions of the same day. This random selection was performed by blind drawing of the required number of prescriptions from a box containing all prescriptions for non-compounded medicines of that day. When there was more than one medicine on the same prescription the first medicine had to be chosen. Non-medicine prescriptions had to be excluded.

Validation of the cases

To check the reliability of the registered data, pharmacists were asked to send not only their registration forms but also anonymous copies of each underlying prescription to the coordinating study centre. When data in the registration form appeared to be incorrect compared with the prescription copy, it resulted in exclusion (which was rarely needed) or in an alteration by the research team.

Classification of prescriptions

All compounded products were classified into therapeutic groups using the Anatomical Therapeutic Chemical (ATC) classification of the WHO Collaborating Centre for Drug Statistics Methodology.[18] When no classification could be found in the official ATC system, we assigned an ATC-like code to the product within the rules and spirit of this classification. When we could not assign such a code, the product was classified as V03AX (other therapeutical products). In addition, the following variables of each prescription were registered: gender and age of patient, type of prescriber, repeat or first prescription, and dosage form.

For all cases, except for the products compounded by specialized compounding companies, the origin of protocols used for compounding purposes was requested (different kinds exist in Dutch community pharmacies). In the first place, national standard protocols are used for the compounding of standard products, the so-called FNA ('Formularium Nederlandse Apothekers' = Formulary Dutch Pharmacists) formulas. These products are well investigated and documented, both technically (e.g. shelf life) and pharmacotherapeutically (rationality). The LNA ('Laboratorium van Nederlandse Apothekers' = Laboratory of Dutch Pharmacists) is responsible for these formulas and compounding protocols. Another category is the semi-standard protocol, which is less well investigated and documented. They are found in specific locations, where local pharmacists have made them for specific products. Another type of semi-standardized protocols concerns an FNA-protocol, which is no longer updated by the LNA. Finally, it is possible to make a protocol at the moment of manufacturing. In most cases these non-standardized protocols are not or at best only slightly documented.
In addition, the pharmacist was asked to determine the value of each compounded medicine in terms of the availability of an industrially compounded product and patient specific reasons.

Data analysis
After inspection, data from the registration forms were entered in a database (Microsoft Access) and statistically analysed using standard descriptive data analysis (SPSS version 10.0). Logistic regression analysis was used to estimate the association between characteristics and compounding.

RESULTS

The basic characteristics of the participating pharmacies are presented in Table 1. There was a large variation in the total number of prescriptions and the number of pharmacists and assistants per pharmacy, which probably reflects the fact that both small and very large pharmacies participated in the study. Compared to the average Dutch pharmacy the enrolled pharmacies processed more prescriptions per day, but had a lower number of personnel. The workload of assistants was consequently higher.
In 2 of 79 enrolled pharmacies (2.6%) compounding of medicines did not take place by the pharmacy itself. On average approximately one employee, mainly an

assistant, was needed for compounding. In relation to the total number of personnel this means that a Dutch pharmacy uses almost 15% of its qualified personnel for compounding related tasks. However, there was a large variation in the mean number of personnel deployed for compounding. Six pharmacies (8.0%) stated that more than 25% of their compounded medicines were delivered to other pharmacies and this share was more than 50% in four pharmacies (5.3%). On the study day, the overall frequency of compounded medicines relative to all dispensed prescriptions was 3.4% (991 cases out of 28711 prescriptions; Table 2). The number of cases per pharmacy varied from 2 to 35 with a mean of 12.5 compounded medicines per pharmacy per day. The frequency of compounded prescription only medicines (POM) as to the total number of POM prescriptions was 5.1% (range between pharmacies from 0.5 to 14.1%).

Table 1: CHARACTERISTICS OF THE INCLUDED PHARMACIES (n=79)

	Mean	Range	Mean data of Dutch pharmacies (n=1602)[a]
Prescription characteristics			
- number of prescriptions/day	372.9	164 – 753	325[a]
- number of POM prescriptions/day	297.7	26 – 654	
Personnel characteristics			
- number of pharmacists	1.4	0.5 – 2.5	1.63
- number of assistants	4.7	2.0 – 8.5	5.90
- number of personnel[b]	6.1		7.53
- workload per assistant[c]	79.3		55.1
- workload per personnel	61.1		43.2
Compounding characteristics			
- number of non-compounding pharmacies, n=78 (100%)	2 (2.6%)		
- mean number of personnel deployed for compounding	0.9	0.1 – 3.0	
- share of compounding for other pharmacies, n=75 (100%)			
0 - 25%	65 (86.7%)		
26 - 50%	6 (8.0%)		
51 - 75%	4 (5.3%)		
76 - 100%	0 (0.0%)		

a) Data obtained from SFK concerning the first quarter of 2001. Estimation of number of prescriptions per day based upon a total of 21 000 prescriptions in first quarter of 2001.
b) Personnel: number of pharmacists plus number of pharmacy assistants (full-time equivalents).
c) Workload assistants: number of prescriptions per full-time assistant per day.

The majority of all dispensed compounded medicines was compounded in the pharmacy itself (657; 66.3%). Almost half of the latter was prepared extemporaneously (302; 30.5%), while the other half (343; 34.6%) was kept as stock (Table 3). A large part (28.4%) of the so-called pharmacy compounded products was purchased from special companies, leaving a small part of products coming from other pharmacies, like the hospital pharmacy (52; 5.2%).

Table 2: FREQUENCY OF PHARMACY COMPOUNDED MEDICINES IN DUTCH COMMUNITY PHARMACIES

	Total number	Number of cases	Frequency[a]	Range[b]
All prescriptions	28 711	991	3.4%	0.4– 6.8%
POM prescriptions	19 347	991	5.1%	0.5–14.1%

a) Frequency = (number of all cases x 100%)/total number of prescriptions.
b) Range concerns the frequency per pharmacy.

Table 3: CHARACTERISTICS OF PHARMACY COMPOUNDED MEDICINES IN DUTCH COMMUNITY PHARMACIES (CASES): COMPOUNDING SITE AND USE OF PROTOCOLS

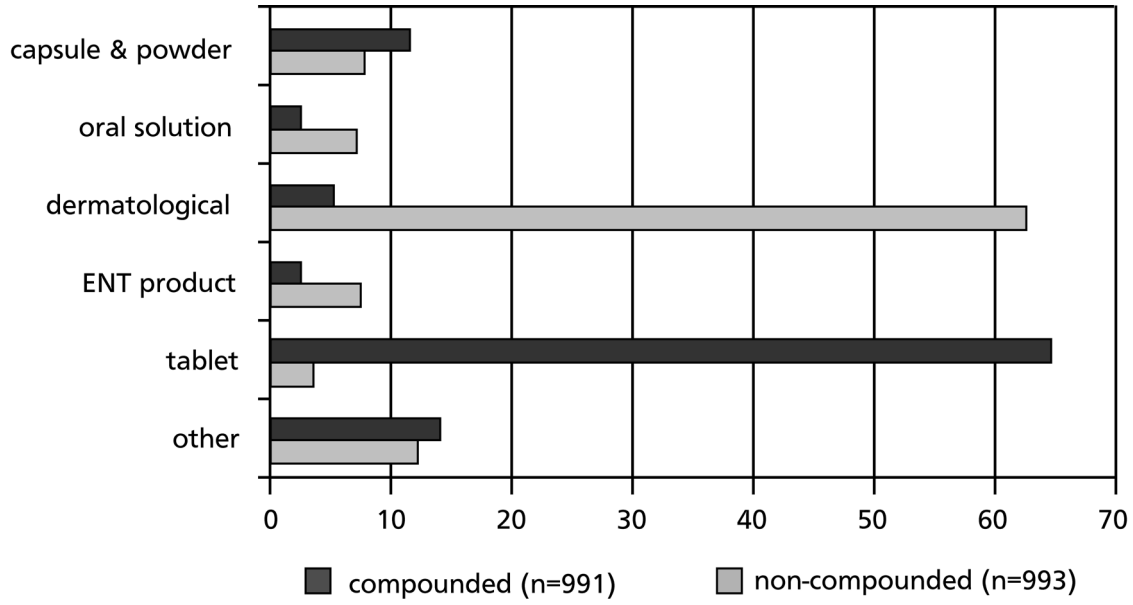
	Number of cases
Compounding site	**n=991 (100%)**
compounded by the pharmacy itself (A)	657 (66.3%)
- extemporaneous manufacturing	302 (30.5%)
- product in stock	343 (34.6%)
compounded by other (hospital) pharmacy (B)	52 (5.2%)
compounded by special company (C)	281 (28.4%)
Use of protocols (A + B)	**n=710 (100%)**
standardized protocol used	218 (30.7%)
semi-standardized protocol used	194 (27.3%)
non-standardized protocol, or no protocol used	296 (41.7%)

Not all data count up to 100% because of missing values.

The use of protocols was considered for the products manufactured in the pharmacy itself and those coming from other pharmacies. In 58% of the cases the pharmacy used a standardized or semi-standardized protocol.
The data of drug related variables like dosage form and type of drug (ATC-code) are presented in Figure 1 and 2 respectively. There was a large share of dermatological dosage forms in the case group (62.1% versus 5.3% in the control

group). Oral solutions and ENT (ear-nose-throat) products were also found relatively more often among compounded medicines.

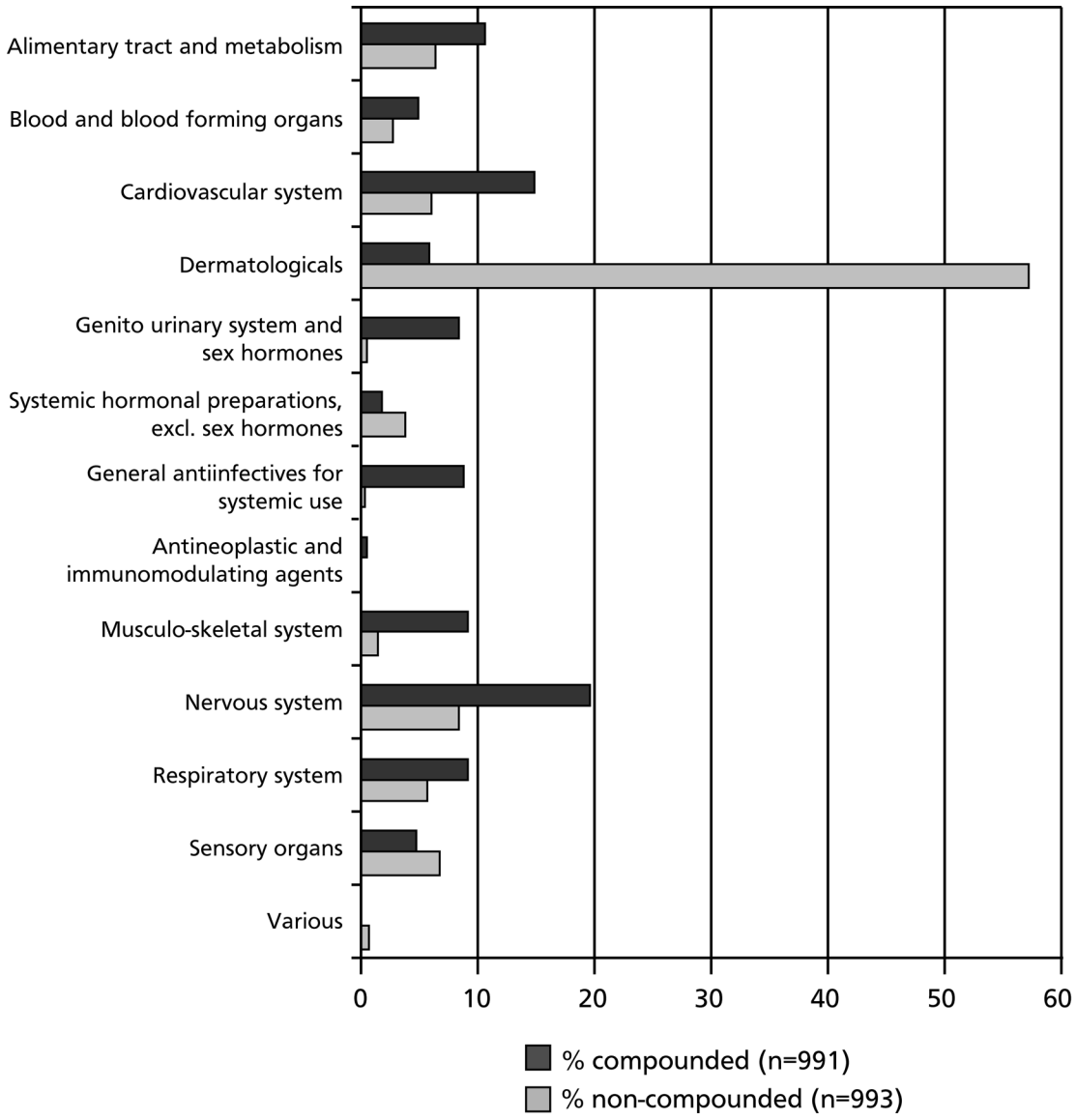
Figure 1: FREQUENCY (%) OF DOSAGE FORMS IN PHARMACY COMPOUNDED AND NON-COMPOUNDED MEDICINES



The large share of dermatological dosage forms is also reflected in the distribution of ATC codes (D; 57%). All other ATC classes within the group of compounded medicines had a relatively small share with the nervous system products as the highest (N; 8.4%). In the control group nervous system medicines were prescribed most frequently (19.6%), followed by cardiological preparations (C; 14.9%) and alimentary tract and metabolism medicines (A; 10.7%).

In Table 4 the determinants of compounded medicines are summarized. Compounding occurred almost twice as often when a medicine was prescribed for the first time compared to a repeat prescription (OR_{adj} 1.8 [1.5-2.2]). With respect to patient-related factors we found that children (12 years or younger) received a considerably higher rate of compounded medicines than people older than 12 years of age (OR_{adj} 3.4 [2.5-4.8]). Correspondingly, the mean age in the case group was somewhat lower than that in the control group: 43.1 (sd 26.3) versus 51.5 (sd 21.7). With respect to other patient related factors, gender did not appear to be significant.

Figure 2: FREQUENCY (%) OF ATC GROUPS IN PHARMACY COMPOUNDED AND NON-COMPOUNDED MEDICINES



Data do not count up to 100% because of missing values or data not shown (low frequency of antiparasitics).

With regard to prescriber related determinants, dermatologists were the most important: the chance of getting a compounded medicine from a dermatologist was more than twelve times as high as that for a general practitioner (OR_{adj} 12.2 [6.3-23.6]). Other prescribers like paediatricians had an impact similar to general practitioners (GPs).

In Table 5 the value of pharmacy compounded products according to the participating pharmacists is shown. In 63.4% of the cases the pharmacist believed an industrially produced medicine could not substitute for the compounded product.

Table 4: DETERMINANTS OF PHARMACY COMPOUNDED MEDICINES (CASES) IN DUTCH COMMUNITY PHARMACIES

Characteristic	Cases n=991 (100%)	Controls n=993 (100%)	OR (95% CI) Crude	OR (95% CI) Adjusted[a]
Patient related				
gender				
male	42.5%	39.1%	1 (reference)	
female	57.5%	60.9%	0.95 (0.87-1.04)	
age (yr)				
<12	15.7%	5.1%	3.44 (2.47-4.80)	3.43 (2.46-4.80)
12-75	70.8%	79.6%	1 (reference)	1 (reference)
>75	13.4%	15.3%	0.98 (0.76-1.27)	0.99 (0.87-1.04)
Prescriber related				
GP	75.1%	81.7%	1 (reference)	1 (reference)
dermatologist	10.9%	1.0%	11.66 (6.06-22.39)	12.23 (6.33-23.60)
paediatrician	1.3%	0.8%	1.77 (0.73-4.30)	0.65 (0.25-1.68)
other prescribers	12.7%	16.5%	0.84 (0.65-1.08)	0.86 (0.67-1.11)
Drug related				
repeat prescription	46.9%	61.9%	1 (reference)	1 (reference)
first prescription	52.5%	36.6%	1.89 (1.58-2.27)	1.80 (1.50-2.16)

Not all data count up to 100% because of missing values.
a) Adjusted for all other characteristics.

The participating pharmacists indicated patient specific reasons in 33.2% (330 of 991 cases) of the pharmacy compounded products: intolerance or contra-indication were mentioned in 0.8% of the cases, convenience to use in 4.4%, and special demand of the prescriber or patient in 8.5% (6.1% and 2.4% respectively). The reason 'special dose needed' was mentioned in 4.2% of the cases. In almost 7% of the cases the product was compounded to avoid (partial) payment by the patient. Some specialities are not remunerated at all or are partially remunerated because of remuneration limits within ATC clusters. In both situations pharmacy compounded medicines may be alternatives for specialities. In 3.3% of the cases (n=33) there was more than one reason to dispense a pharmacy compounded product, a combination of the reasons mentioned above. In 8.5% there was 'another reason' to compound in the pharmacy. With respect to the patient

specific reasons for compounding, the overall picture did not clearly change, when the results were considered without products coming from special companies.

Table 5: VALUE OF PHARMACY COMPOUNDED MEDICINES (CASES) AS PERCEIVED BY THE PARTICIPATING PHARMACISTS: COMMERCIAL AVAILABILITY OF EQUIVALENT PRODUCTS AND PATIENT SPECIFIC REASONS

	Number of cases n=991 (100%)
Equivalent product commercially available	
positive judgement	237 (23.9%)
negative judgement	628 (63.4%)
unknown to pharmacist	115 (11.6%)
Preparations with one patient specific reason	**330 (33.2%)**
intolerance/contraindication	8 (0.8%)
inconvenient to use	44 (4.4%)
special dose needed	42 (4.2%)
demand of patient	24 (2.4%)
demand of prescriber	60 (6.1%)
prevention of (partial) payment by patient or other cost reason	68 (6.9%)
other reason	84 (8.5%)
Preparations with a combination of ≥ two patient specific reasons	**33 (3.3%)**

Not all data count up to 100% because of missing values.

DISCUSSION

In this study we found that 3.4% of all dispensed prescriptions in Dutch pharmacies concern a compounded medicine, which means an average number of 12.5 compounded medicines per pharmacy per day. Two-thirds of these medicines are still manufactured in the pharmacy itself. In comparison with non-compounded medicines, compounded medicines were significantly more often prescriptions for children, dermatological dosage forms and products, prescriptions by dermatologists and first prescriptions. Participating pharmacists estimated that at least 10% of the compounded medicines had a pharmaceutical care reason.

Two other Dutch sources for drug utilisation data give conflicting figures for the year 2000 concerning the frequency of compounded medicines: 3.7% according to the Dutch National Health Insurance[2] and 5.5% according to the SFK.[3,4] Both figures are based on remuneration data, which are based on the Dutch national

pricing list. These data do not differentiate between the origin of pharmacy compounded products. They represent not only pharmacy made products, but also products defined as pharmacy manufactured but coming from other pharmacies or specialized companies. As presented in the introduction, both the Dutch National Health Insurance and the SFK show in percentage terms a decline in compounding. As shown by us the actual compounding by pharmacies is even lower (2.3%).

The considerable proportion (28.4%) of preparations coming from specialized companies is of concern, since the availability of these products on the Dutch medicines market is controversial. Until now these specialized firms have been able to avoid any formal medicine approval procedure. In the United States this phenomenon caused the FDA (Food and Drug Administration) to issue guidance regarding pharmacy compounding.[19] Among others, Dutch specialized companies present a large part of their products as semi-manufactured or almost finished article so that the pharmacy itself has to finish the product, often in a very easy way. The rise of these firms is a consequence of shortage of personnel in the pharmacies and a call among pharmacists for more centralized compounding. Consequently, these firms compound those preparations that are more broadly needed. Patient tailored products are probably more often extemporaneously compounded and remain in the pharmacy itself.

Our study also revealed that pharmacy compounding consists for a large part of dermatological products and dermatological dosage forms (Figures 1 and 2). Correspondingly, the dermatologist is relatively strongly represented within the group of compounded preparations compared with the GP. Although not exactly similar, these data confirm results from others.[4,20]

With respect to patient related determinants, children below 12 years of age received relatively more compounded medicines than other age groups. In a study of Crawford et al., who evaluated frequently extemporaneously compounded drug formulations, the group of infants and children was considerable.[21] This might be explained by the fact that children need patient tailored therapy more frequently, for which commercial products are not available, because a special dose or dosage form is needed.[22] On the one hand there is the benefit that pharmacy compounding makes patient-tailored dosage forms or dose strengths available for children. On the other hand there is the risk that pharmacy compounding thereby supports use of drugs in children which have not yet been evaluated in an appropriate way and which may give rise to considerable adverse drug reactions.[23,24]

With respect to drug related determinants we found that compounded medicines are less chronically prescribed than non-compounded medicines: first prescriptions occur twice as often as repeat prescriptions. This might be related to the fact that some ATC groups (e.g. C and N), for which continuous use is normal, are more pronounced in the control group (Figure 2). Furthermore young people, who generally use medicines less chronically, are more represented in the case group than in the control group (Table 4).

The pharmacies did not use a standardized or semi-standardized protocol in 42% of the cases (Table 3). We have not investigated to what extent the pharmacies were unable to use any protocol, and when they were unwilling to do so. Most likely, both mechanisms have played a role in our sample. When a patient requires a special composition, dosage form or strength that is not commercially available, extemporaneous compounding is needed to provide this patient with an individually tailored medicine.[9,15,16] This type of compounding cannot always be based on the application or adjustment of an existing protocol. We found that younger patients (<12 yr) used significantly more compounded medicines, and it is well established that this age group has a larger need for special dosage forms and strengths than adult patients.[22] We also found other reasons, why medicines were sometimes compounded for individual patients, e.g. because this increased the convenience to use, or because the prescriber or patient insisted on a particular medicine (Table 5).

There were some limitations regarding our study. Although we used a random sample from volunteering community pharmacies throughout the country, we found some differences, like a higher workload, between the average enrolled and average Dutch pharmacy (Table 1). To reduce the risk of overestimation, every reported case was checked on the basis of anonymous copies of the original prescription. But underestimation cannot be totally ruled out, because some cases may not have reached us due to pressure of time or inappropriate handling. Another limitation of our study was that it occurred in a short time period and that it cannot predict possible (but unknown) seasonal variations. Fluctuating patterns within a week however were ruled out by assigning all days of the week equally in the study period.

In the debate with respect to pharmacy compounding one may find several pros and cons. As described in the introduction, the arguments in favour of pharmacy compounding are related to pharmaceutical care suggesting that compounded products are needed in certain patient specific situations.[9,11,12] However, this statement has never been properly investigated. In this study we did a

preliminary estimate based upon the opinion of the participating pharmacists (Table 5). In 33.2% of the pharmacy compounded products pharmacists indicated patient specific reasons. Specific pharmaceutical care issues like intolerance or contraindication, convenience to use and special dose needed, were mentioned in 9.5% of all cases. Therefore, at least 1.2 compounded prescriptions per pharmacy per day had a specific pharmaceutical care reason. A closer look at the category 'combination of reasons' revealed more (1.1%) such indications. It cannot be ruled out that in the other categories mentioned, like 'demand of prescriber', pharmaceutical care issues may have been present. At the same time, we have to emphasize that the opinion of prescribing doctors was not investigated explicitly. One may argue that while prescribing these preparations, they almost certainly had a positive opinion about their value for the individual patient. Cost represented a considerable share (6.9%) of patient specific reasons indicating that the price of compounded medicines is lower in some instances.[1,9] It remains debatable whether avoidance of cost for the patient is a pharmaceutical care issue.

This study gives some indication regarding the value of compounding for the Dutch outpatient. A more in depth analysis is needed to assess the potential clinical relevance of compounded medicines which we intend to do by presenting representative samples of cases of this study and/or other to multidisciplinary rating panels.[25,26]

CONCLUSIONS

Based upon our research, more than 13 000 medicines per day are compounded in Dutch community pharmacies (2.3% of all prescriptions). A remaining part of compounded products (1.1% of all prescriptions) is coming from other pharmacies but in particular from specialized companies. Pharmacy compounded products consist mainly of dermatological preparations. Younger children (<12 yr) receive a significantly higher rate of compounded medicines than others. At least 1.2 compounded prescriptions per pharmacy per day have a specific pharmaceutical care reason according to the pharmacists. It could be that compounding for Dutch outpatients will continue to decline due to external reasons, like the growing availability of the controversial (half-)products from the above-mentioned specialized compounding firms, changes in the remuneration system and a growing pressure in our evidence-based medicine era to rationalize

dispensing and compounding.[8,9] Also organizational aspects like shortage of personnel and efforts of pharmacists to cooperate with prescribers - especially dermatologists - and colleagues to rationalize compounding, will contribute to a further decline.[4] We believe nevertheless that compounding for Dutch outpatients will hold a place, especially because it offers a potentially valuable tool to provide pharmaceutical care to individual patients.

Acknowledgements. We would like to thank all pharmacists who participated in the study. Special thanks to Mrs Antoinette van Yperenburg and Mr Matthijs Engering, pharmacists, who helped in the design of the study, to Mr Frans Dijkman who developed the database for data entry and to Mrs Yvonne Bouwman-Boer for reading the manuscript.

REFERENCES

1. Tel H. Community pharmacy in the Netherlands. Pharm Weekbl 1992;127:956-9.
2. GIPeilingen 1992-2000, Kengetallen farmaceutische hulp. Genees- en hulpmiddelen Informatie Project (GIP). Amstelveen, the Netherlands: College van Zorgverzekeringen; 2001.
3. Van der Heide H, Tinke JL. Data en Feiten 1999. Kostenontwikkeling van de farmaceutische hulp. The Hague: Stichting Farmaceutische Kengetallen *[Foundation for Pharmaceutical Statistics]*; 1999.
4. Stichting Farmaceutische Kengetallen [*Foundation for Pharmaceutical Statistics*]. Minder bereidingen in de apotheek [*Less compounding in the pharmacy*]. Pharm Weekbl 2001;136:619.
5. Hansen JMM. De kwaliteit van de bereidings- en onderzoeksprotocollen in de ziekenhuisapotheek [*The quality of manufacturing and research protocols in hospital pharmacy*]. Pharm Weekbl 1993;128:1355-7.
6. Wagenaar HWG. FNA-preparatencontrole 1995. Momentopname van de kwaliteit van enkele apotheekbereidingen [*Snapshot of quality of drug compounding in community pharmacies*]. Pharm Weekbl 1996;131:1414-7.
7. Bouwman-Boer Y, Wagenaar HWG. Een Gordiaanse vitamineknoop. Kwaliteitsperikelen van vitamine K-prepraten ontrafeld [*A Gordian vitamin knot. Quality perils of vitamin K products unravelled*]. Pharm Weekbl 1999;134:609-13.
8. Bouwman-Boer Y, van de Vaart FJ, Kloeg PHAM. Samen bereiden geeft kwaliteit. Apotheekbereiding in de geneesmiddelenvoorziening 2 [*Compounding together ensures quality. Drug compounding in pharmacies and drug supply 2*]. Pharm Weekbl 1999;134:604-8.

9. Schoenmakers T. Apotheekbereiding heeft de toekomst [*Pharmacy compounding has good prospects*]. Pharm Weekbl 1997;132:1876-81.
10. Joosten AAM. Uiteindelijk beslist de apotheker [*Ultimately the pharmacist decides*]. Pharm Weekbl 2000;135:18-20.
11. Wissenburg A, Dijkgraaf-Feitsma C. Wat schrijft u voor? De rol van apotheekbereidingen [*What do you prescribe? The place of pharmacy compounding*]. Pharm Weekbl 2000;135:12-7.
12. Bouwman-Boer Y, van de Vaart FJ, Kloeg PHAM. Alleen beschikbaar als apotheekbereiding. Apotheekbereiding in de geneesmiddelenvoorziening 1 [*Only available as a pharmacy preparation. Drug compounding in pharmacies and drug supply 1*]. Pharm Weekbl 1999;134:578-81.
13. Nordenberg T. Pharmacy compounding: custimizing prescription drugs. FDA Consumer magazine 2000 (July-August). (http://www.fda.gov/fdac/features/2000/400_compound.html)
14. Smith MC, Brown TR. Dermatologists' referrals of prescriptions requiring compounding. Cutis 1984;34:489-91.
15. Ling MR. Extemporaneous compounding. The end of the road? Dermatol Clin 1998;16:321-7.
16. Thiers BH. Compounding is still appropriate in clinical practice. Dermatol Clin 1998;16:329-30.
17. Buurma H, de Smet PAGM, van den Hoff OP, Egberts ACG. Nature, frequency and determinants of prescription modifications in Dutch community pharmacies. Br J Clin Pharmacol 2001;52:85-91.
18. Anonymous. ATC Index with DDDs. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 1999.
19. Guidance for FDA Staff and Industry. Compliance policy guides manual. Sec. 460.200. Pharmacy compounding. (http://www.fda.gov/ora/compliance_ref/cpg/default.html)
20. Altmeyer P, Bergmeyer V, Wienand W. Analyse magistraler Rezepturen von niedergelassenen Dermatologen [*Practising dermatologists and compounding of prescriptions*]. Der Hautarzt 1997;48:12-20.
21. Crawford SY, Dombrowski SR. Extemporaneous compounding activities and the associated informational needs of pharmacists. Am J Hosp Pharm 1991;48:1205-10.
22. Nahata MC. Pediatric drug formulations: challenges and potential solutions. Ann Pharmacother 1999;33: 247-9.
23. Schirm E, Tobi H, de Jong-van den Berg LTW. Unlicensed and off label drug use by children in the community: cross sectional study. BMJ 2002;324:1312-3.
24. 't Jong GW, Eland IA, Sturkenboom CJM, van den Anker JN, Stricker BHCh. Unlicensed and off label prescription of drugs to children: population based cohort study. BMJ 2002;324:1313-4.

25. Hawksworth GM, Corlett AJ, Wright DJ, Chrystyn H. Clinical pharmacy interventions by community pharmacists during the dispensing process. Br J Clin Pharmacol 1999;47:695-700.
26. Wright DJ, Aykroyd RG, Chrystyn H. Rating clinical pharmacy interventions by clinical panels: Which health professionals should be included? Br J Clin Pharmacol 1998;46:278P.

2.2

Nature, frequency and determinants of prescription modifications in Dutch community pharmacies

Henk Buurma, Peter AGM de Smet,
Olga P van den Hoff, Antoine CG Egberts

Br J Clin Pharmacol 2001;52:85-91

ABSTRACT

Aims

To examine the nature, frequency and determinants of prescription modifications in Dutch community pharmacies.

Methods

A prospective case-control study comparing modified prescriptions with non-modified prescriptions was carried out in 141 Dutch community pharmacies. 2014 modified prescriptions (cases), collected in the selected pharmacies on a predetermined day in a specific period (25 February until 12 March 1999) and 2581 non-modified prescriptions (controls) randomly selected on the same day were studied. The nature and frequency of prescription modifications and patient, drug and prescriber related determinants for a modified prescription were assessed.

Results

The overall incidence of prescription modifications was 4.3%, with a mean of 14.3 modifications per pharmacy per day. For prescription only medicines (POM) the incidence was 4.9%. The majority of modifications of POM prescriptions concerned a clarification (71.8%). In 22.2% a prescription could potentially have had clinical consequences when not altered; in more than half of the latter it concerned a dose error (13.7% of all cases). POM prescriptions of patients of 40-65 years had a significantly lower chance of modification compared with those of younger people (OR=0.74 [0.64-0.86]). With respect to medication-class, we found a higher chance of POM prescription modifications in the respiratory domain (OR=1.48 [1.23-1.79]) and a decreased chance for nervous system POMs (OR=0.71 [0.61-0.83]). With regard to prescriber-related determinants modifications were found three times more often in non-printed prescriptions than in printed ones (OR=3.30 [2.90-3.75]). Compared with prescriptions by the patient's own general practitioner (GP), prescriptions of specialists (OR=1.82 [1.57-2.11]), other GPs (OR=1.49 [1.02-2.17]) and other prescribers such as dentists and midwives (OR=1.95 [1.06-3.57]) gave a higher probability of prescription modifications. When a GP had no on-line access to the computer of the pharmacy the chance of a modification was also higher (OR=1.61 [1.33-1.94]). Multivariate analysis revealed that a non-printed prescription was the strongest independent determinant of prescription modifications (OR=3.32 [2.87-3.84]), remaining so after adjustment for GP computer link to the pharmacy and for type of prescriber.

Conclusions

Dutch community pharmacies corrected on average 2.8 POM prescriptions per pharmacy per working day, which could potentially have had clinical consequences if not altered. If the study sample is representative for the Netherlands, Dutch community pharmacies correct a total of approximately 4400 of these prescriptions per working day. Using computerized systems to generate prescriptions is an important strategy to reduce the incidence of prescription errors.

INTRODUCTION

The management of patient health care can be compromised by drug related morbidity and mortality, which in their turn can be the result of prescription errors.[1] Community pharmacies can contribute to a reduction of potentially harmful prescription errors. A recent UK study of 1503 pharmacy interventions on 201 000 items dispensed (0.75%) estimated that between 71 and 483 interventions (0.04-0.24% of all items) could have prevented harm, whilst 19-242 interventions (0.01-0.12%) might have prevented a drug related hospital admission.[2] Moreover, 748 interventions (0.37%) had the potential to improve clinical outcome and could have saved a visit to or by the general practitioner (GP).

We were interested in the contribution of Dutch community pharmacies to the timely detection of prescription errors, particularly because they have used computerized medication surveillance for about two decades.[3] We were also interested in the determinants of prescription modifications accomplished by community pharmacies, because better insight into the determinants of such prescription modifications may lead to improved or new strategies to reduce prescription errors. The impact of the basic characteristics of the prescription, the patient and the prescriber on prescription modifications for outpatients have not been extensively evaluated in previous studies. Therefore, we have carried out a large-scale study to investigate the frequency, nature and determinants of prescription modifications in Dutch community pharmacies.

METHODS

Setting and design

In January 1999 all Dutch community pharmacies (n=1571) were invited to participate in the study by a letter and by a notice in the Dutch pharmaceutical journal. From 470 community pharmacies, that reacted positively within 3 weeks, 188 (40%) were randomly selected. There were 36 non-responders (mainly because of lack of time and/or personnel or because they had forgotten about it) and 152 responders. Of the latter, 11 pharmacies had to be excluded, because they had not adhered to the study protocol, which left 141 pharmacies (9% of all Dutch pharmacies) that could be enrolled in our evaluation.

All participating pharmacies received a pretested study protocol and three types of registration forms for the documentation of modified prescriptions (cases),

non-modified prescriptions (controls) and basic characteristics of the pharmacy on the day of the study. The protocol advised contact with a telephonic help desk in case of any uncertainty. Each participating pharmacy had to collect all modified prescriptions during one predetermined day between 25 February and 12 March 1999. On the same day they had to collect at random an equal number of non-modified prescriptions. After selection of cases and controls the pharmacists had to fill in a registration form for each case and each control.

Selection of cases

All prescriptions for medicines and other health care products (e.g. dressings, incontinence materials, syringes and needles) that were offered on the predetermined day to the community pharmacy by the patient, or by fax or telephone had to be included. Cases were all prescriptions that were modified by the pharmacy on that particular day (even if actual dispensing took place on another day). Reasons for including a prescription modification as a case were defined in the protocol and in the registration form for cases. If there were two or more reasons for modifying a prescription the pharmacist had to select the one he/she considered most relevant. The protocol excluded the following modifications because of their lack of potential impact on patient care: address incorrect or absent, no or incorrect insurance data, incorrect package size, product not in stock, unit of dosage or package specified incorrectly (e.g. ml instead of g), generic substitution and legal requirements (e.g. for narcotic drugs). During the data management process we divided the nature of prescription modifications into three groups. In the first group a clarification was needed to carry out the prescription order. In most cases an essential administrative feature of the prescription was missing or obviously incorrect. In fact the pharmacy could not have dispensed the drug without clarification. In the second group for items identified as 'correction prescription error' the prescription was administratively correct, but could potentially have had clinical consequences if not altered. Those identified as 'wrong dose' are an important example, for which there are several reasons, like too high/low dose according to standard references or in contrast with the patient's own records. The third group included reasons for modification not covered by the first two categories.

Selection of controls

The pharmacists had to provide an equal number of non-modified prescriptions by selecting this number at random from a box containing all prescriptions of the same day.

Validation of the cases

To control for the reliability of the registered data pharmacists were asked to send in the registration forms as well as copies of the prescriptions and six month medication records of the patients concerned. This information was stripped of personal data. Incorrect data in the registration form when compared with the copies of the prescription and/or medication record could lead to an alteration in the final form registered by the research team. For these reasons various cases were excluded from the study. Where double or triple reasons for modification were given, the one considered most relevant was selected so that only one modification per prescription was counted.

Classification of prescriptions

Following Dutch reimbursement regulations items prescribed were classified as prescription only medicines (POM), over the counter (OTC) medicines (such as paracetamol and miconazole), and non-medicines (such as dressings, incontinence materials, syringes and needles). The number of prescribed OTC medicines were too small to be worth analysing. All medicines were classified into therapeutic groups using the Anatomical Therapeutic Chemical (ATC) classification of the WHO Collaborating Centre for Drug Statistics Methodology.[4]

Analysis

After inspection, data from the registration forms were entered in a Microsoft Access database and statistically analysed using SPSS version 9.0. Logistic regression analysis was used to estimate the association between characteristics and modification of a prescription.

RESULTS

The characteristics of the enrolled pharmacies were comparable with the characteristics of all Dutch community pharmacies in the study period. However, the number of pharmacy assistants in the participating pharmacies was somewhat lower than that in the average Dutch pharmacy, leading to a slightly increased workload per individual (Table 1).

There was a large variation in the total number of prescriptions per pharmacy, which probably reflects the fact that both small and very large pharmacies were involved in our study.

Table 1: CHARACTERISTICS OF THE SELECTED PHARMACIES

Characteristics	Pharmacies n=141 (100%)	Range	Mean (sd)	Mean data of Dutch pharmacies (n=1571)[a]
Urbanization level[b]				
no urbanization	12 (8.5)			9.4%
little urbanization	31 (22.0)			21.7%
moderate urbanization	37 (26.2)			22.4%
strong urbanization	37 (26.2)			25.8%
very strong urbanization	24 (17.0)			20.7%
Prescription characteristics				
number of prescriptions/day		42 – 998	336.0 (140.5)	322.5
number of POM prescriptions/day		34 – 609	259.8 (99.8)	256.1
Personnel characteristics				
number of pharmacists		0.0 – 4.0	1.3 (0.5)	1.55
number of assistants		1.0 – 9.5	4.7 (1.6)	5.85
number of personnel[c]		2.0 – 13.5	6.0 (1.9)	7.40
workload assistants[d]		30.9 – 162.0	73.0 (22.4)	55.1
workload personnel		19.6 – 105.2	55.9 (15.4)	43.6

a) Data obtained from SFK (Stichting Farmaceutische Kengetallen = Foundation for Pharmaceutical Statistics, The Hague) concerning the first quarter of 1999.
b) This measure of urbanization is used by the Central Bureau of Statistics (CBS) in the Netherlands and by SFK as well.[22]
c) Personnel = number of pharmacists plus number of pharmacy assistants.
d) Workload assistants = number of prescriptions per assistant per day.

On the study day, the overall incidence of modifications by the community pharmacies was 4.3% (2014 cases of 47374 prescriptions) (Table 2). The number of modifications per pharmacy varied from 0 to 100 with a mean of 14.3 prescription modifications per pharmacy. The incidence of modifications of POM prescriptions was 4.9% compared to only 1.4% of the prescriptions for non-medicines. Modifications of POM prescriptions were most frequently found in the following therapeutic domains: nervous system (ATC group N), respiratory system (R), alimentary tract and metabolism (A), and cardiovascular system (C) (Table 3a).

In 219 cases (12.2%), the modification of a POM prescription was triggered by a signal of the computerized medication surveillance system of the pharmacy concerning a change in therapeutic regimen (e.g. different strength or dose), a potential drug-drug interaction, contraindication or double medication

(combination of two medicines with the same or similar ingredient). More than half of the problems concerning POM prescriptions (51.2%) were solved by communication with the patient or his representative, and the same was found for non-medicines (52.7%). In 282 instances (15.6%), the pharmacy consulted the prescriber about a POM prescription, but the prescriber was contacted less often for non-medicines (7.5%). Contacts with the prescriber's assistant were similar for POM prescriptions (4.9%) as for prescription modifications of non-medicines (5.5%) (Table 3b).

Table 2: INCIDENCE OF PRESCRIPTION MODIFICATIONS

	Total number	Number of cases	Incidence
All prescriptions	47 374	2014	4.3%
POM prescriptions	36 625	1802	4.9%
Non-medicine prescriptions	10 298	146	1.4%

Table 3a: CHARACTERISTICS OF THE MODIFIED PRESCRIPTIONS (CASES): THE DISTRIBUTION OF ATC CLASSES

	POM prescriptions n=1802 (100%)
ATC class Nervous system	311 (17.3)
ATC class Respiratory system	252 (14.0)
ATC class Alimentary tract and metabolism	227 (12.6)
ATC class Cardiovascular system	216 (12.0)
Other ATC classes	796 (44.2)

Table 3b: CHARACTERISTICS OF THE MODIFIED PRESCRIPTIONS (CASES): SHARE OF COMPUTER SIGNALS AND CONSULTATIONS

Modifications	**POM** prescriptions n=1802 (100%)	Non-medicine prescriptions n=146 (100%)
Based upon a computer signal	219 (12.2)	
After consultation with prescriber	282 (15.6)	11 (7.5)
After consultation with the prescriber's assistant	88 (4.9)	8 (5.5)
After consultation with patient or representative	924 (51.2)	77 (52.7)

In Table 4 the nature of the prescription modifications is summarized. The majority (1294; 71.8%) of the reasons for the 1802 POM prescription modifications concerned the clarification of an insufficiently specified prescription (e.g. dose not specified, insufficient patient data, wrong strength or strength not specified), whereas in 400 cases (22.2%) a prescription error was corrected that might have had clinical consequences ('correction prescription error'). Dose corrections were more prevalent in this latter group (13.7%) than other interventions, such as for a drug-drug interaction, contraindication or double medication (8.5%). In Table 5 we present some individual examples of POM prescription modifications.

In our analysis of determinants, we focused on modifications of POM prescriptions, since these form the most important group (Table 6). Of the patient-related factors, gender was not significant, but patients of 40-65 years had a lower rate of modifications than younger people (OR=0.74 [0.64-0.86]). With respect to drug related factors, we found a higher frequency of POM prescription modifications in the respiratory domain (OR=1.48 [1.23-1.79]), while a decreased frequency was observed for nervous system POMs (OR=0.71 [0.61-0.83]). There was no difference between initial and refill prescriptions for POMs, but when a non-medicine was prescribed for the first time the chance of a modification was much higher than when it was refilled (OR=3.75 [2.07-6.80]).

With regard to prescriber-related determinants modifications were found three times more often in hand written prescriptions than in computer printed ones (OR=3.30 [2.90-3.75]). Compared with prescriptions of the patient's own GP, those of specialists (OR=1.82 [1.57-2.11]), other GPs (OR=1.49 [1.02-2.17]) and other prescribers such as dentists and midwives (OR=1.95 [1.06-3.57]) had a higher rate of prescription modifications. When a GP had no on-line access to the computer of the pharmacy, i.e. to the actual medication record of the patient, the chance of a modification was significantly higher (OR=1.61 [1.33-1.94]).

Multivariate analysis revealed that a hand written (non-printed) prescription remained a strong independent determinant of prescription modifications (OR=3.32 [2.87-3.84]) after adjustment for GP computer link to the pharmacy and for type of prescriber. Conversely, the association between a GP computer link to the pharmacy and a prescription modification as well as the association between type of prescriber and a prescription modification disappeared after adjustment for non-printed prescription.

Table 4: NATURE OF PRESCRIPTION MODIFICATIONS IN DUTCH COMMUNITY PHARMACIES

Description	POMs n=1802 (100%)	Non-medicines n=146 (100%)
Clarification needed	**1294 (71.8)**	**141 (96.6)**
dose not specified (including use known)	409 (22.7)	
no or insufficient patient data	348 (19.3)	8 (5.5)
name or use of non-medicine wrong or insufficiently specified		127 (87.0)
wrong strength (mostly non-existing or incorrect)	125 (6.9)	
strength not specified	122 (6.8)	
wrong dosage form	110 (6.1)	
number of tablets, capsules etc. not specified or incorrect	53 (2.9)	5 (3.4)
medicine, strength or dosage form not on the market	43 (2.4)	1 (0.7)
dosage form not specified	37 (2.1)	
prescription not dispensed (patient still has enough supply	34 (1.9)	
dosage form insufficiently specified	8 (0.4)	
medicine not specified	5 (0.3)	
Correction prescription error	**400 (22.2)**	
wrong dose	246 (13.7)	
wrong medicine	45 (2.5)	
wrong patient data	42 (2.3)	
interaction with other medicines (one prescriber involved)	11 (0.6)	
contraindication allergy	11 (0.6)	
other contraindications	9 (0.5)	
double medication[a] (one prescriber involved)	9 (0.5)	
double medication[a] (two prescribers involved)	9 (0.5)	
medicine obsolete	8 (0.4)	
interaction with other medicines (two prescribers involved)	4 (0.2)	
too prolonged use of a medicine	3 (0.2)	
too short period of use	2 (0.1)	
pregnancy or lactation warning	1 (0.1)	

Other	**108 (6.0)**	**5 (3.4)**
prescription not dispensed (other reason than enough patient's supply)	47 (2.6)	5 (3.4)
various	61 (3.4)	

a) Double medication is a combination of the same substance or different substances from the same therapeutic group.

Table 6: DETERMINANTS OF PRESCRIPTION MODIFICATIONS OF POM IN DUTCH COMMUNITY PHARMACIES

Prescription characteristic	Cases n=1802 (100%)	Controls n=2377 (100%)	OR (95% CI)	Reference
Patient related				
female	1080 (60.3)	1490 (62.8)	0.90 (0.80-1.02)	male
age: <40 yr	596 (33.2)	702 (29.6)	1.00	age: <40 yr
age: 40–65 yr	594 (33.1)	943 (39.7)	**0.74 (0.64-0.86)**	age: <40 yr
age: >65 yr	606 (33.7)	730 (30.7)	0.98 (0.84-1.14)	age: <40 yr
Drug related				
ATC-code N	311 (17.3)	539 (22.7)	**0.71 (0.61-0.83)**	all but N
ATC-code R	252 (14.0)	235 (9.9)	**1.48 (1.23-1.79)**	all but R
ATC-code A	227 (12.6)	258 (10.9)	1.18 (0.98-1.43)	all but A
ATC-code C	216 (12.0)	309 (13.0)	0.91 (0.76-1.10)	all but C
first dispensing	598 (33.6)	796 (33.6)	1.00 (0.88-1.14)	refill prescription
Prescriber related				
non-printed prescription	1070 (59.4)	730 (30.7)	**3.30 (2.90-3.75)**	printed prescription
specialist prescription	494 (27.5)	418 (17.6)	**1.82 (1.57-2.11)**	own GP prescription
other GP prescription	55 (3.1)	57 (2.4)	**1.49 (1.02-2.17)**	own GP prescription
other prescriber prescription	24 (1.3)	19 (0.8)	**1.95 (1.06-3.57)**	own GP prescription
GP without computer link to pharmacy	1620 (89.9)	2012 (84.6)	**1.61 (1.33-1.94)**	GP with computer link to pharmacy

Table 5: SOME EXAMPLES OF POM PRESCRIPTION MODIFICATIONS

- Sildenafil not dispensed because of interaction with isosorbide mononitrate and because of contraindication in angina pectoris.
- Erythromycin changed to doxycycline because of interaction with cisapride.
- Dexamethasone eye drops not dispensed and changed to hypromellose eye drops because of too prolonged use.
- First prescription of itraconazole dispensed for 7 days instead of 3.5 days because of too short use.
- Tablets with paracetamol (500mg) + codeine (20mg) not dispensed because of double medication with naproxen 500mg and paracetamol 500mg, prescribed by other doctor.
- Capsules with paracetamol, dexchlorpheniramine and ephedrine changed to capsules with paracetamol and dexchlorpheniramine because of contraindication in hypertension.
- Amoxicillin altered in clarithromycin because of hypersensitivity.

DISCUSSION

In this study we found an average modification of 14.3 prescriptions per day per pharmacy. The majority of the modifications (88.3%) involved POM prescriptions, but the community pharmacies also intervened with prescriptions for other health care products (such as dressings and incontinence materials), although at a much lower rate (1.4% vs. 4.9%).

We used a random sample from volunteering community pharmacies. These pharmacies represented 9% of all Dutch community pharmacies, but we did not find any major differences between the average enrolled pharmacy and the average Dutch community pharmacy (Table 1). We cannot exclude the possibility that the participating pharmacies were more active or had a more positive attitude towards the provision of professional services than pharmacies which did not volunteer for our study, either in general or on the predetermined, not blinded, study day.[5] To reduce the risk of overestimation, every reported case was checked on the basis of anonymous copies of the original prescription and the medication record of the patient. Underestimation cannot be totally ruled out, because some interventions may not have reached us due to lack of time or inappropriate handling. Another limitation of our study was that it occurred in a short time and that it cannot predict seasonal variations (e.g. fluctuating prescription patterns of drugs such as antibiotics and antihistamines). Fluctuating patterns within a week were ruled out by assigning all days of the week equally in the study period.

It is difficult to interpret the large variation of numbers of modification between individual pharmacies as a quality indicator for pharmacy performance. For instance, a low number of interventions could signify a less perceptive pharmacy, but it could also reflect a very active pharmacy team which had already reduced the daily number of prescription errors by systematic feedback to individual prescribers.[3,6,7] The incidence of modifications may also be related to some of the determinants assessed in this study.

We intend to assess the potential clinical relevance of the POM prescription modifications in depth by presenting representative samples to multidisciplinary rating panels.[2,8] A preliminary estimate based on the nature of the 1802 POM prescription modifications suggests that clarification was needed in 1294 cases (2.7% of all prescriptions), whereas 400 modifications (0.84%) concerned potentially relevant prescription errors (Table 4), a mean of 2.8 per pharmacy per day. This tentative crude intervention rate of 0.84% for real prescription errors lies in the same range as previously reported rates for community pharmacy interventions.[2,9] Our findings only refer to actual modifications of the prescriptions presented on the study day as our protocol did not ask for the recording of other potentially relevant interventions, such as the modification or discontinuation of an already dispensed drug or an instruction to the patient to avoid certain drug problems. We know from our study that modifications of already dispensed drugs occur in daily practice, because our pharmacists submitted various examples as cases (even though our protocol excluded them). It is of interest that at least half of the prescription errors found were not the result of a medication surveillance signal from the pharmacy computer, but were corrected on the basis of another trigger. Further analysis of these modifications is warranted to find out whether and how current medication surveillance systems in Dutch pharmacies can be improved.

For non-medicines the predominant reason for modification was inexact or incorrect specification of name or use. Problems in the pharmacy were significantly higher when a non-medicine was prescribed for the first time, but the prescriber was not often contacted (7.5%). These findings may reflect a tendency among prescribers to leave details of non-medicinal prescriptions to the professional judgement of the community pharmacist.

The chance of a POM prescription modification was similar for young and old patients but reduced among the age group in between (40-65 years). Whether this is related to differences in care, patient vulnerability and/or other causes requires further study. With respect to drug related characteristics no difference

in risk could be found between first-time and repeat prescriptions, indicating that the latter are still an important source of POM prescription modifications.[10,11] With respect to therapeutic groupings, we found a higher chance of modifications for respiratory medicines. One of the reasons may be that changes in dose and switching to another dosage form (i.e. inhaler) occurred relatively often in this group.

One of our most important findings is that the risk of a prescription modification was substantially lower, when the prescriber had used a printer to generate the prescription. The potential relevance of this result was highlighted by a recent US study, which identified illegible handwriting of doctors as a potential cause of fatal medication errors.[12] In the Netherlands, about 80% of the general practitioners are using a computer system to generate prescriptions, but medical specialists are still lagging behind in this respect.[13] A favourable impact of computerized physician order entry systems on medication errors has already been observed in a North American hospital setting.[14,15]

A final consideration is that our study focused on prescription errors that were detected in the community pharmacy before dispensing. Additional strategies are needed to reduce additional avoidable errors that continue to result in drug related problems.[16-19] It should be kept in mind that drug related problems are not limited to problems with dosage, adverse drug reactions and drug-drug interactions, but also comprise such problems as inappropriate drug selection, undertreatment, and drug use without valid indication.[1] It is therefore a promising development that an electronic prescription system is now issued to all general practitioners in the Netherlands,[20] that is similar to the Prodigy system for general practitioners in the UK.[21]

Acknowledgements. We would like to thank all pharmacists who participated in the study. Special thanks are due to Mrs Els Dik, Mrs Annemieke Floor-Schreudering, Mrs Monique S Martens-van Motman and Mr Taco B van Witsen, pharmacists, who helped in the design of the study, to Mr Frans Dijkman who developed the database, and to Mrs Mary-Ann de Vries for her support.

REFERENCES

1. Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. Arch Intern Med 1995;155:1949-56.

2. Hawksworth GM, Corlett AJ, Wright DJ, Chrystyn H. Clinical pharmacy interventions by community pharmacists during the dispensing process. Br J Clin Pharmacol 1999;47:695-700.
3. Van Mil FJW, Tromp DF, McElnay JC, De Jong-Van den Berg LT, Vos R. Development of pharmaceutical care in the Netherlands: pharmacy's contemporary focus on the patient. J Am Pharm Assoc (Wash) 1999;39:395-401.
4. Anonymous. ATC Index with DDDs. Oslo: WHO Collaborating Centre for Drug Statistics Methodoly, 1999.
5. Odedina FT, Hepler CD, Segal R, Miller D. The Pharmacists' Implementation of Pharmaceutical Care (PIPC) model. Pharm Res 1997;14:135-144.
6. Strikwerda P, Bootsma-de Langen AM, Berghuis F, Meyboom-de Jong B. Farmacotherapie in een verzorgingshuis; gunstige invloed van feedback door de apotheker op het voorschrijfgedrag van de huisarts. Ned Tijdschr Geneeskd 1994;138:1770-4.
7. Kocken GA. Medication discussion groups in the Netherlands: five years of experience. Med Educ 1999;33:390-3.
8. Wright DJ, Aykroyd RG, Chrystyn H. Rating clinical pharmacy interventions by clinical panels: which health professionals should be included? Br J Clin Pharmacol 1998;46:278P.
9. Rupp MT, DeYoung M, Schondelmeyer SW. Prescribing problems and pharmacist interventions in community practice. Med Care 1992;30:926-40.
10. Zermansky A. Who controls repeats? Br J Gen Pract 1996;46:643-7.
11. Dijkers FW. Repeat prescriptions, a study in general practice in the Netherlands [dissertation]. Groningen: University of Groningen, 1997.
12. Charatan F. Medical errors kill almost 100000 Americans. BMJ 1999;319:1519.
13. Van Althuis T. NUT 3 Rapport. Verslag van enquete onder huisartsen naar praktijk automatisering (1997). Utrecht: Nederlands Huisartsen Genootschap; 1999.
14. Bates DW, Leape LL, Cullen DJ, Laird N, Petersen LA, Teich JM, et al. Effect of computerised physician order entry and a team intervention on prevention of serious medication errors. JAMA 1998;280:1311-6.
15. Bates DW, Teich JM, Lee J, Seger D, Kuperman GJ, Ma'Luf N, et al. The impact of computerised physician order entry on medication error prevention. J Am Med Inform Assoc 1999;6:313-21.
16. Dartnell JG, Anderson RP, Chohan V, Galbraith KJ, Lyon ME, Nestor PJ, et al. Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs. Med J Aust 1996;164:659-62.
17. Andrews LB, Stocking C, Krizek T, Gottlieb L, Krizek C, Vargish T, et al. An alternative strategy for studying adverse events in medical care. Lancet 1997;349:309-13.

18. Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. JAMA 1997;277:312-7.
19. Bates DW, Miller EB, Cullen DJ, Burdick L, Williams L, Laird N, et al. Patient risk factors for adverse drug events in hospitalised patients. Arch Intern Med 1999;159:2553-60.
20. Anonymous. NHG-adviezen over farmacotherapie gemakkelijker beschikbaar. Huisarts en Wetenschap 1999;42:242-3.
21. Purves IN, Sugden B, Booth N, Sowerby M. The PRODIGY project; the iterative development of the release one model. Proc AMIA Symposium 1999;(1-2):359-63.
22. Vliegen M, van der Stadt H. A new measure of urbanisation: the address density of the surrounding area. In: Beets GCN, et al., editors. Population and family in the low countries 1993: late fertility and other current issues. Lisse (the Netherlands): Swets and Zeitlinger;1994.

2.3

Clinical risk management in Dutch community pharmacies: The case of drug-drug interactions

Henk Buurma, Peter AGM de Smet, Antoine CG Egberts

Drug Safety (in press)

ABSTRACT

Aims

The prevention of drug-drug interactions (DDIs) requires a systematic approach for which the concept of clinical risk management can be used. The objective of our study was to measure the frequency, nature and management of DDI alerts as these occur in daily practice of Dutch community pharmacies.

Methods

In total, 63 Dutch pharmacies collected all DDI alerts during 153 research days (on average 2.4 days/pharmacy), as well as variables related to these alerts, such as involved medicines, first time or recurrent DDI, same or different prescribers, patient data (age, sex) and information about the management of DDIs by the pharmacy. The latter was discriminated into internal procedures only and external action, such as communication with the patient, the prescriber or the anticoagulation clinic and prescription modification. All DDIs were classified into categories of clinical relevance (A-F) and available evidence (0-4).

Results

A total of 43 129 prescription only medicines were dispensed during the study period. On average, 16.8 interaction alerts per day per pharmacy were collected. Approximately 6% of all prescriptions generated a DDI alert. Of all alerts (n=2572), 31.1% occurred for the first time and with 21% two different prescribers were involved. The 20 most frequently occurring DDI alerts accounted for approximately 76% of all alerts. Cardiovascular drugs, NSAIDs, oral contraceptives and antibacterials were most frequently involved. External action was taken in response to 27.3% (n=702) of the alerts, meaning either a modification of one of the concerned prescriptions (n=65; 9.3%), communication with the prescriber or anticoagulation clinic (n=90; 12.8%) or communication with the patient or relative (n=547; 77.9%). Where there was no external action (n=1860; 72.3%), pharmacists concluded in about two-thirds of cases that the DDI had been managed in the past. Other reasons not to intervene externally were for instance: incorrect alert; acceptable DDI; or outcome of the interaction considered irrelevant. Adjusted for several variables, a first alert was found to be a main determinant for external action. After stratifying for first alerts no other significant determinants were found.

Conclusions

A high frequency of DDI alerts was found. Most concerned recurrent alerts, which were the main reason not to act externally. Concerning the assessment phase in the risk-management process, DDIs with no or low evidence/relevance should be reconsidered. Concerning the management of DDIs in pharmacies, the opportunity to actively suppress alerts for a certain period of time should be studied in more detail. There are indicators that the management of patient-oriented advice could be improved and a greater degree of the consistency developed for the management of first and recurrent interaction alerts.

INTRODUCTION

According to the literature, medical errors do not occur from individual recklessness but rather from basic flaws in the organization of the healthcare system.[1] Therefore, effective prevention of medical errors requires a systematic approach towards the healthcare system. Clinical risk management aims to change the organization from organizational vulnerability towards organizational integrity.[2] The clinical risk management process consists of three main phases, i.e. (1) risk assessment, (2) risk management and (3) evaluation of strategies. During the risk assessment phase, potential hazards are identified and stratified in terms of evidence, probability and clinical significance. The risk management phase tries to define the operational strategies needed to minimize these hazards, the identification of resources and the execution of those strategies, which includes the recognition, analysis and management of (potential) health hazards in daily clinical practice. A final and crucial part of clinical risk management is the performance evaluation of risk management strategies, i.e. to determine whether these strategies have actually been effective and efficient.[3]

Prescription errors have been reported to occur in up to 11% of all prescriptions; the majority of which are dose-related errors.[4,5] The occurrence of such errors has been the subject of several studies and is part of the public debate about patient safety.[6] Pharmacists can play a major role in the detection and prevention of drug related problems (DRPs) and medication errors.[7-13] The impact of drug-drug interactions (DDIs) on drug related morbidity, including unnecessary hospital admissions, has been demonstrated.[14-17] In addition, during recent years, DDIs have become a major reason for withdrawal of drugs from the marketplace and labelling changes, partly because adequate risk management could not be established in daily clinical practice.[18]

Several steps of the clinical risk management process can be observed in the prevention and management of prescribing errors related to DDIs in pharmacies. Concerning the assessment phase in the Netherlands, there are two (to some extent different) resources containing information about drug interactions. These resources are translated into drug interaction signalling software by the five pharmacy information systems that in turn are used by Dutch community pharmacies.[19] The pharmacy information system checks a prescription for DDIs using stored information about actual drug use of a patient. Actual drug use is derived from previous prescriptions dispensed to that patient for whom a theoretical duration of use is calculated based upon the number of dose units and

the prescribed daily dose. In general, the conditions for risk management are advantageous in Dutch pharmacies: electronic prescription entry, computerized medication records and a low degree of fragmented prescription filling due to a high pharmacy compliance of the patient.[20,21]

A limited amount of research has been conducted into the magnitude and nature of DDI alerts in community pharmacies as well as the management thereof.[22-24] We were interested in DDI alerts occurring in real daily clinical practice, whereas others counted potential DDIs,[25,26] used large databases,[27] or a few general practices,[28] focused on specific patients,[29] and sometimes included duplicate medications[30] or restricted themselves to potentially hazardous drug combinations.[24,28] We were interested in the frequency of DDI alerts where the number of prescriptions is the denominator, whereas others used the number of patients[31] or the number of DRPs.[4,7,32] Along with the prevalence and nature of DDI alerts (identification of risk), we were interested in the analysis and management phase in the risk management process (the management of alerts). The objective of our study was therefore to measure the frequency, nature and management of DDI alerts as these occur in daily practice of Dutch community pharmacies.

METHODS

Setting and study population

A total of 220 Dutch community pharmacies belonging to the pharmacy practice research networks of the SIR Institute for Pharmacy Practice and Policy and of Utrecht University, the Netherlands, were invited to participate in this study. Of these, 63 pharmacies responded positively and were enrolled in the study. These 63 pharmacies serve approximately 600 000 patients. In the period from July to November 2004, each participating pharmacy was requested to record all DDI alerts that occurred over a period of two or three days. The data had to be collected on one specific day (between Monday and Friday) of the week but pharmacists were free to select which week during the study period they would collect alert data.

Collection and classification of data

On the first form, concerning the documentation of one DDI alert, pharmacists collected information related to the alert itself (the medicines involved in the DDI, first time or recurrent DDI, same or different prescribers), patient data (age,

sex) and information about the management of the pharmacy. Information about management was divided into 'external action' (communication with the patient or relative, communication with the prescriber and prescription modification) and internal procedures that required 'no external action' (e.g. interaction already evaluated in the past, incorrect alert, acceptable interaction or other reason not to intervene). 'Communication with prescriber' included contacts with anticoagulation clinics concerning DDIs, especially for patients using oral anticoagulants.

Table 1: CLASSIFICATION OF DRUG-DRUG INTERACTIONS[a,b]

Quality of evidence categories	
0	Pharmacodynamic animal studies; *in vitro* studies with limited predictive value for the human *in vivo* situation; data on file
1	Incomplete, published case reports (no re- or dechallenge, presence of other explaining factors for the adverse reaction)
2	Well-documented, published case reports; retrospective analyses of case series
3	Controlled, published interaction studies in patients or healthy volunteers, with surrogate end points
4	Controlled, published interaction studies in patients or healthy volunteers, with clinically relevant end points
Clinical relevance categories	
A	No inconvenience, insignificant effect
B	Short-lived inconvenience
C	Inconvenience without residual symptoms; failure of therapy concerning non-serious diseases
D	Inconvenience with residual symptoms; failure of therapy concerning serious but non-fatal diseases
E	Raised risk of dying; failure of life saving therapy; increased risk of pregnancy.
F	Serious, irrecoverable disablement; potentially lethal cardiac arrhythmia; death; increased risk of pregnancy plus risks concerning mother and/or foetus.

a) According to the Working Group on Pharmacotherapy and Drug Information that is responsible for maintenance of the computerized drug interaction surveillance system of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)[19]
b) Several drug-drug interactions have not (yet) been assessed. We separated this remaining group into three categories, i.e.:
   - not classified (particularly interactions with coumarin anticoagulants)
   - no interaction (part of the classification system, but assessed as no interaction)
   - unknown (this type of interaction is only controlled in one computer system not using this classification system and based upon assessment by another Dutch assessment committee)

The second form concerned basic characteristics of each research day, such as the total number of alerts and the number of prescriptions. The third form concerned the basic characteristics of the pharmacy, including the general performance as to the management of DDI alerts. A study protocol advised to contact the helpdesk in case of any uncertainty regarding any of the three forms.
Afterwards, all DDIs were classified by the research team into categories of clinical relevance (A-F) as well as categories of available evidence (0-4) according to the classification system developed and maintained by a working group of the Scientific Institute of Dutch Pharmacists.[19] This classification system is described in brief in Table 1. The classification system means that, for example, subtype 4-F is indicating an interaction with a substantial greater risk than that classified as 1-A. It is related to the classification system used in Sweden, which has been described for research purposes elsewhere.[25]

Data analysis

After inspection, data from the registration forms were entered into a database (Microsoft Access 2000) and analysed using standard descriptive data analysis (SPSS version 12.0). Logistic regression analysis was used to measure the strength of the association between alert characteristics and external action by the pharmacists.

RESULTS

The 63 participating pharmacies comprised almost 4% of all Dutch pharmacies (about 1750 in total). There was a large variation between pharmacies with respect to the daily number of prescriptions (average 282; range 95-750), which reflects that both small and large pharmacies participated in the study. Thirty pharmacies (47.6%) collected data for three days, another 30 (47.6%) for two days and three (4.8%) for one day. This was an average of 2.4 research days per pharmacy.
A total of 43 129 prescription only medicines were dispensed during the study period of 153 research days. The pharmacies collected data on 2572 DDI alerts during this time, meaning that 16.8 alerts per day per pharmacy (range 2-53) were reported. About 6% of all presented prescriptions generated a DDI alert (on average one DDI alert per 16.8 prescriptions). The interaction alerts occurred in 1891 patients, an average of 1.4 interaction alerts per patient (range 1-12).

Of all alerts, about two-thirds (n=1613) concerned women and almost 80% concerned people >50 years of age (30.9% concerned people >75 years of age). Of all alerts, 31.1% (n=800) occurred for the first time and in 21.0% of the alerts (n=539) two different prescribers were involved.

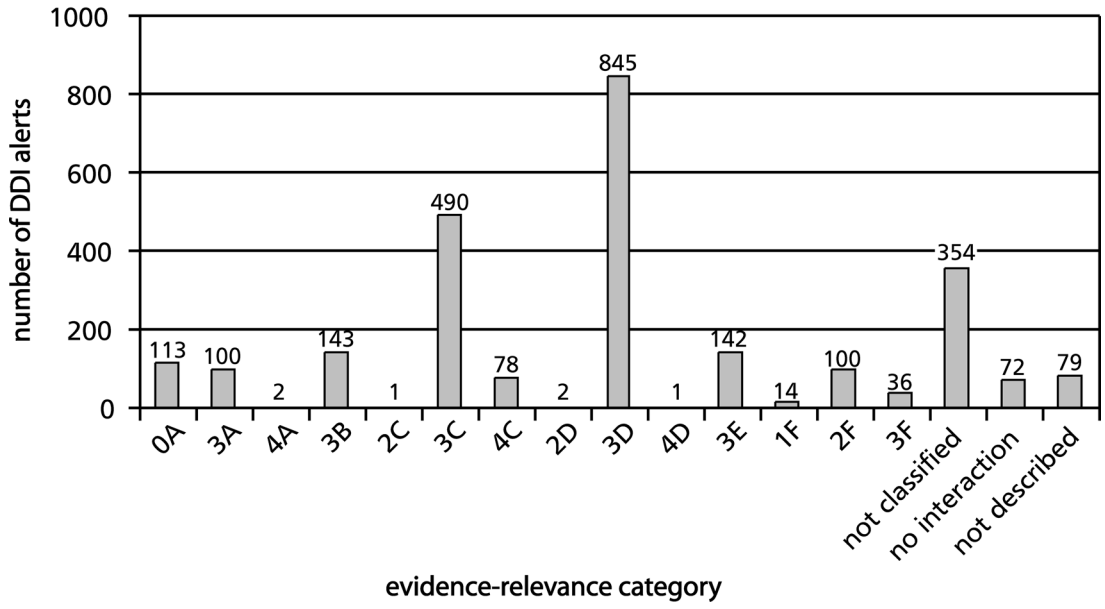
Table 2: FREQUENCY AND NATURE OF THE 20 MOST FREQUENTLY ENCOUNTERED DRUG-DRUG INTERACTION ALERTS

Description of interaction	Number of alerts n=2572 (100%)	Evidence—relevance[a]
renin-angiotensin system inhibitors — diuretics	348 (13.5)	3—D
β-adrenoreceptor antagonists (β-blockers) — NSAIDs	278 (10.8)	3—C
NSAIDs — renin-angiotensin system inhibitors	266 (10.3)	3—D
diuretics — NSAIDs	154 (6.0)	3—D
bisphosphonates — complex forming divalent metallic ions	111 (4.3)	0—A
renin-angiotensin system inhibitors — potassium-sparing diuretics/potassium supplements	100 (3.9)	2—F
oral contraceptives — antibacterials	94 (3.7)	Not classified
NSAIDs (excluding selective COX-2 inhibitors) — SSRIs	78 (3.0)	4—C
corticosteroids — NSAIDs	66 (2.6)	3—C
coumarin anticoagulants — antibacterials	61 (2.4)	Not classified
digoxin — diuretics	57 (2.2)	3—A
β-blockers/calcium antagonists — α-adrenoreceptor antagonists	51 (2.0)	3—B
coumarin anticoagulants — NSAIDs	47 (1.8)	Not classified
calcium antagonists — β-blockers	42 (1.6)	3—E
methotrexate — NSAIDs/salicylates	39 (1.5)	3—E
levothyroxine — iron	39 (1.5)	3—C
simvastatin/atorvastatin — diltiazem/verapamil	38 (1.5)	3—E
non-selective β-blockers — β-adrenoreceptor agonists	33 (1.3)	3—C
oral hypoglycaemic drugs — selective β-blockers	32 (1.2)	3—B
insulin — selective β-blockers	26 (1.0)	3—B

COX = cyclo-oxygenase; SSRIs = selective serotonin reuptake inhibitors
a) See Table 1.

The 20 most frequently occurring DDI alerts are presented in Table 2.[a] These account for approximately 76% of all alerts (n=1960). The top ten most frequently reported DDIs accounted for 60% (n=1556) and the top five for 45% (n=1157) of all alerts. Cardiovascular drugs were predominantly involved, such as renin-angiotensin system inhibitors, diuretics, β-adrenoreceptor antagonists (β-blockers), potassium-sparing diuretics, coumarin anticoagulants and digoxin. NSAIDS, oral contraceptives and antibacterials were also frequently encountered. Figure 1 shows the number of alerts per evidence-relevance category. Most occurring DDIs that occur are generally evidence-based (category 3) and have a risk of moderate-to-serious inconveniences (categories C and D). DDIs that might have serious clinical consequences (categories E and F) were found less frequently: 292 (0.7%) of all prescriptions (n=43 129).

Figure 1: NUMBER OF DRUG-DRUG INTERACTION(DDI) ALERTS REPORTED DURING THE STUDY, CLASSIFIED BY EVIDENCE-RELEVANCE CATEGORY



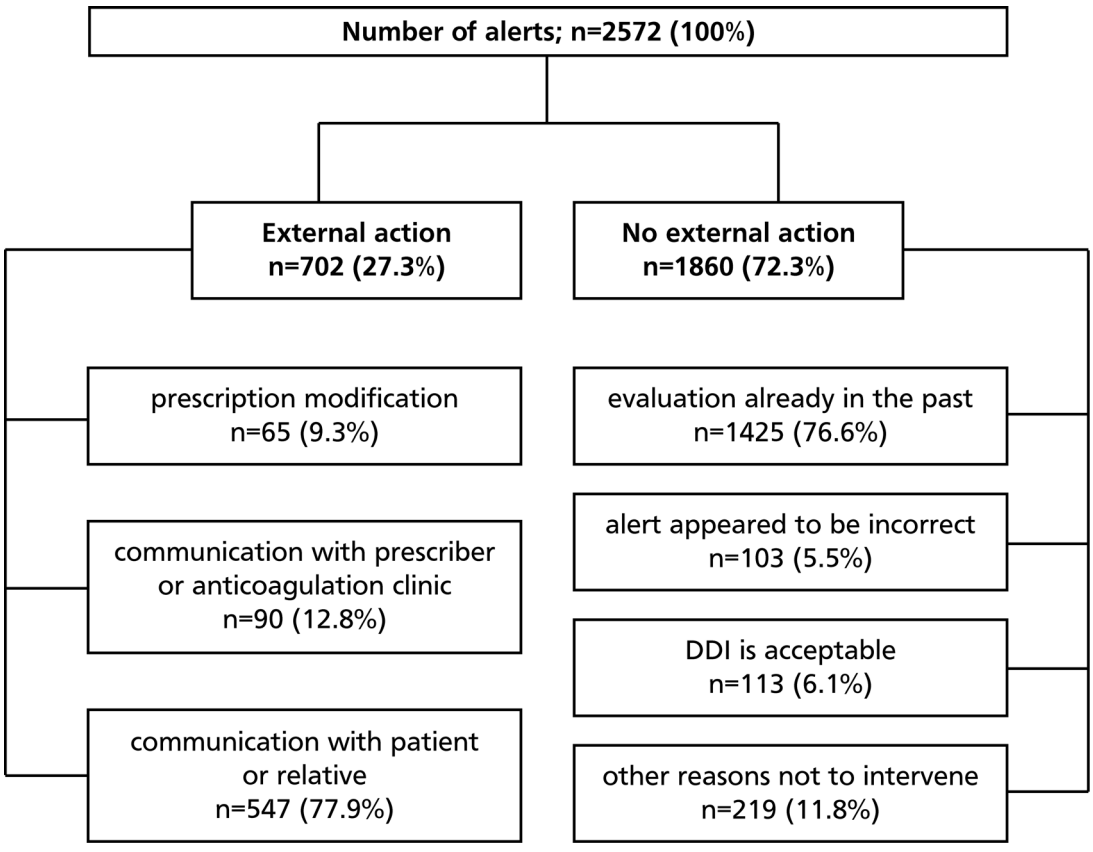
See Table 1 for explanation of evidence-relevance categories.

In Figure 2, we report on the process of the management of alerts in the selected pharmacies. A total number of 702 alerts (27.3%) led to external action of the

[a] All DDI alerts found in this study are presented on our website http://www.stevenshof.nl.

pharmacy, meaning either a modification of one of the concerned prescriptions (n=65; 9.3%), communication with the prescriber or anticoagulation clinic (n=90; 12.8%) or communication with the patient or relative (n=547; 77.9%). Modifications of a prescription concerned the last prescribed drug (n=25), the first prescribed drug (n=25), a dosage alteration (n=6), a temporary discontinuation of use of the first medicine (n=4) and an addition of an extra drug, particularly proton pump inhibitors (n=4). Communication with the prescriber could take place before or after dispensing and concerned mostly communication with the anticoagulation clinic (70%). This communication was largely carried out by fax: an average of once every 4-5 days per pharmacy.

Figure 2: DRUG-DRUG INTERACTION (DDI) ALERT MANAGEMENT IN DUTCH COMMUNITY PHARMACIES



Total does not count up to 100% because of missing values.

Communication with the patient mostly concerned advice to separate the timing of intake of the two medications (interval of ≥2 hours; 19%), advice to check blood pressure regularly (16%), advice to use extra contraceptive measures (10%), warning concerning the potential deterioration of heart failure/oedema (6%), advice to contact their doctor about influence on potassium level (3%), warning concerning potential stomach problems (3%) and warning as to probable disturbance of the menstrual cycle (3%). In addition, pharmacies provided specific written information concerning the DDI (16%) or advised the patient to inform the anticoagulation clinic about the DDI with respect to coumarin anticoagulant use (9%).

In the other instances, there was no external intervention (n=1860; 72.3%) (Figure 2). Slightly more than 76% (1425 of 1860) concerned internal procedures, concluding that evaluation of the DDI alert had already taken place in the past. In 5.5% (103 of 1860), the evaluation led to the conclusion that the alert appeared to be incorrect, mainly because one of the interacting drugs prescribed in the past had already been stopped by the patient. In 6.1% (113 of 1860) the pharmacist decided that the DDI was acceptable since the latest prescribed drug, mostly NSAIDs, was only prescribed for a short period of time. In 4.2% (n=78) the pharmacist assessed the outcome of the interaction not to be relevant. There were several other reasons (n=141; 7.6%) presented by the pharmacists not to intervene, such as discharge from hospital, drug prescribed by a specialist, stomach protection already in use, blood pressure control is well known or first prescribed drug already stopped by prescriber.

Adjusted for several variables, we found that DDI alerts occurring for the first time had a considerably higher probability (OR 7.48; 95%CI 6.06-9.24) for external action by pharmacists (Table 3). Other determinants for external action were female sex (OR 1.35; 95%CI 1.09-1.68) and youngest age category (<50 years) (OR 1.43; 95%CI 1.08-1.89). A higher relevance category (D-F) unexpectedly signified a lower probability for external action (OR 0.77; 95%CI 0.60-0.99). Stratifying for first alerts, however, we found no significant (95%CI) differences between sex, age and prescriber categories as well as between relevance and evidence categories.

Comparing coumarine DDIs, which are not classified by the assessment committee (see Table 1), with other DDIs and stratifying for first alerts, we found a considerably higher probability for external action by pharmacies (OR 5.8; 95%CI 3.3-10.2; adjusted for age, sex and prescriber) (data not shown).

Table 3: DETERMINANTS FOR EXTERNAL ACTION OF PHARMACIES AFTER HAVING A DRUG-DRUG INTERACTION ALERT

Characteristic	External action (n=702)			No external action	OR (95% CI)	
	Modification prescription n=65 (100%)	Communication prescriber n=90 (100%)	Communication patient n=547 (100%)	n=1860 (100%)	Crude	Adjusted[a]
Patient related						
sex						
male	30 (46.2%)	42 (46.7%)	145 (26.5%)	732 (39.4%)	1 (reference)	1 (reference)
female	35 (53.8%)	48 (53.3%)	401 (73.3%)	1124 (60.4%)	1.45 (1.21-1.75)	1.35 (1.09-1.68)
age (yr)						
0-50	20 (30.8%)	12 (13.3%)	191 (34.9%)	308 (16.6%)	2.19 (1.73-2.77)	1.43 (1.08-1.89)
51-65	22 (33.8%)	20 (22.2%)	113 (20.7%)	511 (27.5%)	0.92 (0.72-1.17)	0.91 (0.69-1.20)
66-75	10 (15.4%)	16 (17.8%)	101 (18.5%)	445 (23.9%)	0.86 (0.67-1.11)	0.80 (0.60-1.07)
>75	13 (20.0%)	42 (46.7%)	142 (26.0%)	596 (32.0%)	1 (reference)	1 (reference)
Prescriber related						
same prescriber	37 (56.9%)	58 (64.4%)	409 (74.8%)	1509 (81.1%)	1 (reference)	1 (reference)
different prescriber	24 (36.9%)	32 (35.6%)	138 (25.2%)	343 (18.4%)	1.69 (1.38-2.07)	1.13 (0.89-1.44)
DDI related						
recurrent alert	7 (10.8%)	25 (27.8%)	214 (39.1%)	1481 (79.6%)	1 (reference)	1 (reference)
first alert	56 (86.2%)	65 (72.2%)	324 (59.2%)	352 (18.9%)	7.61 (6.27-9.24)	7.48 (6.06-9.24)
relevance categories[b]						
A–C	22 (33.8%)	19 (21.1%)	204 (37.3%)	681 (36.6%)	1 (reference)	1 (reference)
D–F	27 (41.5%)	25 (27.8%)	154 (28.2%)	928 (49.9%)	0.62 (0.50-0.76)	0.77 (0.60-0.99)
evidence categories[b]						
1–2	4 (6.2%)	3 (3.3%)	12 (2.2%)	96 (5.2%)	1 (reference)	1 (reference)
3–4	45 (69.2%)	41 (45.6%)	295 (53.9%)	1451 (78.0%)	1.33 (0.80-2.20)	1.02 (0.58-1.78)

Not all values count up to 100% because of missing values.
a) Adjusted for all other characteristics.
b) Only categories with assessment of certain degree of relevance or evidence are presented (see Table 1).

DISCUSSION

We found a high frequency of DDI alerts of which most appeared to be recurrently occurring. These kinds of alerts turned out to be the main reason for pharmacies not to act externally. In a minority of alerts, the pharmacy acted externally, especially directed at the patient. A first alert was the main determinant for acting externally.

The frequency of DDI alerts, about 6% of all prescriptions, was almost twofold higher than was found in another Dutch study by Van Mil et al.[22] A limitation of the latter study was its dependence on the active registering of all DRP alerts by participating pharmacies over a long period of time.

The DDI alerts particularly involved cardiovascular drug classes and NSAIDs, in accordance with other studies.[26] Due to differences regarding setting, study population or definition of DDIs, some authors have found other drugs or drug classes to be (more frequently) involved in interaction alerts.[27,30] The frequency of alerts for DDIs that can have serious clinical consequences (categories E and F in the Dutch classification system) was half as high as was found by Merlo (0.7% of all prescriptions versus 1.4%, respectively).[25] However, in the study conducted by Merlo,[25] an irrelevant dosage form (non-nebulised forms of asthma drugs) accounted for 52.2% for this high relevance category (category D in Swedish system). On the other hand, in our study, such a problem may not be excluded as well, and moreover, an important group of DDIs concerning coumarins was part of the 'not classified' category.

A large part of all DDI alerts concerned renewals of drug combinations. Too many alerts, of which most are not relevant anymore, may be a main reason to override the alerts.[33] Moreover, DDI alerts are only one of many alerts presented on pharmacy computer screens, such as those concerning duplicate medications, dose-related problems, drug-disease interactions and intolerabilities.[4,7,22,32] Most pharmacy computer systems offer ample opportunity to actively suppress alerts for a certain period of time, a system flexibility that is advocated elsewhere.[33] About one-third of the participating pharmacies in this study used this function; however, as far as we could verify, not systematically. The opportunity to actively suppress alerts for a certain period of time, but also to produce (certain) alerts only in case of prescriptions for new medicines or in case of dosage changes, should be studied in more detail.

Algorithms may also be applied by the system so that in certain instances no alert will show up (e.g. NSAIDs prescribed for a short period of time). This problem

is amplified by the fact that some DDI alerts (we counted 12 different combinations of drugs leading to a DDI) occur that have been classified as having no relevance (n=72; 2.8% of all alerts). In addition, it is necessary to alert in some instances when certain drugs are discontinued.

In this study we found that 1.6% of all dispensed prescriptions resulted in external action being taken in response to an interaction alert. In his study, van Mil et al.[22] is less specific: 0.46% of all prescriptions led to an advice or change of dose. One may estimate it as positive that pharmacies acted significantly more externally in case a drug combination occurred for the first time. In addition, following stratification for first alerts, other determinants for external action, such as female sex and youngest age category, were no longer found to be significantly different between pharmacies. However, there are some data indicating that improvements are possible.

We found a high incidence of pharmacy actions directed at the patient, approximately 78% of all external actions. In a study about prescription modifications, we found a high frequency of patient contacts to solve prescription related problems.[4] Contrary to this, Knapp et al.[23] found that in his study about DRPs, US pharmacies contacted the prescriber in 56.1% of cases, reviewed the patient profile in 21.0% and interviewed the patient or his representative in 18.9%. The question is whether all patients can deal with all types of information reported in this study. In particular, the information about serum potassium level measurements may cause problems. Contacting the anticoagulation clinic may be problematic for some patients as well, such as older people. In these cases, pharmacists should reconsider this type of action, of which we would think the doctor (or anticoagulation clinic) is the best target.

Reversibly, we revealed a high frequency of internal pharmacy proceedings (72.3%) not leading to communication with doctors or patients. Recurrent alerts were a main reason for this (n=1481; 79.6%). Nevertheless, in 14.2% of the recurrent alerts, such alert was followed by external action, mostly communication with the patient (see Table 3). This may be understandable in cases where the information was given months or even years after the previous alert. Information about a possible deterioration of oral contraceptive effectiveness (because of antibacterial use, see Table 2) is probably a good example of a repeated intervention. In this example, 15 recurrent alerts led to 13 communication actions towards patients. On the other hand, of all first alerts only 55.8% was followed by external action.

Let us look at one important DDI, i.e. a renin-angiotensin system inhibitor administered with a diuretic (see Table 2), to find some explanations. There were 60 first alerts of this DDI, for which there is only a need for action in case of a first prescription of a renin-angiotensin system inhibitor. Excluding missing values and incorrect classifications, we found 38 of such cases, for 22 of which the pharmacy undertook no action. Indeed, the actual clinical significance of an alert and therefore the management of the pharmacy will also depend on other information, such as the patient's history, co-morbidities, preferences for treatment and specialization of the prescriber.[27] Based upon the descriptions of actions that the pharmacies gave, we may conclude that for 15 cases the management was accurate (e.g. discharge from hospital); however, for seven cases, no action or an incorrect management was described.
We found that for some alerts that were followed by internal-only procedures, the pharmacist registered a reason not to intervene such as discharging the patient from the hospital or that the drug was prescribed by a specialist. We were unable to study whether these reasons were appropriate or not. The adherence to guidelines concerning the management of DDIs as well as the reasons (not) to adhere to these, is a worthwhile subject for further study. This also applies to our unexpected finding that DDIs with a high grading of clinical relevance led less often to external action than those with a lower grading.

Limitations

This study has some limitations. The participating pharmacies constituted a voluntary sample, which may have led to a positive selection bias concerning the performance of pharmacies. Secondly, it may be possible that some DDI alerts were not registered because the registering pharmacist or technician overlooked them or because of omissions of the software systems, meaning that not all alerts were shown on the daily reports that contain all DRP alerts from the day before. The degree of under-reporting may be even higher when we realize that over the counter drugs, such as NSAIDs or herbal medicines such as St John's wort, are seldom registered in the Netherlands. These examples are assessed in literature as important DDIs.[18,34] In his study about DRPs concerning non-prescription drugs, Westerlund et al.[7] found several DDIs, about 3% of all registered problems. There is a low risk of under-reporting because of a low degree of fragmented prescription filling in the Netherlands.[20,21] The absolute and relative frequency of DDI alerts depends on the type of surveillance programme. Basically, there are two drug interaction knowledge systems used in Dutch

community pharmacies. There are several differences with respect to the surveillance of DDIs between these two systems. Some DDIs, covered by one system (we found 79 cases in our study), will not be covered by the other one (we found 115 cases in our study), meaning a lower frequency of the respective DDIs in this study. Moreover, the level of relevance of DDIs is sometimes differently assessed in both systems, which has consequences as to the management of the pharmacist. Divergent assessments of DDIs, made by the two working groups maintaining and developing the two knowledge systems, account for the observed differences. Similar differences as to the judgement of DDIs have been described concerning important drug interaction compendia.[35]

CONCLUSIONS

A high frequency of DDI alerts in daily pharmacy practice was found. Most concerned recurrent alerts, which were also the main reason not to act externally. An abundance of apparently non-relevant alerts implies the risk of overriding these. DDIs with no or low evidence/relevance should be reconsidered as part of computerized drug interaction surveillance systems. The opportunity to actively suppress alerts for a certain period of time or to produce (certain) alerts only in case of prescriptions for new medicines or in case of dosage changes should be studied in more detail.

There are indicators that the management by pharmacies can be improved concerning patient-oriented advices and a consistent way of managing recurrent alerts, first alerts and alerts concerning important but avoidable DDIs. Since the pharmacy organization is a potential determinant of drug-drug interaction-associated dispensing, pharmacists should focus on knowledge, instructions and supervision to ameliorate their part of the risk management process of medicines.[36]

Acknowledgements. We would very much like to thank all 63 pharmacists who participated in this study. Special thanks to Mrs Martine Kruijtbosch, MSc. and Mr Willem Rump, PhD, for their support in collecting the data and developing the technical infrastructure, and Mr Tom Schalekamp, PharmD, for his critical comments on drafts of the manuscript.

REFERENCES

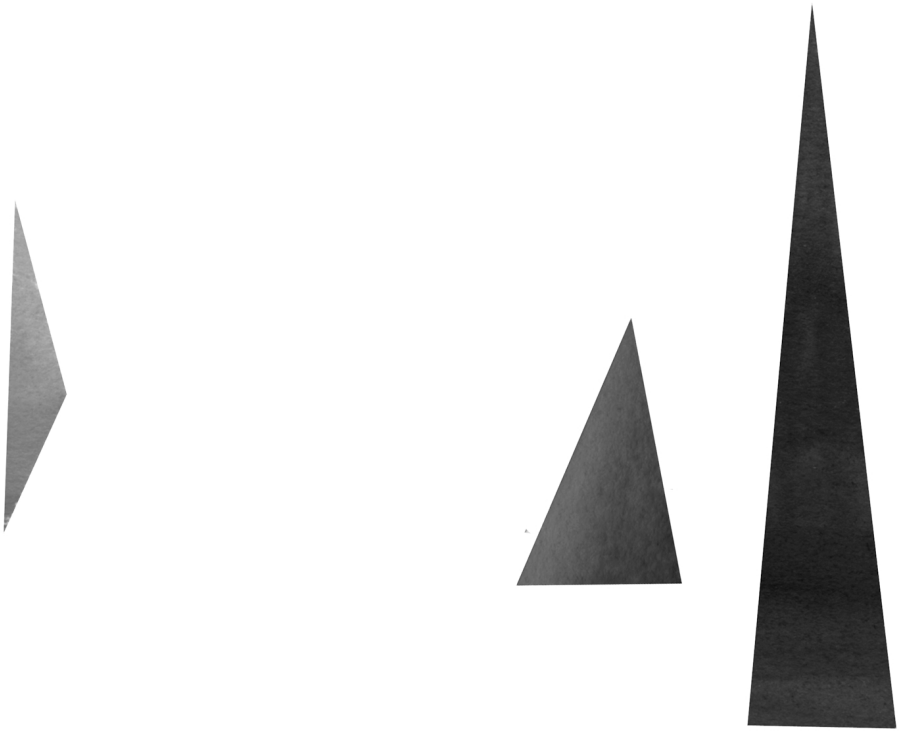
1. Misson JC. A review of clinical risk management. J Qual Clin Pract 2001;21:131-4.
2. Madar J. Clinical risk management in newborn and neonatal resuscitation. Semin Fetal Neonatal Med 2005;10:45-61.
3. Anonymous. Guideline on Risk Management Systems for Medicinal Products for Human Use. London: European Medicines Evaluation Agency; 2005.
4. Buurma H, de Smet PA, van den Hoff OP, Egberts ACG. Nature, frequency and determinants of prescription modifications in Dutch community pharmacies. Br J Clin Pharmacol 2001;52:85-91.
5. Sandars J, Esmail A. The frequency and nature of medical error in primary care: understanding the diversity across studies. Fam Pract 2003;20:231-6.
6. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human. Building a safer health system. Washington, DC: National Academy Press; 1999.
7. Westerlund LT, Marklund BR, Handl WHA, Thunberg ME, Allebeck P. Nonprescription drug-related problems and pharmacy interventions. Ann Pharmacother 2001;35:1343-9.
8. Boyko WL Jr., Yurkowski PJ, Ivey MF, Armistead JA, Roberts BL. Pharmacist influence on economic and morbidity outcomes in a tertiary care teaching hospital. Am J Health Syst Pharm 1997;54:1591-5.
9. Bouvy ML, Buurma H, Egberts TC. Laxative prescribing in relation to opioid use and the influence of pharmacy-based intervention. J Clin Pharm Ther 2002;27:107-10.
10. Beney J, Bero LA, Bond C. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes. Cochrane Database Syst Rev 2000(3):CD000336.
11. Singhal PK, Raisch DW, Gupchup GV. The impact of pharmaceutical services in community and ambulatory care settings: evidence and recommendations for future research. Ann Pharmacother 1999;33:1336-55.
12. Tully MP, Seston EM. Impact of pharmacists providing a prescription review and monitoring service in ambulatory care or community practice. Ann Pharmacother 2000;34:1320-31.
13. Buurma H, De Smet PA, Leufkens HG, Egberts ACG. Evaluation of the clinical value of pharmacists' modifications of prescription errors. Br J Clin Pharmacol 2004;58:503-11.
14. Jankel CA, Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. Drug Saf 1993;9:51-9.
15. Raschetti R, Morgutti M, Menniti-Ippolito F, Belisari A, Rossignoli A, Longhini P, et al. Suspected adverse drug events requiring emergency department visits or hospital admissions. Eur J Clin Pharmacol 1999;54:959-63.

16. Bouvy ML, Heerdink ER, Hoes AW, Leufkens HG. Effects of NSAIDs on the incidence of hospitalisations for renal dysfunction in users of ACE inhibitors. Drug Saf 2003;26:983-9.
17. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA 2003;289:1652-8.
18. Huang SM, Lesko LJ. Drug-drug, drug-dietary supplement, and drug-citrus fruit and other food interactions: what have we learned? J Clin Pharmacol 2004;44:559-69.
19. Van Roon EN, Flikweert S, le Comte M, Langendijk PN, Kwee-Zuiderwijk WJ, Smits P, et al. Clinical relevance of drug-drug interactions: a structured assessment procedure. Drug Saf 2005;28:1131-9.
20. Klungel OH, de Boer A, Paes AH, Herings RM, Seidell JC, Bakker A. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in the Netherlands. Pharm World Sci 1999;21:217-20.
21. Monster TB, Janssen WM, de Jong PE, de Jong-van den Berg LT. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. Pharmacoepidemiol Drug Saf 2002;11:379-84.
22. Van Mil JW, Dudok van Heel MC, Boersma M, Tromp TF. Interventions and documentation for drug-related problems in Dutch community pharmacies. Am J Health Syst Pharm 2001;58:1428-31.
23. Knapp KK, Katzman H, Hambright JS, Albrant DH. Community pharmacist interventions in a capitated pharmacy benefit contract. Am J Health Syst Pharm 1998;55:1141-5.
24. Halkin H, Katzir I, Kurman I, Jan J, Malkin BB. Preventing drug interactions by online prescription screening in community pharmacies and medical practices. Clin Pharmacol Ther 2001;69:260-5.
25. Merlo J, Liedholm H, Lindblad U, Bjorck-Linne A, Falt J, Lindberg G, et al. Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study. BMJ 2001;323:427-8.
26. Bjerrum L, Andersen M, Petersen G, Kragstrup J. Exposure to potential drug interactions in primary health care. Scand J Prim Health Care 2003;21:153-8.
27. Peng CC, Glassman PA, Marks IR, Fowler C, Castiglione B, Good CB. Retrospective drug utilization review: incidence of clinically relevant potential drug-drug interactions in a large ambulatory population. J Manag Care Pharm 2003;9:513-22.
28. Chen YF, Avery AJ, Neil KE, Johnson C, Dewey ME, Stockley IH. Incidence and possible causes of prescribing potentially hazardous/contraindicated drug combinations in general practice. Drug Saf 2005;28:67-80.

29. Bergk V, Gasse C, Rothenbacher D, Loew M, Brenner H, Haefeli WE. Drug interactions in primary care: impact of a new algorithm on risk determination. Clin Pharmacol Ther 2004;76:85-96.
30. Guedon-Moreau L, Ducrocq D, Duc MF, Quieureux Y, L'Hote C, Deligne J, et al. Absolute contraindications in relation to potential drug interactions in outpatient prescriptions: analysis of the first five million prescriptions in 1999. Eur J Clin Pharmacol 2003;59:689-95.
31. Viktil KK, Blix HS, Reikvam A, Moger TA, Hjemaas BJ, Walseth EK, et al. Comparison of drug-related problems in different patient groups. Ann Pharmacother 2004;38:942-8.
32. Roughead EE, Barratt JD, Gilbert AL. Medication-related problems commonly occurring in an Australian community setting. Pharmacoepidemiol Drug Saf 2004;13:83-7.
33. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians' decisions to override computerized drug alerts in primary care. Arch Intern Med 2003;163:2625-31.
34. De Smet PA. Health risks of herbal remedies: an update. Clin Pharmacol Ther 2004;76:1-17.
35. Abarca J, Malone DC, Armstrong EP, Grizzle AJ, Hansten PD, van Bergen RC, et al. Concordance of severity ratings provided in four drug interaction compendia. J Am Pharm Assoc (Wash DC) 2004;44:136-41.
36. Becker ML, Kallewaard M, Caspers PW, Schalekamp T, Stricker BH. Potential determinants of drug-drug interaction associated dispensing in community pharmacies. Drug Saf 2005;28:371-8.

Chapter 3

QUALITY



3.1

Disease and intolerability documentation in electronic patient records

Henk Buurma, Peter AGM de Smet, Martine Kruijtbosch,
Antoine CG Egberts

Ann Pharmacother 2005;39:1640-6

ABSTRACT

Aims

Documentation of diseases and intolerabilities in electronic patient records (EPRs) in pharmacies is needed to produce an alert in case a contraindicated medicine is prescribed. Limited research is available concerning EPRs in pharmacies. The objective was to study the prevalence and quality of documentation of diseases and intolerabilities in EPRs in a sample of Dutch community pharmacies.

Methods

Each participating pharmacy (n=79) collected data on one day in May 2003 for each patient enrolled into the study (n=687) concerning demographics, drug use and documentation of diseases and intolerabilities.

Results

In 57.4% of the EPRs, at least one disease, and in 7.9%, at least one intolerability was documented. Higher age, number of drugs used and chronic disease score were associated with any documentation of a disease/intolerability in the EPR. The highest sensitivity scores (completeness) were found for diabetes (84.7%), asthma/chronic obstructive pulmonary disease (strict definition; 75.9%) and hypothyroidism (75.0%). Rather low values were found for prostatic hyperplasia (55.6%) and heart failure (29.4%). The positive predictive value (reliability) was high for hypothyroidism (100%) and diabetes (87.1%).

Conclusions

In a selection of Dutch pharmacies, at least one documented disease and/or intolerability was found in the EPR of almost 60% of the patients. Certain diseases were documented to a relatively high degree; others had poorer levels of documentation. For optimal surveillance of drug-disease interactions in pharmacies, the frequency and quality of disease and intolerability documentation need further improvement.

INTRODUCTION

The occurrence of drug related problems (DRPs) has been the subject of several studies[1,2] and is part of the public debate about patient safety and medication errors.[3] Pharmacists can play a major role in the detection and prevention of DRPs and medication errors.[4-8]

Information technology in Dutch community pharmacies commenced 30 years ago with the electronic recording of simple patient data (e.g. gender, age, address) and documentation of drugs dispensed to the patient. Thereafter, a medication surveillance program was introduced enabling the pharmacist to check for several potential DRPs, especially dosing problems, drug-drug interactions and duplicate medications. With the documentation of clinical data in the electronic patient record (EPR), which included diseases and intolerabilities, it became possible to check for drug-disease interactions and drug intolerabilities (including allergies).[7] These are considered important and preventable DRPs.[8-11]

Dutch pharmacy medication surveillance software can advise the pharmacist to document a certain disease (e.g. diabetes) for a specific patient based on a dispensed medication (e.g. insulin). It can form part of a network linking several pharmacies with each other and/or with practices of general practitioners (GPs). It is, however, the pharmacist who has to decide whether to document the disease in question. In addition, clinical information provided by the prescriber or patient may lead to documentation of relevant clinical information by the pharmacist. After having documented the specific disease or intolerability, each new prescription is checked against the database for drug-disease interactions, leading to an alert on the computer screen in case of a relevant interaction (i.e. contraindication).

Adequate documentation of relevant diseases and intolerabilities is thus essential for this type of medication surveillance. A limited amount of research has, however, been conducted on the magnitude, nature and quality of the documentation of diseases and intolerabilities in the EPRs in pharmacies. This in contrast to practices of GPs, where a considerable quantity of research regarding documentation in EPRs has been performed.[12-15]

We therefore studied the prevalence, nature, and quality of documentation of diseases and intolerabilities in EPRs in a sample of Dutch community pharmacies that were considered a vanguard in possessing the best possibilities for using the

EPR. Additionally, we were interested in identifying determinants related to the documentation of any disease and/or intolerability in the EPR.

METHODS

Setting and population

All Dutch community pharmacies using the Pharmacom information technology system, particularly the Care Concept Electronic Programme[16] (n=455) were invited to participate in this study in 2003, of which 79 (17.4%) were ultimately enrolled. All participating pharmacies received a pretested study protocol and the coordinating research centre was available for questions. On one predetermined day in May 2003, each participating pharmacy randomly enrolled patients by using a predefined procedure that selected one (2.5%) out of every 40 patients to whom a prescription had been dispensed that day.

The procedure selected the highest prescription number ending with a nine on the study day (e.g. 4909) followed by all preceding prescriptions, each separated by 40 prescriptions (e.g. 4869, 4829). In case this procedure led to possible inclusion of the same patient more than once, another patient was included according to the procedure described in the protocol.

The inclusion procedure selected only patients who were prescribed drugs (n=687); three patients who had been dispensed other products (e.g. incontinence material) were excluded from data analysis.

Collection and classification of data

One registration form was used to collect basic characteristics of the participating pharmacy. On another form, the pharmacist documented patient-specific information (age, gender, current drug use) as well as clinical information (diseases, intolerabilities) that were recorded in the patient's EPR. The diseases and conditions that can be documented in the EPR using a specific code are listed in Appendix A.

Pharmacists were requested to send also anonymous copies of the medication-dispensing history of each study patient. When data on the registration form concerning current drug use conflicted with the medication-dispensing history, it resulted in an alteration by the research team. If necessary, consultation with the pharmacist was required in these cases. In the case of questions arising from the registration forms, the pharmacist was contacted as well.

All medicines were classified into therapeutic groups using the Anatomical Therapeutic Chemical (ATC) classification of the World Health Organization Collaborating Centre for Drug Statistics Methodology. For each patient the chronic disease score (CDS), a validated measure of the chronic disease status, was determined based upon the drugs used on the study day.[17]

Data analysis

Data were entered into a database (Microsoft Access 2000) and analysed using standard descriptive data analysis (SPSS version 10.0). Logistic regression analysis was used to measure the association between characteristics and recording of diseases and intolerabilities in the EPR.

For the assessment of the quality of the documentation of disease information in the EPR, the use of certain drugs was considered as a proxy parameter for the presence of a disease. This definition of the disease served as the 'gold standard' when calculating the quality parameters. Electronic prescription data have become accepted as sensitive and highly predictive for diagnosis validation when used appropriately.[18,19] Documentation of the disease in the EPR was considered the diagnostic test. As was done for diagnostic tests, sensitivity (completeness) and positive predictive value (PPV accuracy) were calculated.[13-15] The quality assessment was performed for diseases that were frequently encountered in the study population and/or with a high level of relevance as a contraindication for the use of certain drugs. In Appendix B, these diseases are presented as well as the proxy used for it, based upon current drug use (ATC codes).

RESULTS

The participating 79 pharmacies comprised almost 5% of all Dutch pharmacies (~1700). Compared with the average Dutch pharmacy, these pharmacies had advanced possibilities for using the EPR, had slightly more personnel, participated in more structured meetings with GPs, and were more often equipped with a certified Quality System[a] (33% versus 11%). There was a large variation among pharmacies with respect to the daily number of prescriptions

[a] In the Netherlands, the Royal Dutch Association for the Advancement of Pharmacy (KNMP) developed the Dutch Pharmacy Standard (NAN) with general and pharmacy-specific rules. The NAN is based on general international standards. Third parties (e.g. physicians and patients) advised the KNMP. Individual pharmacies can achieve certification when they apply these standards according to certain rules.

and the number of pharmacists and assistants, which reflects the fact that both small and large pharmacies participated in the study.

Table 1: BASELINE CHARACTERISTICS OF THE STUDY POPULATION (n=687)

Characteristic	No. of patients	%
Gender		
female	420	61.1
male	267	38.9
Age (yr)		
mean 55.5 (range 0-97)		
0–40[a]	153	22.3
41–55	167	24.3
56–70	178	25.9
>70	189	27.5
Current prescribers involved		
GP only	459	66.8
specialist only	55	8.0
GP and specialist	155	22.6
other	18	2.6
Drugs (n)		
mean 4.3 (range 1-18)		
1–2	250	36.4
3–5	244	35.5
>5	193	28.1
Drug group (ATC class)		
cardiovascular system	326	47.5
nervous system	306	44.5
alimentary tract and metabolism	251	36.5
blood and blood-forming organs	190	27.7
respiratory system	173	25.2
genital-urinary system and sex hormones	145	21.1
musculoskeletal system	137	19.9
dermatologicals	124	18.0
general antiinfectives for systemic use	63	9.2
sensory organs	63	9.2
systemic hormonal preparations, excluding sex hormones	53	7.7
antineoplastic and immunomodulating agents	17	2.5
various	8	1.2
antiparasitic products, insecticides, and repellents	4	0.6
Chronic disease score[b]		
0	290	42.2
1–3	208	30.3
>3	189	27.5

a) Thirty-six patients were ≤16 years of age.
b) The chronic disease score is a validated measure of the chronic disease status. This measure is based on expert opinion on the use of drugs as a validated proxy for chronic diseases.[17]

Data from 687 patients were collected (average 8.7 patients/pharmacy, range 3-17). The characteristics of these patients are presented in Table 1.

Table 2: PREVALENCE OF DISEASE AND INTOLERABILITY DOCUMENTATION PER PATIENT

Category *(range of items/patient)*	**Patients with ≥ 1 item[a] (n=687)**		
	n	**%**	**95% CI**
Disease and/or intolerability *(0-14)*	411	59.8	56.1 – 63.5
Disease *(0-7)*	394	57.4	53.6 – 61.1
hypertension	155	22.6	19.5 – 25.9
asthma/COPD	100	14.6	12.0 – 17.4
hypercholesterolaemia	76	11.1	8.8 – 13.7
depression	73	10.6	8.4 – 13.2
angina pectoris	72	10.5	8.3 – 13.0
diabetes types 1 and 2	70	10.2	8.0 – 12.7
dyspepsia	47	6.8	5.1 – 9.0
ulcus pepticum	43	6.3	4.6 – 8.3
tachyarrhythmia	35	5.1	3.6 – 7.0
reflux oesophagitis	22	3.2	2.0 – 4.8
prostatic hyperplasia	19	2.8	1.7 – 4.3
hypothyroidism	18	2.6	1.6 – 4.1
thrombosis	18	2.6	1.6 – 4.1
epilepsy	14	2.0	1.1 – 3.4
heart failure	10	1.5	0.7 – 2.7
psoriasis	10	1.5	0.7 – 2.7
Intolerability/allergy (*0-14)*	54	7.9	6.0 – 10.1
penicillin	17	2.5	1.5 – 3.9
salicylates/NSAIDs	12	1.7	0.9 – 3.0
sulfonamides	7	1.0	0.4 – 2.1
tetracyclines	7	1.0	0.4 – 2.1
nitrofuranes	5	0.7	0.2 – 1.7
trimethoprim	5	0.7	0.2 – 1.7
tramadol	4	0.6	0.2 – 1.5

NSAIDs = nonsteroidal anti-inflammatory drugs

a) In the electronic patients records of all 687 selected patients we found a total of 973 disease and intolerability documentations.

In the EPR of all selected patients, a total number of 973 diseases and intolerabilities were documented. At least one documented disease and/or intolerability was found in the EPR of 59.8% of the patients (n=411; Table 2).
For several patients, more than one disease and/or intolerability was registered: more than one-third (34.6%) had ≥3 registered items. The most frequently documented diseases were hypertension, asthma/chronic obstructive pulmonary disease (COPD), hypercholesterolaemia, depression, angina pectoris, and diabetes

type 1 and 2. In the EPR of 7.9% of the patients, at least one intolerability for a certain drug (group) was documented, especially antibiotics and analgesics.
Adjusted for all other variables, we found that older people (>55 yr), patients using ≥3 drugs, and those with a chronic disease score of ≥1 had a higher probability for any documentation of a disease/intolerability in their respective EPR (Table 3). The use of several drugs, such as cardiovascular, blood and blood organ, nervous system, and respiratory system agents, was also associated with the documentation of a disease/intolerability.
Concerning the quality of documentation, we found the highest sensitivity scores (completeness) for diabetes, asthma/COPD (strict definition), and hypothyroidism (Table 4). A rather low value was found for the documentation of prostatic hyperplasia and a remarkably low one for heart failure. The PPV, representing accuracy, was 100% for hypothyroidism. Relatively high values were found for diabetes and all cardiovascular diseases. Low data were found for asthma/COPD (strict definition) and angina pectoris.

DISCUSSION

To our knowledge, no previous study has examined the prevalence, nature and quality of disease documentation in the EPR performed within a sample of community pharmacies. In a systematic review evaluating the quality of EPRs in GP practices, the completeness (sensitivity) of documentation of a summary of all conditions considered ranged from 55 to 96.[14] Our data concerning the investigated diseases are within this range except for heart failure. In the aforementioned review, sensitivity values for angina and diabetes were 40 and 74-100 respectively. This is somewhat lower or comparable with our data. The PPV ranged from 96 to 100 for all conditions. For angina and diabetes, PPV data of 100 and 99-100 were revealed.[14] Our data are lower, with the exception of hypothyroidism.
In our study, antibiotics in particular (40% attributed to penicillins) and, to a lower extent, analgesics accounted for most of the intolerability documentations. In several studies, these agents, particularly antibiotics (mostly penicillins), are mentioned as the most common cause of reactions.[20,21] In our study, intolerabilities that are not necessarily anaphylactic in nature were documented; those may not automatically lead to the same event if the documented drugs are given in the future.

A number of limitations to this study should not be ignored. As the participating pharmacies constituted a voluntary sample, there may have been a positive selection bias. In addition, it concerned a specific sample of Dutch pharmacies, which were considered as having advanced possibilities for using the EPR. It is therefore possible that the more patient- and quality-oriented pharmacies participated. On the other hand, both small and large pharmacies, located in different parts in the Netherlands, were included.

Secondly, we considered current drug use as a proxy for having the disease concerned.[18,19] In studies concerning GP electronic records, this method of drug-morbidity pairing has frequently been used. It is a simple measure, however, it will not always provide a precise matching and 100% may not be a reasonable absolute target.[22] The only patients included were those being pharmacologically treated. Patients not yet pharmacologically treated, such as in the case of diabetes, but for whom adequate surveillance of drug-disease interactions is also relevant, could not be included. Sensitivity estimates are therefore likely to be positively biased.

We used different types of drug-morbidity pairing. Three diseases have an almost unambiguous relationship with currently used medication: diabetes, hypothyroidism and prostatic hyperplasia. This suggests the highest integrity of sensitivity and PPV data among the investigated diseases, bearing in mind the abovementioned limitation. We found relatively high, but still improvable, values concerning diabetes and hypothyroidism, but low values regarding prostatic hyperplasia. These diseases could be used as performance indicators concerning the documentation of diseases in the EPR.

Data concerning completeness and accuracy of recording need more consideration regarding the other diseases. There are two diseases with a rather restricted definition: asthma/COPD strict and angina pectoris (Appendix B). We may conclude that there is an almost unambiguous relationship between these diseases and the defined and currently used medications. We may have obtained a relatively clear impression about the completeness of recording (sensitivity) with these patients, indicating that completeness is also a good quality indicator. The accuracy represented by a PPV of only 22% and 28% provides a rather contrasting picture. These low and unreliable data are understandable, however, because there are more drugs related to asthma/COPD or angina pectoris for which the pharmacist documented the disease in the EPR. As a result, there is an abundance of disease coding leading to a low PPV value.

Table 3: DETERMINANTS OF DOCUMENTING ANY DISEASE AND/OR INTOLERABILITY IN THE ELECTRONIC PATIENT RECORD

Characteristic	Documentation	No documentation	OR (95% CI)[a]	
	n=411 (100%)	n=276 (100%)	Crude	Adjusted[b]
Patient related				
gender				
male	165 (40.1)	102 (37.0)	1 (reference)	1 (reference)
female	246 (59.9)	174 (63.0)	0.87 (0.64-1.20)	0.99 (0.67-1.45)
age (yr)				
0–40	49 (11.9)	104 (37.7)	1 (reference)	1 (reference)
41–55	86 (20.9)	81 (29.3)	**2.25 (1.43-3.55)**	1.57 (0.95-2.61)
56–70	135 (32.8)	43 (15.6)	**6.66 (4.11-10.80)**	**3.08 (1.80-5.31)**
>70	141 (34.3)	48 (17.4)	**6.24 (3.89-9.99)**	**2.02 (1.16-3.51)**
Prescriber related				
GP only	258 (62.8)	201 (72.8)	1 (reference)	1 (reference)
specialist only	25 (6.1)	30 (10.9)	0.65 (0.37-1.14)	0.58 (0.30-1.11)
both GP and specialist	121 (29.4)	34 (12.3)	**2.77 (1.82-4.23)**	1.16 (0.71-1.91)
other	7 (1.7)	11 (4.0)	0.50 (0.19-1.30)	0.49 (0.16-1.50)
Drugs in use (n)				
1–2	88 (21.4)	162 (58.7)	1 (reference)	1 (reference)
3–5	156 (38.0)	88 (31.9)	**3.26 (2.26-4.72)**	**1.74 (1.12-2.69)**
>5	167 (40.6)	26 (9.4)	**11.82 (7.26-19.26)**	**3.91 (2.00-7.63)**
ATC class[c]				
cardiovascular system			**5.23 (3.73-7.34)**	
nervous system			**2.10 (1.53-2.87)**	
alimentary tract and metabolism			**3.96 (2.78-5.66)**	
blood and blood-forming organs			**4.05 (2.70-6.05)**	
respiratory system			**2.03 (1.40-2.95)**	
genital-urinary system and sex hormones			**0.47 (0.32-0.68)**	
musculoskeletal system			1.02 (0.69-1.49)	
dermatologicals			1.05 (0.70-1.56)	
general antiinfectives for systemic use			**0.59 (0.35-0.99)**	

sensory organs			1.40 (0.81-2.42)	
systemic hormonal preparations, excl. sex hormones			**3.60 (1.73-7.49)**	
antineoplastic and immunomodulating agents			1.65 (0.57-4.73)	
various			4.81 (0.59-39.27)	
antiparasitic products, insecticides and repellents			0.68 (0.10-4.84)	
Chronic disease score				
0	98 (23.8)	192 (69.6)	1 (reference)	1 (reference)
1–3	154 (37.5)	54 (19.6)	**5.59 (3.77-8.29)**	**3.48 (2.26-5.37)**
>3	159 (38.7)	30 (10.9)	**10.38 (6.56-16.45)**	**3.22 (1.73-5.98)**

a) Bold values indicate statistical significance.
b) Adjusted for all other variables, except for ATC-class.
c) Reference, all but respected code.

Table 4: QUALITY MEASUREMENT OF DISEASE DOCUMENTATION

Disease	Prevalence of disease[a] n=687 (100%)	Prevalence of documentation[b] n=687 (100%)	Sensitivity (95% CI)	PPV (95% CI)
Diabetes types 1 and 2	72 (10.5)	70 (10.2)	84.7 (74.7–91.2)	87.1 (77.3–93.1)
Asthma/COPD strict definition	29 (4.2)	100 (14.6)	75.9 (57.9–87.8)	22.0 (15.0–31.1)
Asthma/COPD broad definition	99 (14.4)	100 (14.6)	68.7 (59.0–77.0)	68.0 (58.3–76.3)
Angina pectoris	30 (4.4)	72 (10.5)	66.7 (48.8–80.8)	27.8 (18.8–39.0)
Heart failure	17 (2.5)	10 (1.5)	29.4 (13.3–53.1)	50.0 (23.7–76.3)
All cardiovascular diseases	326 (47.5)	229 (33.3)	65.0 (59.7–70.0)	92.6 (88.4–95.3)
Prostatic hyperplasia	18 (2.6)	19 (2.8)	55.6 (33.7–75.4)	52.6 (31.7–72.7)
Hypothyroidism	24 (3.5)	18 (2.6)	75.0 (55.1–88.0)	100.0 (82.4–100.0)

COPD = chronic obstructive pulmonary disease; PPV = positive predictive value
a) Number of patients with disease (based on gold standard as described in Appendix B) x 100%/total number of patients (N=687).
b) Number of patients with disease code in the electronic patient record x 100%/total number of patients (N=687).

We used two broad definitions concerning a disease: asthma/COPD broad and all cardiovascular diseases. We found reasonable but not high sensitivity values for both diseases. The broad definition will provide favourable opportunities for matching documentation in the EPR with the disease. On the other hand, pharmacists may have been reluctant to document the diseases in case of incidental use or first use (e.g. sympathomimetic agents) or because they were not sure about the exact indication (e.g. with cardiovascular disease). For the same reasons one will find a reasonable PPV for asthma/COPD in this case.
Finally, we examined a disease (heart failure) for which the computer will not prompt for documentation based on current drug use. Hence in this case, the pharmacist is confronted with a relatively poor representation of the actual number of patients with heart failure. The only way to document the disease is by reviewing a patient's medication record and/or communicating with physicians or patients. For heart failure, not surprisingly, a very low sensitivity score was found, highly disadvantageous in terms of providing optimal pharmaceutical care.
We did not investigate the quality of drug intolerability documentation. There is the question of underreporting in the EPR. In a recent study, a prevalence of self-reported drug allergy of 7.8% was found.[21] Our findings are comparable with the latter data. In contrast, many patients mistakenly believe that an increased sensitivity to known adverse effects is caused by allergy. This may lead to misclassification in the EPR, preventing the prescribing of a justifiable and possibly very essential medicine, such as penicillin.[23]
Our study shows that, for some diseases, the documentation is quite accurate, but for others the quality requires further improvement. Pharmacists should be aware of this, since complete documentation of information may help reduce iatrogenic risks. A program of assessments, feedback and training may help to increase this awareness. In some studies with respect to medical EPRs, such programmes, although uncontrolled, appear to improve data quality.[22]
To further develop adequate documentation of diseases, pharmacists should seek cooperation with physicians. This cooperation will improve patient data in the physician's practice as well. Joint EPRs for physicians and pharmacists should be encouraged. Furthermore, it may be advisable that physicians state the reason for prescribing on the prescription so that pharmacies can use that information for disease documentation and, hence, more efficient medication surveillance. Finally, pharmacists should more efficiently gather reliable information from

patients, as patients with well-defined chronic conditions have an accurate recall of medical and drug usage history.[24]

To ensure optimal medication safety, pharmacies are responsible for a system of medication surveillance and, hence, for high-quality EPRs. There are various reasons: prescriber systems are not completely reliable,[25] the contents are not always comparable to that of the pharmacy,[6,27] physicians do not always react in a justified way,[28] they do not always use all items provided in the medical record system,[29] there might be a lack of awareness of allergies (and other adverse drug reactions that a patient has experienced) and a high degree of allergy alert overrides among physicians.[20,30]

Finally, we would like to argue that to have no alert is actually more problematic than a false alert. After all, by communicating with the patient (or prescriber), the signal for a disease-drug interaction can be verified. When the surveillance of this DRP is no longer appropriate, the disease must be removed from the EPR. In this respect, we would like to argue that lower sensitivity scores are of more (negative) importance than lower PPVs. On the other hand, however, it is important to limit the number of false-positive alerts since a high number may be a main reason to turn off alerts or to override them.

CONCLUSIONS

In a selected population of Dutch community pharmacies, at least one documented disease and/or intolerability was found in the EPR of almost 60% of the patients. There was an association between documenting a disease and/or intolerability and older people, patients using ≥3 drugs and those with a chronic disease score of ≥1. Certain diseases, such as diabetes and hypothyroidism, were coded to a relatively high degree; others had poorer levels of coding, especially heart failure. For optimal surveillance of drug-disease interactions in pharmacies, the frequency and quality of disease and intolerability documentation need further improvement.

Acknowledgements. We thank all 79 pharmacists who participated in the study. Special thanks to Mr J Kappe, Mrs EN Reitsma, Mrs MM Tuijn, pharmacists, and Mrs G Meyvis, pharmacy technician, who helped in the design and implementation of the study.

REFERENCES

1. Weingart SN, Wilson RMcL, Gibberd RW, Harrison B. Epidemiology of medical error. BMJ 2000;320:774-7.
2. Gandhi TK, Seger DL, Bates DW. Identifying drug safety issues: from research to practice. Int J Qual Health Care 2000;12:69-76.
3. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human. Building a safer health system. Washington, DC: National Academy Press; 1999.
4. Westerlund LT, Marklund BR, Handl WH, Thunberg ME, Allebeck P. Nonprescription drug-related problems and pharmacy interventions. Ann Pharmacother 2001;35:1343-9.
5. Bouvy ML, Buurma H, Egberts TC. Laxative prescribing in relation to opioid use and the influence of pharmacy-based intervention. J Clin Pharm Ther 2002;27:107-10.
6. Beney J, Bero LA, Bond C. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes. Cochrane Database Syst Rev 2000;3:CD000336.
7. Buurma H, De Smet PA, van den Hoff OP, Egberts AC. Nature, frequency and determinants of prescription modifications in Dutch community pharmacies. Br J Clin Pharmacol 2001;52:85-91.
8. Buurma H, de Smet PA, Leufkens HG, Egberts AC. Evaluation of the clinical value of pharmacists' modifications of prescription errors. Br J Clin Pharmacol 2004;58:503-11.
9. Goldberg RM. Mabee J, Chan L, Wong S. Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population. Am J Emerg Med 1996;14:447-50.
10. Hanlon JT, Schmader KE, Boult C, Artz MB, Gross CR, Fillenbaum GG, et al. Use of inappropriate prescription drugs by older people. J Am Geriatr Soc 2002;50:26-34.
11. Williams CM. Using medications appropriately in older adults. Am Fam Physician 2002;66:1917-24.
12. Mitchell E, Sullivan F. A descriptive feast but an evaluative famine: systematic review of published articles on primary care computing during 1980-97. BMJ 2001;322:279-82.
13. Hassey A, Gerrett D, Wilson A. A survey of validity and utility of electronic patient records in a general practice. BMJ 2001;322:1401-5.
14. Thiru K, Hassey A, Sullivan F. Systematic review of scope and quality of electronic patient record data in primary care. BMJ 2003;326:1070-2.
15. Jordan K, Porcheret M, Croft P. Quality of morbidity coding in general practice computerized medical records: a systematic review. Fam Pract 2004;21:396-412.

16. De Gier JJ. The Electronic Pharmaceutical Dossier: an effective aid to documenting pharmaceutical care data. Pharm World Sci 1996;18:241-3.
17. Von Korff M, Wagner EH, Saunders K. A chronic disease score from automated pharmacy data. J Clin Epidemiol 1992;45:197-203.
18. Klungel OH, de Boer A, Paes AH, Herings RM, Seidell JC, Bakker A. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in the Netherlands. Pharm World Sci 1999;21:217-20.
19. Monster TB, Janssen WM, de Jong PE, de Jong-van den Berg LT. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. Pharmacoepidemiol Drug Saf 2002;11:379-84.
20. Abookire SA, Teich JM, Sandige H, Paterno MD, Martin MT, Kuperman GJ, et al. Improving allergy alerting in a computerized physician order entry system. Proc AMIA Symp 2000:2-6.
21. Gomes E, Cardoso MF, Praca F, Gomes L, Marino E, Demoly P. Self-reported drug allergy in a general adult Portuguese population. Clin Exp Allergy 2004;34:1597-601.
22. Porcheret M, Hughes R, Evans D, Jordan K, Whitehurst T, Ogden H, et al. Data quality of general practice electronic health records: the impact of a program of assessments, feedback and training. J Am Med Inform Assoc 2004;11:78-86.
23. Shepherd GM. Hypersensitivity reactions to drugs: evaluation and management. Mt Sinai J Med 2003;70:113-25.
24. Kehoe R, Wu SY, Leske MC, Chylack LT. Comparing self-reported and physician-reported medical history. Am J Epidemiol 1994;139:813-8.
25. Fernando B, Savelyich BSP, Avery AJ, Sheikh A, Bainbridge M, Horsfield P, et al. Prescribing safety features of general practices computer systems: evaluation using simulated test cases. BMJ 2004;328:1171-3.
26. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians' decisions to override computerized drug alerts in primary care. Arch Intern Med 2003;163:2625-31.
27. Rahimtoola H, Timmers A, Dessing R, Hudson S. An evaluation of community pharmacy records in the development of pharmaceutical care in the Netherlands. Pharm World Sci 1997;19:105-13.
28. Laerum H, Ellingsen G, Faxvaag A. Doctors' use of electronic medical records systems in hospitals: cross sectional study. BMJ 2001;323:1344-8.
29. Loomis GA, Ries JS, Saywell RM, Thakker NR. If electronic medical records are so great, why aren't family physicians using them? J Fam Pract 2002;51:636-41.
30. Hsieh TC, Kuperman GJ, Jaggi T, Hojnowski-Diaz P, Fiskio J, Williams DH, et al. Characteristics and consequences of drug allergy alert overrides in a computerized physician order entry system. J Am Med Inform Assoc 2004;11:482-91.

Appendix A: DISEASES OR CONDITIONS THAT CAN BE DOCUMENTED IN THE INFORMATION TECHNOLOGY SYSTEM OF THE INCLUDED PHARMACIES

Angina pectoris	Hypercholesterolaemia
Angle-closure glaucoma	Hypertension
Asthma/chronic obstructive pulmonary disease (both also separately)	Hyperthyroidism
	Hypothyroidism
Bipolar disorder	Lactation
Breast cancer	Myasthenia
Contact lenses	Open-angle glaucoma
Crohn's disease/ulcerative colitis	Parkinson's disease
Depression	Peptic ulcer disease
Diabetes type 1	Porphyria
Diabetes type 2	Pregnancy (divided into three trimesters)
Diminished kidney function	Prolonged QT interval syndrome
Diminished liver function	Prostatic hyperplasia
Dyspepsia	Psoriasis
Endometrial cancer	Raynaud's phenomenon
Endometriosis	Reflux oesophagitis
Epilepsy	Sports
Glucose-6 phosphate dehydrogenase deficiency	Tachycardia
	Tardive dyskinesia
Gout	Thrombosis
Heart failure	

Appendix B: DISEASES AND DRUGS USED AS A PROXY FOR THESE DISEASES

Disease	Drugs (ATC codes) used as a proxy
Diabetes types 1 and/or 2	insulin (A10A) and/or oral antidiabetics (A10B)
Asthma/COPD strict definition	theophylline (R03DA04) and/or combination of long-acting sympathomimetics and corticosteroids (R03AK06/-07)
Asthma/COPD broad definition	all asthma/COPD medication (R03)
Angina pectoris	nitrate sublingual spray (C01DA02) and/or sublingual isosorbide dinitrate tablet 5mg, both intended for use in acute angina
Heart failure	loop diuretics (C03CA01/-02) and at least two medications from the following groups: (1) spironolactone (C03DA01), (2) ACE inhibitor/ angiotensin II antagonist, (3) specific β-blocker (C07AB02/-07/C07AG02), (4) digoxin (C01AA05)
All cardiovascular diseases	all cardiovascular drugs (C)
Prostatic hyperplasia	α_1-adrenergic receptor blockers (G04CA01/-02/-03) and/or finasteride (G04CB01) (other α_1-adrenergic receptor blockers were excluded since they are also indicated for hypertension, however, they were not found in the cohort)
Hypothyroidism	levothyroxine (H03AA01); the combination with thioamides was excluded since this combination is used for hyperthyroidism

ACE = angiotensin-converting enzyme

3.2

Adherence to a national guideline for the management of drug-drug interactions in Dutch community pharmacies

Henk Buurma, Tom Schalekamp,
Antoine CG Egberts, Peter AGM de Smet

ABSTRACT

Aims

Pharmacists contribute to the detection and prevention of certain drug therapy related problems including drug-drug interactions (DDIs). Little is known about adherence to pharmacy practice guidelines for the management of DDI alerts. The objective of this study was to measure the adherence of community pharmacies to a Dutch guideline for the management of DDIs as well as patient- and prescriber related determinants for non-adherence.

Methods

Sixteen clinically relevant DDIs were included in the study based upon certain criteria. From June till August 2005, Dutch pharmacists (n=149) collected alerts occurring in daily patient care for these interactions as well as information related to the patient, the alert itself, the prescriber and the management of the alert. The (non)adherence was measured by comparing the management executed by the pharmacy with the national guideline.

Results

The overall adherence to the guideline amounted to 69.3% (n=423) with large differences between the various DDIs. Adjusted for all variables, male gender (OR 2.25; 95%CI 1.52-3.31), the highest age category (>75yr) (OR 1.97; 95%CI 1.03-3.75) and current use of more than seven medications (OR 2.35; 95%CI 1.46-3.80) were associated with a higher probability for non-adherence to the guideline by pharmacies. Prescriber related variables had no influence on non-adherent management. The degree of adherence varied not only with the nature of the DDI, but also with its management characteristics. Substitution of one of the involved agents, recommended for most of the DDIs, was only executed in a small minority of cases. A substitution, a dose reduction, or a temporary stop of one of the agents as a result of interaction management was frequently not consistent with the guideline.

Conclusions

Non-adherence to a guideline for the management of DDI alerts occurs frequently in community pharmacies. There are several, sometimes unexpected, reasons for non-adherent management. Further research into underlying reasons is warranted to guide efforts to improve this situation.

INTRODUCTION

One of the most consistent findings in research of health services is the gap between available evidence and clinical practice. Results of studies from the USA and the Netherlands indicate that 30-40% of patients do not receive care according to current scientific evidence, and 20-25% of the provided care is not needed or is potentially harmful.[1] Contrary to (general) medical practice with an abundance of published studies of this subject, very little is known about adherence to pharmacy practice guidelines, e.g. those concerning the management of drug-drug interaction (DDI) alerts.

Pharmacists contribute to the detection and prevention of drug therapy related problems including medication errors, the occurrence of which has been subject of several studies and part of the public debate about patient safety.[2-5] The impact of one category of these medication errors, i.e. DDIs, on drug related morbidity including avoidable hospital admissions has been repeatedly demonstrated.[6-8]

Guidelines play an important role in the management of DDI alerts by physicians and pharmacists. In the Netherlands, guidelines for the management of DDIs have been developed and are kept up to date by working groups on the basis of published evidence of DDIs.[9] This evidence is transformed into alerts with concrete recommendations for the management of alerts that are incorporated into the software programs used by community pharmacies for handling and recording prescriptions. The pharmacy software program checks new prescriptions for DDIs using stored information about drugs that will be dispensed simultaneously or have already been dispensed to the patient in question. Conditions in Dutch pharmacies, in general, are advantageous for clinical risk management: electronic medication records, sophisticated DDI signalling software and a low degree of fragmented prescription filling due to a high pharmacy compliance of patients.[10]

Several steps in the process of clinical risk management can be observed concerning the prevention and management of prescribing errors related to DDIs in pharmacies, i.e. risk assessment by the above mentioned working groups, risk management by the pharmacist (partly in cooperation with the prescriber) and evaluation of strategies, of which our study is an example.[11,12] The objective of our study was to explore the adherence of community pharmacies to a national guideline for the management of DDI alerts as well as patient related and prescriber related determinants for non-adherence.

METHODS

Setting and study population

All Dutch community pharmacies using the Pharmacom® information technology system (n=791) were invited to participate in this study, of which 172 (21.7%) positively responded. Ultimately 149 (18.8%) - serving approximately 1.4 million patients, which is almost 9% of the Dutch population - were able to participate in this study. During a three months period (June - August 2005) each participating pharmacy was requested to collect alerts of those DDIs selected for this study (see below) as encountered during routine daily patient care. The participating pharmacies received a pre-tested study protocol and the coordinating research centre was available for questions throughout the study.

Selection of the drug-drug interactions included in this study

The Pharmacom® information technology system monitors approximately 300 different DDIs.[13] For our study we selected those DDIs that fulfilled the following criteria. The available evidence had to be classified as three or higher, and the clinical relevance had to be classified as C or higher, according to the classification system developed and maintained by a working group of the Scientific Institute of Dutch Pharmacists (WINAp) that has been described in detail elsewhere.[9] In brief, within that classification system DDIs are classified on a six-point relevance scale ranging from not serious to very life-threatening (category A to F, respectively) and on a five-point evidence scale ranging from not proven to very well proven (category 0 to 4, respectively). A similar classification system is used in Sweden and has been described for research purposes elsewhere.[14] In other words, all the included DDIs had to have potentially harmful consequences for patients' safety. An additional criterion was that the management of these DDIs alerts according to the national guideline had to involve the substitution of one of the interacting drugs, sometimes presented as the only option, sometimes accompanied by an alternative option. This led to the inclusion of 16 DDIs (Table 1). An important feature of the selected DDIs is the relative low frequency of recurrent alerts, because of the nature of one of the interacting agents (antibiotics, antimycotics, PDE-5-inhibitors). This decreased the chance that the DDI had already been managed in the past for the same patient.

Collection and classification of data

PharmaPartners, the owner of the Pharmacom® information technology system, developed a computer program, enabling each pharmacy to extract and collect

automatically the preselected DDI alerts that had occurred during the previous week. These data extractions were sent to the coordinating research centre electronically. For each DDI alert a questionnaire was returned to the community pharmacy by email. Subsequently, filled questionnaires were sent to the coordinating study centre by email, post or fax.

On the questionnaire form pharmacists recorded information related to the patient (age, gender, estimated current drug use), the alert itself (medicines involved, same or different prescribers for the interacting drugs, type of prescriber of latest prescription - i.e. general practitioner (GP) or medical specialist), and information about the management of that DDI alert by the pharmacy. Management was categorized as external action or not. External action was defined as an intervention directed at the prescriber, advice given to the patient, or other, such as communication with the anticoagulation clinic. In case no external action was undertaken one was asked to give reasons for that (e.g. recurrent alert or alert already managed in the past).

The nature or output of the management process had to be specified: substitution of one of the interacting medicines, dose change of one of the interacting medicines, content of advice to the patient, content of advice as to plasma levels, kidney function, et cetera.

Adherence to guideline

In Table 1 we summarized the management guidelines for the selected 16 DDIs that is presented to pharmacies on the computer screen each time that the DDI alert occurs as well as in a yearly updated textbook.[13] A working group of Health Base Foundation, a knowledge centre that is closely connected to the Pharmacom® information technology system, is responsible for the content of this textbook, which provides background information about several drug therapy related problems, such as DDIs and drug-disease interactions. Moreover, algorithmic strategies for management (management guidelines) are provided, which were used as the gold standard for the evaluation of the management by pharmacies of the 16 DDIs in our study (Table 1). The comparison between the management output as described on the questionnaires and the guideline was made by one of the authors (HB) and checked by another (TS). The outcome of this comparison was threefold: adherent, non-adherent or uncertainty as to assessment. A recurrent alert with no further information was the main reason for the latter outcome.

Table 1: DESCRIPTION OF THE GUIDELINES FOR THE MANAGEMENT OF THE 16 INCLUDED DRUG-DRUG INTERACTIONS

Description of drug-drug interaction	Possible consequences	Proposed management in the guideline
statins — microlides	myopathy and rhabdomyolysis	Macrolide only for one day: patient instruction to contact physician immediately in case of severe myopathy. In other cases: stop or dose reduction of simvastatin or atorvastatin during macrolide course (max of 20 and 40mg respectively). No problems with fluvastatin, pravastatin, rosuvastatin. In case of maintaining use of statin with low dose: patient instruction (see above).
statins — antimycotics	myopathy and rhabdomyolysis	At start of statin: postpone use of statin until end of antimycotic course or choose pravastatin or rosuvastatin. At start fluconazol (≤200mg dd): no action. At start fluconazol (>200mg dd) or other antimycotic: substitution by another antimycotic (e.g. terbinafine) or temporary stop of statin or choose for pravastatin or rosuvastatin.
coumarins — co-trimoxazole	bleeding	Substitution of co-trimoxazole or warning to anticoagulation clinic (fax).[a]
digoxin — macrolides	digoxin toxicity	Substitution of macrolide (with high serum level of digoxin as risk factor, daily dose ≥ 0,25mg).
PDE-5 inhibitors — nitrates	drop of systolic and diastolic blood pressure	Substitution of PDE-5 inhibitor.In case of maintenance treatment with nitrate: substitution by beta-blocking agent.
theophylline — macrolides	theophylline toxicity	At start macrolide: substitution macrolide or monitor theophylline serum level.[b] At start theophylline: begin with low dose, later increase of dose guided by serum level.
coumarins — antimycotics	bleeding	Fluconazole (one day course): no intervention. Other regimes of azole antimycotics: substitution (particularly miconazole, fluconazole or voriconazole) or warning to anticoagulation clinic (fax).[a]
tricyclic antidepressants (TCA) — terbinafine	TCA toxicity	At start of TCA: low dose of TCA to max of 50mg daily; older people: 25mg daily.

		At start of terbinafine: substitution of terbinafine or dose reduction TCA to max of 50mg daily; older people: 25mg daily (starting dose regimens and dose reductions of TCA preferably guided by serum level control).
Theophylline — quinolones	theophylline toxicity	Substitution of quinolon (not by macrolide) or dose decrease of theophylline to 50% in case of ciprofloxacin or pipemidic acid.
phenytoin — co-trimoxazole/ trimethoprim/ sulfonamides	phenytoin toxicity	At start of co-trimoxazole/ trimethoprim/ sulfonamide: substitution by another antibiotic (no fluorquinolon). At start of phenytoin: begin with low dose, later increase of dose guided by serum level/clinical effect.
methotrexate — co-trimoxazole/ trimethoprim	bone marrow suppression	Substitution of co-trimoxazole/ trimethoprim (no safe time interval is known).
digoxin — itraconazole	digoxin toxicity	Substitution of itraconazole or dose decrease of digoxin, guided by serum level.
PDE-5 inhibitors — CYP3A4 inhibitors	sildenafil or vardenafil toxicity	Sildenafil — ritonavir: avoidance of sildenafil or dose reduction to max 25mg/48 hrs. Sildenafil — other CYP3A4 inhibitors: dose reduction of sildenafil to max 25mg/48 hrs. Vardenafil — indinavir or very strong CYP3A4 inhibitors: avoidance of vardenafil or substitution of CYP3A4 inhibitor. Vardenafil — other CYP3A4 inhibitors: dose reduction vardenafil to max 5mg/24 hrs.
carbamazepine — macrolides	carbamazepine toxicity	Substitution of CYP3A4 inhibiting macrolide (i.e. erythromycin or clarithromycin).
terfenadine — QT-interval prolongers	QT-interval prolonging; ventricular arrhythmia's	Substitution of terfenadine by other antihistaminic agent.
St John's wort — digoxin	digoxin toxicity	Avoidance of combination.

a) In this study warning to the anticoagulation clinic was also assessed as adherent when the warning was given to the patient or its relative. Every patient is acquainted with the telephone number of the clinic.
b) In this study warning to the patient was also assessed as adherent.

Finally, the association between non-adherence to the guideline and several patient related characteristics (i.e. gender, age, number of drugs in use) and prescriber related characteristics (different prescribers for the interacting drugs; prescriptions prescribed during different consultations; latest prescription from other prescriber, not GP) were examined.

Data analysis

Data from the registration forms were entered into a database (Microsoft Access 2000) and analysed using standard descriptive data analysis (SPSS version 12.0). Logistic regression analysis was used to estimate the strength of the association between characteristics and non-adherence to the guideline and expressed as odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

From the 858 returned forms, all cases concerning unjustified alerts (n=97; mostly because the first drug had already been stopped) and all alerts missing essential information (n=17) were excluded from the analysis. The remaining 744 DDI alerts were collected by 149 pharmacies with a range of 1 till 17 alerts per pharmacy (average=5). The alerts concerned an approximately equal fraction men and women. The mean age was 64.5 years (sd 14.7) with a range of 2 till 99. About 84% of the patients were older than 50 years. The number of drugs used at the moment of the alert was 6.4 medications on average (sd 3.3; excluding dermatological preparations) with a range of 0 till 22.

The frequency of alerts for the 16 included DDIs (Table 2) was rather divergent: it ranged from 205 alerts for statins – macrolides to just one alert for St John's wort – digoxin. A number of 134 cases (18.0%) could not be evaluated because it concerned, mainly, a recurrent alert with no further information about the management of the alert.

For all alerts for which an assessment was possible (n=610), pharmacists undertook external action in 79.5% (n=485) (Figure 1). In case of external action the prescriber was consulted in 28.2% (137/485), advice given to the patient in 72.8% and another action undertaken in 14.4%, mainly information giving to the anticoagulation clinic. Twofold actions occurred several times.

The overall adherence to the guideline amounted to 69.3% (n=423) with large differences between the 16 selected DDIs. A high adherence was found for the two interactions involving coumarin anticoagulants (92.3% and 95.8%).

Adherence was also relatively high for tricyclic antidepressants – terbinafine (90.9%), statins – macrolides (89.8%), statins – antimycotics (82.2%) and PDE-5 inhibitors – CYP3A4 inhibitors (75.0%). A relatively low adherence was found for the two interactions involving theophylline (45.0% and 21.6%), digoxin – macrolides (8.9%) and PDE-5 inhibitors – nitrates (2.8%).

Table 2: ADHERENCE TO THE GUIDELINE FOR THE MANAGEMENT OF SIXTEEN DRUG-DRUG INTERACTIONS

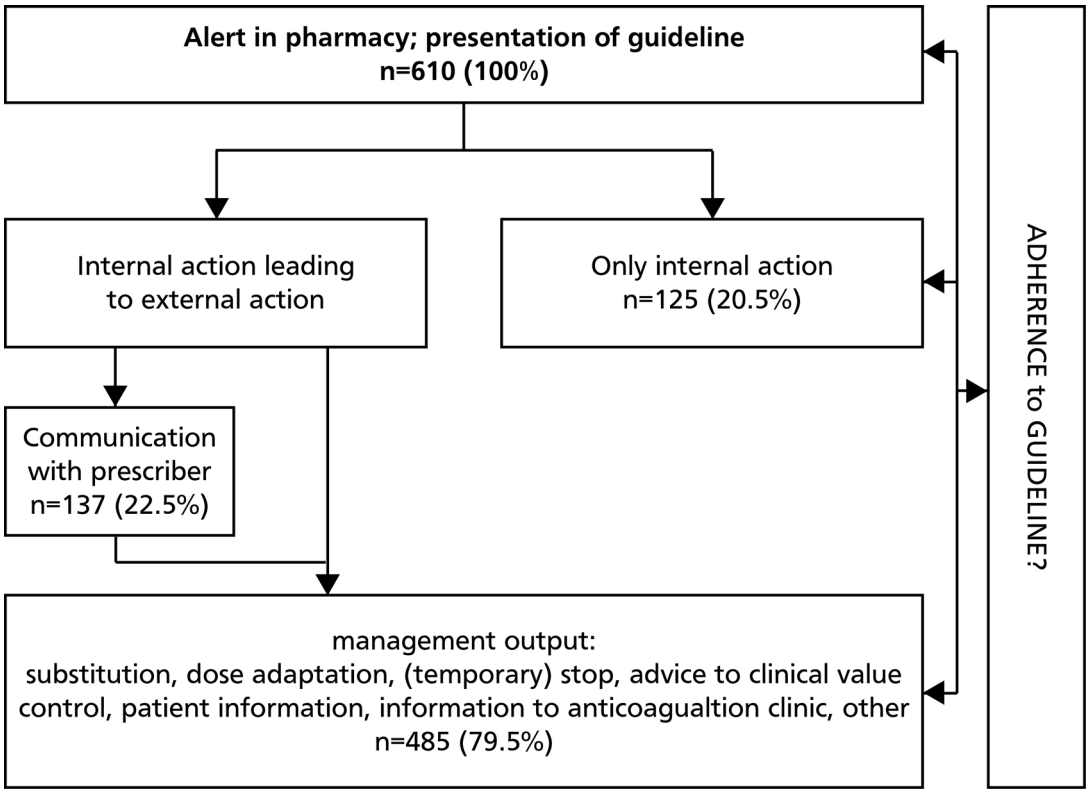
Drug-drug interaction	Number	Uncertainty as to assessment n (%)	Adherence (after adjustment)[a]
Total	**744**	**134 (18.0%)**	**69.3% (423/610)**
statins — macrolides	205	8 (3.9%)	89.8% (177/197)
statins — antimycotics	119	12 (9.7%)	82.2% (88/107)
coumarins — co-trimoxazole	90	18 (20.0%)	95.8% (69/ 72)
digoxin — macrolides	75	19 (24.7%)	8.9% (5/ 56)
PDE-5 inhibitors — nitrates	62	26 (40.6%)	2.8% (1/ 36)
theophylline — macrolides	53	16 (28.1%)	21.6% (8/ 37)
coumarins — antimycotics	49	9 (18.8%)	92.3% (37/ 40)
tricyclic antidepressants — terbinafine	34	12 (35.3%)	90.9% (20/ 22)
theophylline — quinolones	24	4 (16.7%)	45.0% (9/ 20)
phenytoin — co-trimoxazole/ trimethoprim / sulfonamide	10	4 (40.0%)	50.0% (3/ 6)
methotrexate — co-trimoxazole/ trimethoprim	7	4 (57.1%)	33.3% (1/ 3)
digoxin — itraconazole	5	1 (20.0%)	50.0% (2/ 4)
PDE-5 inhibitors — CYP3A4 inhibitors	5	1 (20.0%)	75.0% (3/ 4)
carbamazepine — macrolides	3	0 (0.0%)	0% (0/ 3)
terfenadine – QT-interval prolongers	2	0 (0.0%)	0% (0/ 2)
St John's wort — digoxin	1	0 (0.0%)	0% (0/ 1)

a) Minus cases with uncertainty as to assessment.

The degree of adherence varied not only with the nature of the DDI, but also with management characteristics. For alerts for which substitution was the only proposed management option we found a low adherence (9.2%) to the guideline (digoxin – macrolides; methotrexate – co-trimoxazole/trimethoprim, carbamazepine – macrolides, terfenadine – QT-interval prolongers, St-John's Wort – digoxin). For alerts for which in addition to substitution a clear alternative option was possible, the adherence amounted to 82.2% (statins –

macrolides, statins – antimycotics, coumarins – co-trimoxazole, theophylline – macrolides, coumarins – antimycotics, tricyclic antidepressants – terbinafine, theophylline – quinolones, digoxin – itraconazole).

Figure 1: ALERT MANAGEMENT OF SIXTEEN POTENTIALLY HARMFUL DRUG-DRUG INTERACTIONS IN DUTCH COMMUNITY PHARMACIES



A temporary stop of one of the agents was executed in 30 cases (4.9%) of which 19 (63.3%) were consistent with the guideline. Dose adaptation was carried through in 17 cases (2.8%) of which about half (8 cases) was in accordance with the guideline.

The association between patient- and prescriber related variables and non-adherence to the guideline is presented in Table 3. Adjusted for all other variables male gender (OR 2.25; 95%CI 1.52-3.31), the highest age category (>75yr) (OR 1.97; 95%CI 1.03-3.75) and current use of more than seven medications (OR 2.35; 95%CI 1.46-3.80) signify a higher probability for non-adherence to guidelines by pharmacies concerning the whole group of selected

DDIs (n=610). Prescriber related variables, such as different prescribers for both drugs, had no influence on the non-adherent management of DDI alerts.

DISCUSSION

To our knowledge, this is the first multicentre study evaluating adherence to a national guideline concerning the management of DDI alerts in community pharmacies. The overall adherence amounted to 69.3%. However, the degree of adherence varied with the nature of the DDI, patient characteristics and the nature of the advised management actions in the guideline.

The degree of and variation in non-adherence to a clinical guideline in our study matches the outcomes of other studies concerning medical practice.[1,15,16] Just as with medical guidelines, the mere introduction of a guideline for the management of DDIs by community pharmacists does not guarantee adherence to it.[1,17,18] However, it is questionable whether this issue concerning pharmacists' adherence can be fully compared with GP's adherence to diagnostic or therapeutic guidelines. An important difference in this study on DDIs is that pharmacists have to present the problem with some management options to the prescriber, who, however, ultimately decides on the management of the DDI. In our study pharmacists directly discussed the problem with the prescriber in 22.5% of the cases (137/610). The adherence rate of these cases was lower (56.2%; 77/137) than average (69.3%; 423/610).

There were considerable differences in the quality of the adherent as well as the non-adherent management of pharmacies. Adherent management can imply a rigorous intervention, meaning for instance contact with the prescriber as well as communication with the patient and with a substitution of one of the interacting drugs as an outcome. On the other hand adherent management can imply no action, for example in case of a one day course with fluconazole (coumarins – antimycotics) or in case of starting with fluconazole with a dose lower than 200mg (statins - antimycotics). The same applies to non-adherent interventions. On the one hand we found superfluous interventions, such as a warning to the anticoagulation clinic in case of a one day course of fluconazole combined with a coumarin anticoagulant. On the other hand, we found interventions which could be considered potentially doubtful or even potentially negative concerning patient outcomes. Examples were a temporary stop of digoxin use and a temporary stop of theophylline use. Finally, it has to be emphasized that some

non-adherent interventions made by pharmacies, which were mostly in concordance with the prescriber, were certainly realistic: low dosage of digoxin with relatively young age, rise of serum level assessed as not problematic since the physician was just about to increase the dosage (carbamazepine), substitution of terbinafine tablet by terbinafine creme.

There are several possible reasons for non-adherent management. Although we did not find any associations with prescriber related characteristics described in Table 3, we cannot exclude that the relation with the prescriber might have affected the intervention. Substitution of one of the interacting drugs was only executed in a limited number of cases, even when substitution was the only proposed intervention. Perhaps many pharmacists find substitution of one of the interacting drugs a difficult and time-consuming type of management, because it requires intervention towards the prescribing physician and persuasiveness to convince the physician of the desirability of the substitution. Possible perceived interprofessional barriers have been identified concerning the relationship between community pharmacists and physicians.[19] In a majority of cases, more easily applicable management options were preferred, such as a warning to the anticoagulation clinic, temporary stop of a statin or dose reduction of one of the medicines. Nevertheless, a recent Dutch study revealed that pharmacists and GPs largely agree on the pharmacotherapeutic signalling role that a pharmacist should fulfil.[20] In addition, we observed that in several instances the prescriber (ultimately) decided not to change one of the prescribed medicines, implicitly accepting the described risk. It is an intriguing question whether this is associated with the decision frequently made by physicians to override DDI alerts or with a lack of professional persuasiveness of the pharmacist.[21]

Patient characteristics may contain potential reasons for non-adherence as well, but our finding of a higher probability of non-adherence for some patient variables, such as male gender, high age and polypharmacy (use of more than 7 drugs) is hard to explain. We would have expected more vigilance concerning this drug therapy related problem in elderly patients with a complex pharmacotherapy and being on average at higher risk. Remarkably, however, a similar finding has been reported by Halkin et al., and the same factors have also been found to be influential in several studies concerning other aspects of medical care.[22-25] This phenomenon, that has been described as the treatment-risk paradox or risk-treatment mismatch, needs further exploration, for instance concerning each DDI separately for which too little data were available in this study.[24, 25]

Table 3: DETERMINANTS FOR NON-ADHERENCE OF PHARMACIES TO GUIDELINES AS TO DRUG-DRUG INTERACTIONS

Characteristic	Management to drug-drug interaction guideline:		OR (95% CI)	
	Non-adherent n=187 (100%)	Adherent n=423 (100%)	Crude	Adjusted[a]
Patient related				
gender				
male	117 (62.6%)	192 (45.4%)	**2.05 (1.44 – 2.93)**	**2.25 (1.52-3.31)**
age (yr)				
0–50	22 (11.8%)	73 (17.3%)	1 (reference)	1 (reference)
51–65	55 (29.4%)	136 (32.2%)	1.34 (0.76-2.37)	1.25 (0.67-2.34)
66–75	53 (28.3%)	127 (30.0%)	1.39 (0.78-2.46)	1.24 (0.66-2.33)
>75	56 (29.9%)	85 (20.1%)	**2.19 (1.22-3.92)**	**1.97 (1.03-3.75)**
Drugs in use (n)				
0–4	43 (23.0%)	151 (35.7%)	1 (reference)	1 (reference)
5–7	59 (31.6%)	137 (32.4%)	1.51 (0.96-2.39)	1.51 (0.93-2.45)
>7	80 (42.8%)	124 (29.3%)	**2.27 (1.46-3.52)**	**2.35 (1.46-3.80)**
Prescriber related				
different prescribers for interacting drugs	59 (31.6%)	136 (32.2%)	1.01 (0.69-1.46)	1.00 (0.62-1.61)
prescriptions during different consultations	166 (88.8%)	383 (90.5%)	0.81 (0.46-1.41)	0.78 (0.42-1.45)
latest prescription from other prescriber (mostly specialist), not GP	43 (23.0%)	106 (25.1%)	0.90 (0.60-1.35)	0.77 (0.46-1.30)

Not all values count up to 100% because of missing values
a) Adjusted for all other characteristics.

Last but not least, a clinical guideline itself may give rise to non-adherence, when it is unclear, incomplete or outdated.[1] Although not the focus of our research we would like to suggest further study into the quality of Dutch medication surveillance guidelines. Sometimes, algorithms in the guideline specified risk factors without making sufficiently clear how the presence of these factors could affect the management of the DDI (for instance, in the case of digoxin – macrolides). The working group responsible for these guidelines should better explain the meaning of risk factors and it should also pay more attention to at first sight illogically different management guidelines for DDIs with similar mechanisms (e.g. both interactions with statins). Another problem to be considered is the management of recurrent alerts.

Finally, we would like to underline that further research is warranted on the utilisation of guidelines in daily pharmacy practice, not only those concerning DDIs. Another interesting study question for community pharmacy is a possible variation in individual professional practice, which is seen in medical practice already for many years.[26] The development towards research into quality indicators is an interesting possibility to answer this question as well.[27]

Our study had some limitations. First, the participating pharmacies constituted a voluntary sample, which may have resulted in a positive selection bias concerning the performance of pharmacies. Secondly, it may be possible that some DDI alerts were not selected or reported. Pharmacies were free to extract data every week, send them to the research centre and finally fill in and return the questionnaires. The burden of a high workload as a consequence of participation in this research project and/or in the pharmacy and the holiday season in the Netherlands (several pharmacies mentioned not to participate during certain weeks) resulted in a varied participation of pharmacies (range of one to 17 DDI alerts per pharmacy). In other words, some pharmacies may have affected the results more than others. A certain degree of underreporting is also possible, because over the counter drugs, such as St John's wort, are seldom recorded in Dutch pharmacies and thus will not contribute to DDI alerts. However, overall there is a low risk of underreporting because of a low degree of fragmented prescription filling in the Netherlands.[10] Finally, in this cohort a relatively low occurrence was found for several DDIs, meaning large confidence intervals as to adherence rates.

CONCLUSIONS

The overall adherence to the guideline amounted to 69.3% with large differences between the various drug-drug interactions. Substitution of one of the involved agents, recommended for most of the drug-drug interactions, was only executed in a minority of cases. A substitution, a dose reduction, or a temporary stop of one of the agents as a consequence of the management of a drug-drug interaction, was frequently not consistent with the guidelines. An unexpectedly higher probability for non-adherence to guidelines was found for male gender, the highest age category (>75yr) and the current use of more than seven medications. Although no associations were found between non-adherence and some prescriber related characteristics, the relation between pharmacist and prescriber has been discussed. Further research into underlying reasons is warranted to guide efforts to improve this partly unsatisfactory situation.

Acknowledgements. We would very much like to thank all pharmacists who participated in the study. Special thanks to Mrs Rohini van Exel, pharmacy student, for her support in collecting the data and some preliminary research. Special thanks to PharmaPartners company, especially Mr Eric Hiddink, PharmD, and Mr Martijn Nieuwhof, for their support to start this study and developing a special computer program, enabling each pharmacy to extract and collect automatically the selected drug-drug interactions. Thanks also to Mrs Martine Kruijtbosch, MSc., for her help in developing the database.
A small funding from the PRISMA foundation (Practice Research In Cooperation With Pharmacists) was used to assist in the preparation of this study.

REFERENCES

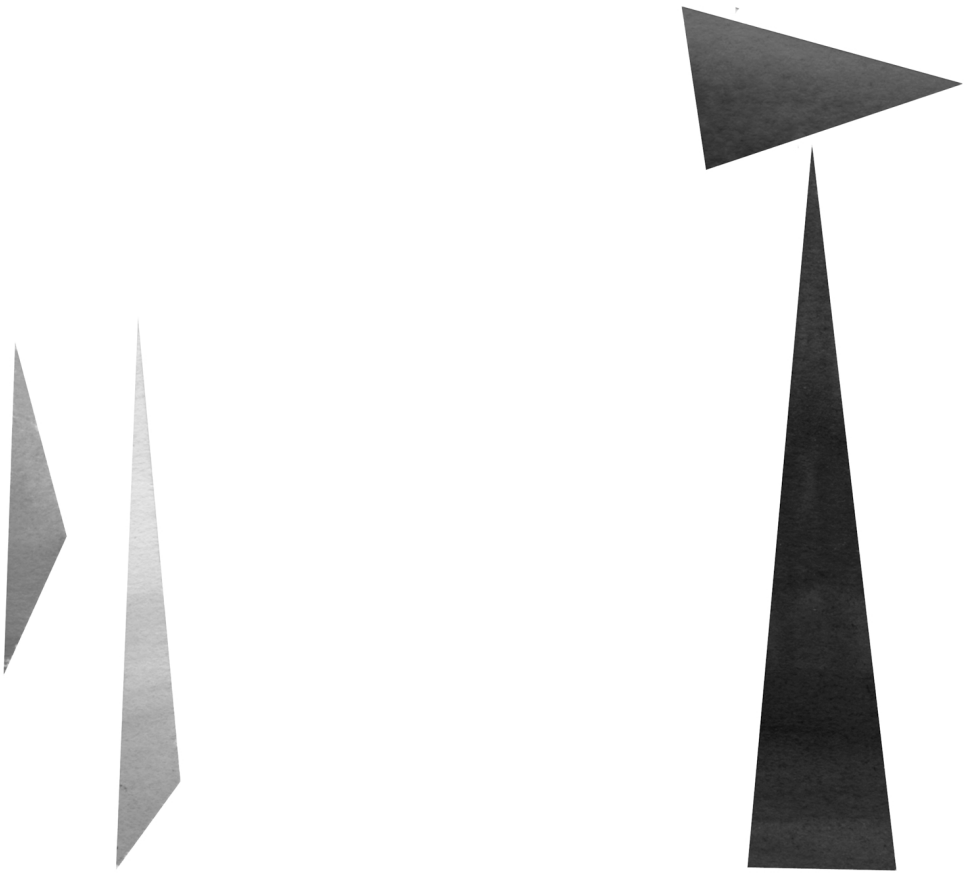
1. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362:1225-30.
2. Sandars J, Esmail A. The frequency and nature of medical error in primary care: understanding the diversity across studies. Fam Pract 2003;20:231-6.
3. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human. Building a safer health system. Washington, DC: National Academy Press; 1999.
4. Singhal PK, Raisch DW, Gupchup GV. The impact of pharmaceutical services in community and ambulatory care settings: evidence and recommendations for future research. Ann Pharmacother 1999;33:1336-55.

5. Buurma H, De Smet PA, Leufkens HG, Egberts AC. Evaluation of the clinical value of pharmacists' modifications of prescription errors. Br J Clin Pharmacol 2004;58:503-11.
6. Jankel CA, Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. Drug Saf 1993;9:51-9.
7. Bouvy ML, Heerdink ER, Hoes AW, Leufkens HG. Effects of NSAIDs on the incidence of hospitalisations for renal dysfunction in users of ACE inhibitors. Drug Saf 2003;26:983-9.
8. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. Jama 2003;289:1652-8.
9. Van Roon EN, Flikweert S, le Comte M, Langendijk PN, Kwee-Zuiderwijk WJ, Smits P, et al. Clinical relevance of drug-drug interactions: a structured assessment procedure. Drug Saf 2005;28:1131-9.
10. Klungel OH, de Boer A, Paes AH, Herings RM, Seidell JC, Bakker A. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in the Netherlands. Pharm World Sci 1999;21:217-20.
11. Misson JC. A review of clinical risk management. J Qual Clin Pract 2001;21:131-4.
12. Madar J. Clinical risk management in newborn and neonatal resuscitation. Semin Fetal Neonatal Med 2005;10:45-61.
13. Commentaren Medicatiebewaking 2004-2005 [*Commentaries medication surveillance*]. Houten, the Netherlands: Health Base; 2004.
14. Merlo J, Liedholm H, Lindblad U, Bjorck-Linne A, Falt J, Lindberg G, et al. Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study. BMJ 2001;323:427-8.
15. Opstelten W, van Essen GA, Moons KG, van Wijck AJ, Schellevis FG, Kalkman CJ, et al. Do herpes zoster patients receive antivirals? A Dutch National Survey in General Practice. Fam Pract 2005;22:523-8.
16. Van Duijn HJ, Kuyvenhoven MM, Schellevis FG, Verheij TJ. Determinants of prescribing of second-choice antibiotics for upper and lower respiratory tract episodes in Dutch general practice. J Antimicrob Chemother 2005;56:420-2.
17. Grimshaw JM, Shirran L, Thomas R, Mowatt G, Fraser C, Bero L, et al. Changing provider behavior: an overview of systematic reviews of interventions. Med Care 2001;39:II2-45.
18. Davis DA, Taylor-Vaisey A. Translating guidelines into practice. A systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. CMAJ 1997;157:408-16.
19. Hughes CM, McCann S. Perceived interprofessional barriers between community pharmacists and general practitioners: a qualitative assessment. Br J Gen Pract 2003;53:600-6.

20. Muijrers PE, Knottnerus JA, Sijbrandij J, Janknegt R, Grol RP. Changing relationships: attitudes and opinions of general practitioners and pharmacists regarding the role of the community pharmacist. Pharm World Sci 2003;25:235-41.
21. Weingart SN, Toth M, Sands DZ, Aronson MD, Davis RB, Phillips RS. Physicians' decisions to override computerized drug alerts in primary care. Arch Intern Med 2003;163:2625-31.
22. Halkin H, Katzir I, Kurman I, Jan J, Malkin BB. Preventing drug interactions by online prescription screening in community pharmacies and medical practices. Clin Pharmacol Ther 2001;69:260-5.
23. Hanlon JT, Schmader KE, Ruby CM, Weinberger M. Suboptimal prescribing in older inpatients and outpatients. J Am Geriatr Soc 2001;49:200-9.
24. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. JAMA 2004;291:1864-70.
25. Lee DS, Tu JV, Juurlink DN, Alter DA, Ko DT, Austin PC, et al. Risk-treatment mismatch in the pharmacotherapy of heart failure. JAMA 2005;294:1240-7.
26. Veninga CC, Lundborg CS, Lagerlov P, Hummers-Pradier E, Denig P, Haaijer-Ruskamp FM. Treatment of uncomplicated urinary tract infections: exploring differences in adherence to guidelines between three European countries. Drug Education Project Group. Ann Pharmacother 2000;34:19-2.
27. Morris CJ, Cantrill JA, Hepler CD, Noyce PR. Preventing drug-related morbidity-determining valid indicators. Int J Qual Health Care 2002;14:183-98.

Chapter 4

THE PATIENT



4.1

Evaluation of the clinical value of pharmacists' modifications of prescription errors

Henk Buurma, Peter AGM de Smet,
Hubert GM Leufkens, Antoine CG Egberts

Br J Clin Pharmacol 2004;58:503-11

ABSTRACT

Aims

Our objective was to examine the clinical value of pharmacists' interventions to correct prescription errors.

Methods

In this study, we reviewed a random sample of prescriptions that had been modified in pharmacies. These prescriptions were collected on one pre-determined day between 25 February and 12 March 1999 from 141 Dutch community pharmacies. Each prescription modification was evaluated by a panel of reviewers, including representatives of five groups of health care professionals. After generally rating each modification as positive, negative, or neutral, the reviewers assessed its outcome (in terms of prevention of an adverse drug reaction (ADR), an improvement in effectiveness, both, or other), the probability and importance of improvements in effectiveness and/or the probability and seriousness of an ADR in the case of a non-intervention. Our analyses included 144 interventions from the first general assessment and a selection of 90 consistently positively rated interventions (from all assessments).

Results

On average, one in 200 prescriptions (0.49%) was found to have been positively modified by Dutch community pharmacists. About half of these interventions (49.8%) were aimed at preventing ADRs; 29.2% were rated as a positive modification in the effectiveness of pharmacotherapy and 8.6% affected both effectiveness and ADR. Reviewers' ratings varied widely between different categories of drug related problems (DRPs). The impact of individual interventions (n=83) varied, and for 53% of these interventions it was estimated to be relatively high.

Conclusions

Pharmacists' interventions led to modification of prescriptions for an array of DRPs. Such interventions can contribute positively to the quality of pharmacotherapy. By extrapolating our data, we estimated a daily occurrence of approximately 2700 positive interventions in all Dutch pharmacies (1.6 per pharmacy per day). Reviewers rated the impact of interventions on a patient's health as significant in a substantial number of cases.

INTRODUCTION

Since the 1990s, a growing awareness of medical and in particular drug related errors[1-3] has led to research of pharmacists' tactics for dealing with these errors. Several, mainly observational, studies describe and, to some extent, support the positive contribution of pharmacists in detecting and reducing the impact of drug related problems (DRPs).[4-9]

In a previous report, we described the frequency, nature and determinants of prescriptions modified by pharmacists that were sampled on one working day from 141 Dutch community pharmacies.[10] We found that the overall incidence of modifications for prescription only medicines (POMs) was 4.9%. The problems could be divided into two main categories: unclear prescriptions (illegible or with omissions) (71.8%) and prescriptions with errors (22.2%). The incidence of POM-related modifications of errors (n=400) was 0.84%, corresponding to an average of 2.8 modifications per pharmacy per day.

The assessment of the actual clinical value of these prescription-error modifications on an individual patient level can be challenging. One would ideally like to compare the outcomes of patients whose pharmacotherapy was modified to those for whom the prescription error was not modified, but of course this would be unethical. An alternative method is the use of multidisciplinary panels consisting of experienced medical and pharmaceutical professionals who judge the clinical value and, in some cases, the humanistic or economic value of the modified prescriptions.[11] Different parameters have been used for this purpose, including estimates of harm, adverse health outcomes of a DRP, evaluations of the intensity of health care needed (such as hospital admission) and finally evaluations of the effectiveness of the patient's therapeutic management.[11-15] Partly based on these studies, we developed a method using a multidisciplinary panel to discriminate between different categories of DRP and different outcomes of prescription modifications to assess the clinical value of pharmacists' interventions.

METHODS

Setting and design

Our previous study was a comparison of modified and non-modified prescriptions that were collected from 141 Dutch community pharmacies on one predetermined day.[10] Of the total 2014 modified prescriptions collected, 400

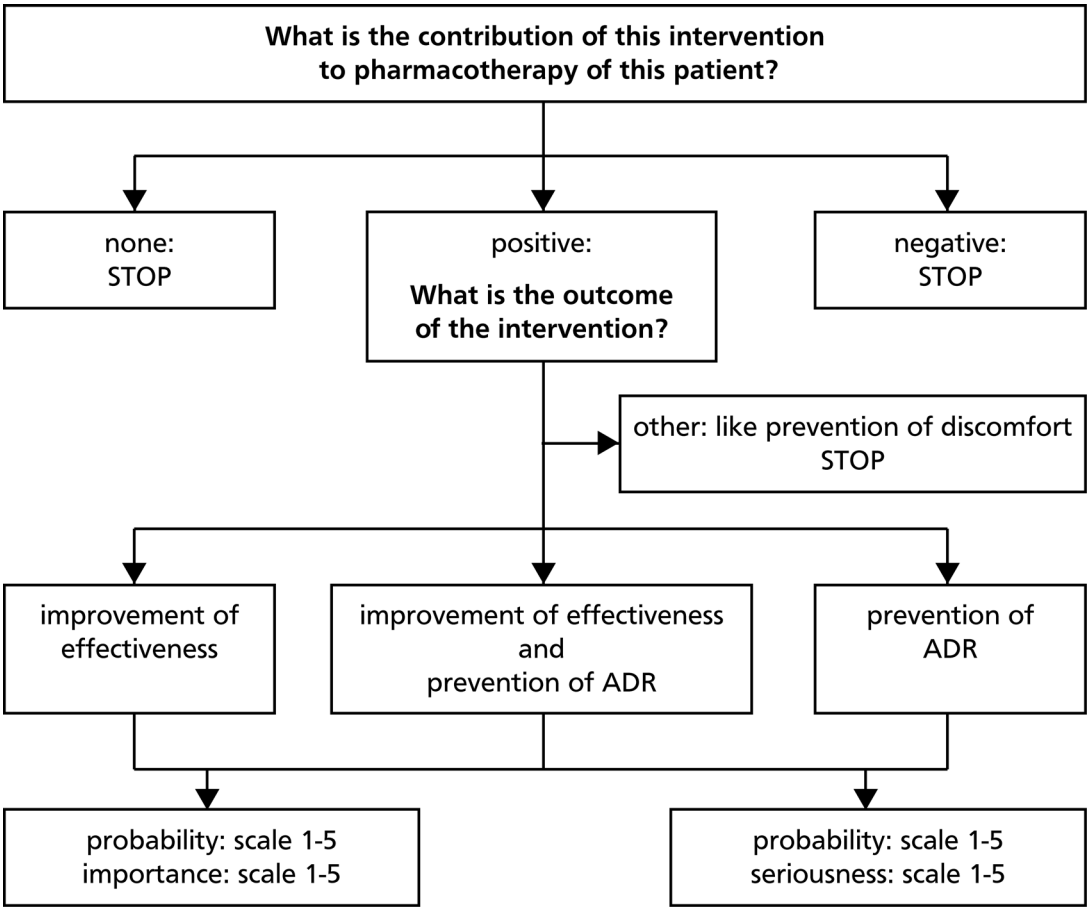
(22.2%) were considered to be corrections for errors related to several potential DRPs, namely wrong dose (n=246), wrong medicine (n=45), wrong patient data (n=42), interaction (n=15), contraindication (n=21), medicine obsolete (n=8), double medication (n=18) and duration of use (n=5). These modifications (or interventions) to prescription errors represent the domain for this study. We excluded 99 interventions because they could not be assessed according to this study methodology, e.g. wrong patient data as reason for intervention, insufficient data available or misclassification.
The majority (n=208; 69.1%) of the selected interventions (n=301) was attributed to wrong-dose interventions. In order to limit the number of cases to be reviewed and reduce the number of similar cases, we randomly selected 52 (25%) wrong-dose interventions. We included all other potentially relevant interventions (n=93), with the exception of one randomly chosen intervention to make the total number of cases an even number.

Assessment of clinical value

Our panel comprised five groups of health care professionals: community pharmacists, hospital pharmacists, general practitioners, specialists for internal diseases, or other non-practising medical/pharmaceutical experts. Each group had four members. All panel members were experts in pharmacotherapy and drug use.
Each reviewer received 72 interventions for evaluation. Twenty-six wrong-dose interventions were randomly assigned to both category A and B and 46 other interventions to both category C and D. Each reviewer received A or B, and C or D. Within each group, the reviewers received another combination (n=4). All reviewers evaluated their cases independently.
On an A4 page we presented an evaluation form and one intervention providing the following information: gender and age of the patient, the drug initially prescribed, type of prescriber, first use or repeat prescription, nature of DRP, person consulted, and the medicine ultimately dispensed. We asked reviewers to provide their opinions based upon their experience as a general practitioner, community pharmacist, or other. Additional guidance was provided concerning the necessity of conscientiously reading the forms, the use of literature, and requesting help or extra information on drug use.
Reviewers had to rate the contribution of each intervention on the pharmaco-therapy of the patient as 'positive, negative or neutral'. In the event of a 'positive' rating, the reviewer had to gauge whether the intervention resulted in an

improvement of effectiveness, prevention of an adverse drug reaction (ADR) or both. Finally, the judged improvement of effectiveness and/or prevention of ADR had to be rated on a five-point scale on two further points: probability and importance or seriousness. The algorithm used by reviewers for rating interventions is presented in Figure 1.

Figure 1: ALGORITHM REPRESENTING THE FLOW OF QUESTIONS FOR RATING INTERVENTIONS



Information on patient's disease status or other relevant clinical or private data (except for the prescription and the patient medication record) was not available, therefore the reviewers had to make the following three assumptions:

- the patient is reasonably normal, for instance, not an alcoholic;

- previous choice of (the combination of) the medicine(s) and its dosing was correct; and
- the patient complies with the text on the label.

A small number of questionnaires were returned to reviewers due to conflicting information and/or ratings.

Data analysis

After inspection, data from the evaluation forms were entered into a Microsoft Access database and statistically analysed using SPSS version 10.

Based upon the rating of the first elementary question as to the contribution of pharmacist's intervention to pharmacotherapy, the interventions that were most consistently rated as 'positive' (n=90), were selected for further analysis. Box 1 provides further information on the selection and exclusion of interventions in this study. The data derived from the selected 144 cases were adjusted for the sampling procedure (n=301).

Box 1: STUDY SELECTION PROCEDURES

1) **400** interventions of pharmacies related to several drug related problems.[10]
   ⇓ Exclusion of 99 interventions because these interventions could not be assessed according to the proposed system in this study: wrong patient data as reason of intervention, insufficient data available, and misclassification.
2) **301** interventions to be examined.
   ⇓ At random exclusion of 156 'wrong dose' interventions and 1 'other' intervention.
3) **144** randomly selected interventions to be examined.
   ⇓ Randomly assignment of 26 'wrong dose'-interventions to both group A and B, 46 'other interventions' to both group C and D. Every reviewer received A or B, and C or D; this means 72 interventions to assess.
   ⇓ 1367 Ratings presented in *Table 1*.
   ⇓ Exclusion of 54 interventions with the following exclusion criteria:
   - One negative rating unless there is just one negative against more than 88% positive ratings or unless there is just one negative and one missing value against all other positive ratings.
   - No negative ratings but two or more 'no contribution' ratings.
4) **90** consistently positively judged interventions.
   ⇓ Number of interventions in different stages of exclusion/inclusion presented in *Table 2*.
   ⇓ 779 Positive ratings presented in *Table 3*: the outcome of the intervention with respect to effectiveness improvement, ADR prevention and other.
   ⇓ 7 Interventions excluded because of insufficient ratings (<4).
5) **83** consistently positively judged interventions.
   ⇓ Visualisation in *Figure 2* of estimated impact per intervention stratified according to categories of DRP.

RESULTS

Nineteen of the 20 reviewers (response rate of 95%) returned our evaluation forms. All groups had participated with four members except for the group of internal medicine specialists (n=3). We received 71 evaluation forms instead of 72 from one internist. This means that every intervention was evaluated by ten or nine reviewers except for one intervention which was assessed by only eight reviewers. The reviewers spent on average 3.8 (1.5–9.0) hours for all 72 interventions, which corresponds with approximately three minutes per intervention. The mean number of interventions for which literature was required was 24 (33.3%). Of all ratings (n=1367), adjusted for sampling, 77.0% was judged positive with regard to the contribution of the intervention to the pharmacotherapy of that patient, including double medication interventions (93.7%), duration of use (89.7%), contraindication (88.0%) and interactions (79.7%) (Table 1). Interventions that were judged to have no or neutral contributions to the quality of the pharmacotherapy comprised 11.8% of the assessments. A relatively small percentage of ratings were negative (adjusted: 8.2%).

Subsequently, 90 interventions that were consistently judged as providing a positive contribution to pharmacotherapy were selected for further analysis (59.1%, after adjustment for sampling) (Table 2). The highest yields were found in the double medication-category and the duration of use-category (93.3% and 100%, respectively).

Table 3 further categorizes reviewers' opinions as to the outcome of the consistently positively rated pharmacy interventions. After adjustment for sampling, positive judgements were related to effectiveness of pharmacotherapy in 29.2% of the cases, 49.8% to ADRs and in 8.6% to both effectiveness and ADRs. Except for the wrong medicine category, prevention of ADRs was considered to be the most important outcome of pharmacist's intervention in all DRP groups. Contraindication interventions were almost exclusively related to ADRs. Wrong medicine interventions were mostly related to effectiveness (34.4%) or to both effectiveness and ADRs (21.6%). In 12.0% of all positive evaluations, there were other reasons judged as positive contributions by the pharmacy: 32.3% concerned prevention of discomfort for the patient, 23.1% prevention of cost and, remarkably, 3.8% prevention of ADR. There were also other reasons (9.2%) and reasons not specified (27.7%) (data not shown).

Table 1: THE RATINGS (n=1367) FOR ALL INTERVENTIONS (n=144) BY ALL REVIEWERS (n=19)

Drug related problem category		Positive contribution	No contribution	Negative contribution	Missed rating
Contraindication	(n= 22; 209 ratings)	184 (88.0%)	18 (8.6%)	6 (2.9%)	1 (0.5%)
Double medication[a]	(n= 15; 142 ratings)	133 (93.7%)	4 (2.8%)	3 (2.1%)	2 (1.4%)
Interaction	(n= 14; 133 ratings)	106 (79.7%)	22 (16.5%)	3 (2.3%)	2 (1.5%)
Duration of use	(n= 3; 29 ratings)	26 (89.7%)	1 (3.4%)	0 (0.0%)	2 (6.9%)
Medicine obsolete	(n= 8; 76 ratings)	55 (72.4%)	17 (22.4%)	1 (1.3%)	3 (3.9%)
Wrong medicine	(n= 30; 284 ratings)	215 (75.7%)	38 (13.4%)	21 (7.4%)	10 (3.5%)
Wrong dose	(n= 52; 494 ratings)	368 (74.5%)	59 (11.9%)	50 (10.1%)	17 (3.4%)
All interventions	(n=144; 1367 ratings)	1087 (79.5%)	159 (11.6%)	84 (6.1%)	37 (2.7%)
All interventions adjusted for sampling	(n=301; 2857 ratings)	2199 (77.0%)	337 (11.8%)	234 (8.2%)	88 (3.1%)

For the selection procedure of the judged interventions see the Methods section and/or Box 1.
a) Double medication is a combination of the same substance or different substances from the same therapeutic group.

Table 2: THE SHIFT OF INTERVENTIONS FROM THE TOTAL GROUP TO THE CONSISTENTLY POSITIVELY RATED GROUP AFTER SAMPLING AND AFTER SELECTION

Drug related problem category	Interventions before sampling	Interventions after sampling	Interventions after selection	Interventions after selection, adjusted
Total	**n=301 (100.0%)**	**n=144 (100.0%)**	**n=90 (100.0%)**	**n=178 (100.0%)**
Contraindication	23 (7.6%)	22 (15.3%)	17 (9.0%)	18 (10.0%)
Double medication[a]	15 (5.0%)	15 (10.4%)	14 (15.5%)	14 (7.9%)
Interaction	14 (4.7%)	14 (9.7%)	9 (10.0%)	9 (5.1%)

Duration of use	3 (1.0%)	3 (2.1%)	3 (3.3%)	3 (1.7%)
Medicine obsolete	8 (2.7%)	8 (5.6%)	3 (3.3%)	3 (1.7%)
Wrong medicine	30 (10.0%)	30 (20.8%)	15 (16.7%)	15 (8.4%)
Wrong dose	208 (69.1%)	52 (36.1%)	29 (32.2%)	116 (65.2%)

Not all data count for 100% because of rounding off.
a) Double medication is a combination of the same substance or different substances from the same therapeutic group.

Table 3: OPINION AS TO THE OUTCOME OF THE CONSISTENTLY POSITIVELY JUDGED PHARMACY INTERVENTIONS (n=90)

		Improvement of effectiveness	Prevention of ADR	Both effectiveness and ADR	Other outcome	Missed ratings
Contraindication	(n= 17; 155 ratings)	1 (0.6%)	143 (92.3%)	4 (2.6%)	7 (4.5%)	0 (0.0%)
Double medication[a]	(n= 14; 126 ratings)	1 (0.8%)	76 (60.3%)	3 (2.4%)	45 (35.7%)	1 (0.8%)
Interaction	(n= 9; 78 ratings)	19 (24.4%)	55 (70.5%)	3 (3.8%)	1 (1.3%)	0 (0.0%)
Duration of use	(n= 3; 26 ratings)	9 (34.6%)	16 (61.5%)	0 (0.0%)	1 (3.8%)	0 (0.0%)
Medicine obsolete	(n= 3; 24 ratings)	7 (29.2%)	14 (58.3%)	1 (4.2%)	2 (8.3%)	0 (0.0%)
Wrong medicine	(n= 15; 125 ratings)	43 (34.4%)	19 (15.2%)	27 (21.6%)	31 (24.8%)	5 (4.0%)
Wrong dose	(n= 29; 245 ratings)	91 (37.1%)	107 (43.7%)	23 (9.4%)	24 (9.8%)	0 (0.0%)
All interventions	(n= 90; 779 ratings)	171 (22.0%)	430 (55.2%)	61 (7.8%)	111 (14.2%)	6 (0.8%)
All interventions adjusted for sampling	(n=301; 1521 ratings)	444 (29.2%)	758 (49.8%)	130 (8.6%)	183 (12.0%)	6 (0.4%)

For the selection procedure of the judged interventions see the Methods section and/or Box 1.
a) Double medication is a combination of the same substance or different substances from the same therapeutic group.

Table 4: SOME EXAMPLES OF INTERVENTIONS PRESENTED IN FIGURE 2

Coordinates[a]	DRP Category	Description of initial prescription	Outcome
3.7 – 4.4	Dosing	Woman; 1962; GP; ethinyl estradiol 1mg; 1dd1; no. 5; first prescription.	GP consulted; Stediril D®; within 12 h two tablets, after 24 h again two tablets.
4.1 – 3.9	Dosing	Woman; 1969; specialist; amoxicillin 500mg; 1dd1; no. 15; first prescription.	Specialist consulted; amoxicillin 500mg; 3dd1; no. 15.
3.5 – 3.6	Dosing	Woman; 1913; GP; isosorbide dinitrate 5mg sublingual; 4-6dd1; repeat prescription.	Communication with patient; one tablet only when needed.
4.0 – 3.7	Contraindication	Woman; 1920; GP; amoxicillin 500mg; 3dd1; first prescription; penicillin intolerance.	Other GP consulted; ofloxacin 200mg.
4.2 – 3.1	Contraindication	Woman; 1923; GP; diclofenac 50mg; 3dd1; diclofenac intolerance.	Assistant GP consulted; tramadol 50mg; 3dd1.
3.8 – 3.8	Duration of use	Man; 1954; GP; itraconazole 100mg; 2dd1; no. 7.	GP consulted; 2dd1; no. 14.
1.9 – 4.3	Interaction	Man; 1943; GP; sildenafil; first prescription; in combination with isosorbide-5-mononitrate retard 50mg and nitroglycerin spray.	GP consulted; not dispensed.
1.8 – 4.6	Interaction	Woman; 1950; GP; erythromycin 500mg; 4dd1; no 30; first prescription; in combination with cisapride.	GP consulted; doxycycline 100mg instead of erythromycin; first day two tablets, then 1dd1.
1.8 – 1.8	Double medication	Woman; 1950; GP; flunitrazepam 1mg; ante noctem 2; stock at home.	Pharmacist consulted; no dispensing.
1.5 – 1.5	Double medication	Woman; 1922; GP; amoxicillin 750mg; 2dd1; first prescription; already in use ofloxacin 1dd1 (urologist).	Consultation assistant GP; no dispensing.
1.0 – 2.0	Obsolete	Woman; 1981; GP; ointment with combination of hydrocortisone and neomycin.	Pharmacist consulted; ointment with combination of hydrocortisone and tetracycline.

GP = **general practitioner**
a) Probability score – importance/seriousness score

The wrong medicine group (24.8%) and the double medication group (35.7%) yielded relatively high scores in this category of other reasons.
The impact of an intervention can be described as the product of the probability and seriousness of an ADR or as the product of the probability and importance of effectiveness improvement. In Figure 2, average ratings of these products per intervention are presented. This analysis could be made for only 83 interventions (92.2%) because of insufficient (less than four) ratings for seven interventions. Most interventions (47%) are situated in the left lower quadrant C followed by the right upper quadrant B (27.7%). The left upper quadrant A (14.5%) shows some interventions with very high scores for importance/seriousness concerning two interactions and one duration of use intervention. Of the interaction interventions 50% (4 out of 8) belong to this quadrant. The fewest interventions were found in the right lower quadrant D (10.8%), but all scores are quite close to the level of 50% importance/seriousness. Some examples of the interventions shown in Figure 2 are described in Table 4.

DISCUSSION

Our study reports an incidence of 0.49% for prescription modifications by Dutch community pharmacists, which were consistently rated as positive by our expert review panel. This incidence would translate to about 1.6 interventions per pharmacy per day, or approximately 2700 in all Dutch pharmacies on one day. These interventions by pharmacists were not exclusively aimed at the prevention of ADRs (49.8%), but also at effectiveness of pharmacotherapy (29.2%) and both (8.6%). We found large differences with respect to judgements of interventions in different groups of DRPs. The impact of individual interventions (n=83), as perceived by the panel, varied greatly. For 53% of these interventions this impact was estimated as relatively high.
The incidence is comparable to those reported in other studies. In a UK-based study by Hawksworth et al., 49.8% of interventions were judged positively by a multidisciplinary but unspecified panel of reviewers, which corresponds to an incidence of 0.37% positively valued interventions.[12] In a US-based study using only three reviewers, Rupp revealed that 28.3% of the identified problems could have resulted in patient harm, implying toxic or side-effects, hypersensitivity and poor disease control, corresponding to an incidence of 0.54%.[13] The panel in Hawksworth's study related 48.7% of the interventions to improvement of

effectiveness and 64.6% to harm prevention, presumably meaning that 13.3% were related to both.[12] In an Australian study, 41.0% of the pharmacy interventions were associated to a toxic or side-effect outcome, followed by 33.5% for inadequate control of the patient's condition.[14] Unlike these studies, we were also able to investigate different groups of DRPs and to estimate the impact of individual interventions.

Figure 2 presents the variation of the impact between individual interventions of pharmacies, as estimated by our panel. The real impact of pharmacists' (non-)interventions concerning different categories of DRPs has to be studied in other settings; for instance, by linking data concerning hospital admissions to confirmed DRPs, such as dosing problems or obsolete medicine. Juurlink et al. found that hospital admissions were associated with previous drug-drug interactions.[15] The variation of the estimated impact between individual interventions of pharmacies can be described as: the higher the probability rating for an intervention, the higher its importance, or seriousness, rating. There were just a few extreme results regarding assessment of the impact of the recorded interventions, which may be explained by the fact that average data were used (i.e. regression to the mean in most cases).

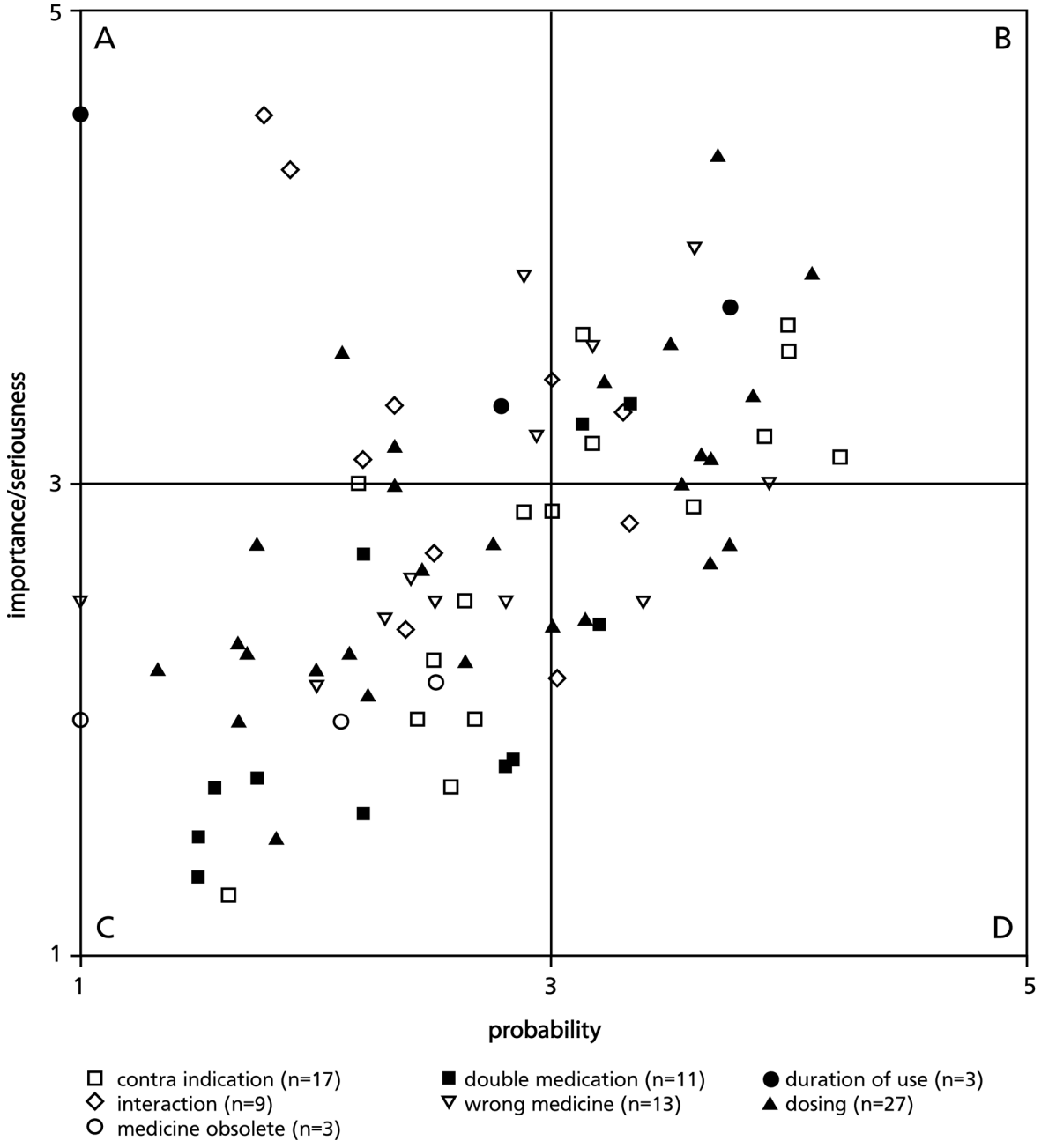
We found some interesting differences between the different DRP categories. The variety between the dosing problem interventions can be specified by the highest yield of negative judgements found in this group on the one hand (10.1%; Table 1), while on the other hand, 28.8% of these interventions received a relatively high impact score (quadrants A, B, and D in Figure 2). The dosing problems did not only concern overdoses or wrong doses, but also underdose as can be seen in Table 4.

Drug-drug interactions (DDIs) are generally well defined, i.e. most of the interventions are more or less well documented in literature.[16-18] In this study, DDIs were not all selected for the group of consistently positively estimated interventions (Table 2). Although there was only a low yield of negative opinions (2.3%) there was a considerable share of neutral judgements (16.5%) (Table 1). Most of the consistently positively judged DDI interventions were found in the left upper quadrant A in Figure 2. This illustrates a relatively low probability but a high (and in some instances very high) importance/seriousness score. Likewise, by linking hospital admissions to previous DDIs, Juurlink et al. recently demonstrated the high seriousness factor related to DDIs.[15]

For many of the contraindication interventions reviewers were strongly cautious (Table 2). More than 41% (seven out of 17) of the contraindication interventions

shown in Figure 2 were located in the right upper quadrant B, meaning a relatively high probability score and a high seriousness score (e.g. penicillin allergy).

Figure 2: THE AVERAGE ESTIMATED IMPACT OF 83 INTERVENTIONS



A large contingent of ratings in the double medication group (35.7%) was not directly related to health issues such as ADR and effectiveness, but to prevention of discomfort and prevention of cost. The double medication issue was clearly interpreted as unpleasant for the patient, but apparently was not perceived as an immediate threat to the health status of the patient. This is illustrated by several individual cases in Figure 2. On the other hand, the duration of use interventions (n=3) were highly estimated and mainly related to effectiveness improvement and prevention of ADR.

Despite the strong development of evidence-based medicine during the last two decades, this study shows that interventions of pharmacists with respect to obsolete medicines were not highly estimated - a large number of exclusions (Table 2) and a relatively low impact score (Figure 2). An explanation may be found in the fact that the most important obsolete medicines have already been withdrawn from the (Dutch) market. Interventions for wrong medicine showed a rather diffuse picture.

A number of limitations to this study should not be ignored. It should be noted that the presented incidence rates of modifications and consistently positively judged modifications in Dutch community pharmacies correspond to only a segment of community pharmacy interventions. For instance, we did not analyse modifications in the regimens of already used medicines, which may be the outcome of the same signal as, for example, a DDI. Furthermore, other interventions may have taken place without leading to a modification but to advice concerning proper use of the drug or a combination of drugs. There are also a few restrictions when comparing our results to the studies mentioned above. Hawksworth et al., for instance, had a broader definition of intervention, which included enquiries by the pharmacist about the dose or the dose interval, recommendations concerning the monitoring of blood plasma parameters, and discussions with the prescriber about a patient's pharmacotherapy.[12]

A large group of reviewers from different professional backgrounds was recruited to comply with the requirements based upon the literature[11] and our group of reviewers was favourable to the above-mentioned studies.[12-14] For some questions, we investigated the inter-rater differences by using the kappa value,[19] although we initially expected relatively low values based upon the literature.[11,14] For our second question concerning the 90 selected interventions, the overall kappa value was moderate (0.49) with differences between the reviewer categories of 0.35 (general practitioners) to 0.58 (hospital pharmacists). For a combination of

question one and two (n=90), we found an overall kappa value of 0.40 and differences between the reviewer categories of 0.19 (internists) to 0.52 (non-practising specialists).

Although the kappa value is the most preferable variable in describing inter-rater differences, the problem is that even in a simple situation with two categories, the same proportional agreement can lead to markedly different kappa values.[20] The higher the prevalence in one category (as in our case: positive judgement in question one, especially regarding the 90 selected cases), the higher the proportion of units for which agreement is expected by chance. Another important difficulty in the interpretation of these values occurs when several variables and subvariables are involved, as in our study.[14,20] Perhaps more meaningful data are derived when the proportion of agreement overall and between the reviewer categories are considered. For instance, the mean percentage of positive evaluations (question 1, n=90) was overall 93.5% (variance=0.6%) with differences between the reviewer categories of 89.3% (variance=5.9%; internists) to 97.8% (variance=1.1%; non-practising professionals).

Our very strict second selection after the first general question excluding 54 interventions (out of 144) does not mean that the excluded interventions were overall poorly rated. We would like to emphasize that 18 (33.3%) of these exclusions received a 70-80% positive score. Furthermore, there were no interventions with 100% negative and/or neutral ratings. Only a small group of 10 interventions (6.9%) received less than 50% positive ratings, of which four received no negative ratings but especially 'neutral' ratings. We found three interventions that received more negative ratings than positive ones.

In conclusion, part of pharmacists' interventions included modifying prescriptions for an array of DRPs. A large panel of medico-pharmaceutical professionals consistently positively judged almost 60% of these modifications. According to this panel, at least 1.6 such interventions per pharmacy per day can contribute positively to patients' quality of pharmacotherapy. By extrapolating our data to all pharmacies in the Netherlands, this corresponds to approximately 2700 positive interventions in all Dutch pharmacies on one day. Community pharmacists may not only have avoided adverse drug reactions but also improved the effectiveness of pharmacotherapy. According to the expert panel, the impact of an intervention on patient's health was likely to be significant in a substantial number of cases.

Acknowledgements. We would very much like to thank all 19 medical and pharmaceutical professionals who evaluated the interventions. Likewise, we like to thank the pharmacists who participated in the study, Mrs Martine Kruijtbosch for her help in analysing the data and Mrs Svetlana Belitser for her help in calculating kappa values.

REFERENCES

1. Weingart SN, Wilson RMcL, Gibberd RW, Harrison B. Epidemiology of medical error. BMJ 2000;320:774-7.
2. Gandhi TK, Seger DL, Bates DW. Identifying drug safety issues: from research to practice. Int J Qual Health Care 2000;12:69-76.
3. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human. Building a safer health system. Washington, DC: National Academy Press; 1999.
4. Westerlund LOT, Marklund BR, Handl WHA, Thunberg ME, Allebeck P. Non-prescription drug-related problems and pharmacy interventions. Ann Pharmacother 2001;35:1343-9.
5. Boyko WL, Yurkowski PJ, Ivey MF, Armistead JA, Roberts BL. Pharmacist influence on economic and morbidity outcomes in a tertiary care teaching hospital. Am J Health-Syst Pharm 1997;54:1591-5.
6. Bouvy ML, Buurma H, Egberts TC. Laxative prescribing in relation to opioid use and the influence of pharmacy-based intervention. J Clin Pharm Ther 2002;27:107-10.
7. Beney J, Bero LA, Bond C. Expanding the roles of outpatient pharmacists: effects on health services utilisation, costs, and patient outcomes. Cochrane Database Syst Rev 2000;3:CD000336.
8. Singhal PK, Raisch DW, Gupchup GV. The impact of pharmaceutical services in community and ambulatory care settings: evidence and recommendations for future research. Ann Pharmacother 1999;33:1336-55.
9. Tully MP, Seston EM. Impact of pharmacists providing a prescription review and monitoring in ambulatory care or community practice. Ann Pharmacother 2000;34:1320-31.
10. Buurma H, De Smet PAGM, van den Hoff OP, Egberts ACG. Nature, frequency and determinants of prescription modifications in Dutch community pharmacies. Br J Clin Pharmacol 2001;52:85-91.
11. Wright DJ, Aykroyd RG, Chrystyn H. Rating clinical pharmacy interventions by clinical panels: which health professionals should be included? Br J Clin Pharmacol 1998;46:278P.
12. Hawksworth GM, Corlett AJ, Wright DJ, Chrystyn H. Clinical pharmacy interventions by community pharmacists during the dispensing process. Br J Clin Pharmacol 1999;47:695-700.

13. Rupp MT. Value of community pharmacists' interventions to correct prescribing errors. Ann Pharmacother 1992;26: 1580-4.
14. Caleo S, Benrimoj SI, Collins D, Lauchlan R, Stewart K. Clinical evaluation of community pharmacists' interventions. Int J Pharm Pract 1996;4:221-7.
15. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA 2003;289:1652-8.
16. Hansten PD, Horn JR. Drug interactions analysis and management. St. Louis, Missouri: Facts and comparisons; 2002.
17. Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum M. Metabolic drug interactions. Philadelphia: Lippincott Williams & Wilkins; 2000.
18. Stockley IH. Drug Interactions, 6th ed. London: The pharmaceutical press; 2002.
19. Fleiss. JL. Measuring nominal scale agreement among many raters. Psychol Bull 1971;76:378-82.
20. Altman DG. Practical statistics for medical research. London: Chapman and Hall; 1995.

4.2

Pharmacy shopping: determinants and the relation with heavy use of psychotropic drugs

Henk Buurma, Marcel L Bouvy, Annemieke Floor-Schreudering,
Peter AGM de Smet, Antoine CG Egberts

ABSTRACT

Aims

Discontinuity of care bears the risk of medication errors and poor clinical outcomes. Little is known about continuity of care related to pharmacies. The objective was to explore the prevalence and determinants of pharmacy shopping behaviour and, in addition, the association between shopping behaviour and heavy use of psychotropic drugs.

Methods

All beneficiaries from a Dutch health insurance pharmacy claims database who had visited two or more pharmacies in 2001 were indicated as 'shoppers' (n=45 805). A random sample was taken from all other beneficiaries who had received at least one prescription and these were indicated as 'non shoppers' (n=45 805). Shoppers were classified into three mutually exclusive categories (light, moderate, heavy). Gender, age, number of different type of prescribers, and number of different drugs dispensed, were investigated as determinants of shopping behaviour. We investigated the association between the use of any dispensing of ATC classes of drugs in 2001 and shopping behaviour. The association between shopping behaviour and the heavy use of (a combination of) categories of psychotropic drugs (hypnotics and anxiolytics, antidepressants, antipsychotics, and opioids) was examined. Heavy use was defined as the use of more than 365 Defined Daily Doses dispensed in 2001.

Results

Of all beneficiaries 10.8% were identified as shoppers, of which the vast majority (98.8%) could be described as 'light shoppers' and a small minority (0.2%) as 'heavy shoppers'. Female gender (OR_{adj} 1.2; 95%CI 1.1-1.2), younger age (≤40 yr) (OR_{adj} 1.7; 95%CI 1.7-1.8), the use of three or more different drugs (OR_{adj} 2.9; 95%CI 2.8-3.0) and visiting different kind of prescribers (OR_{adj} 2.4; 95%CI 2.4-2.5) were associated with shopping behaviour. Shoppers more frequently received at least one prescription for systemic anti-infectives (51.7% vs. 30.8%) and for nervous system drugs (46.2% vs. 29.3%). There was a clear association between the degree of shopping behaviour and heavy use of one or more categories of the psychotropic drugs. For example, between heavy shopping behaviour and the heavy use of hypnotics and anxiolytics (OR_{adj} 17.3; 95%CI 10.4-28.9), and the heavy use of opioids (OR_{adj} 19.4; 95%CI 4.3-87.8).

Conclusions

Pharmacy shopping behaviour is still limited in the Netherlands. However, it may put the patient at risk for unintentional problems, such as drug-drug interactions with systemic antibiotics and antimycotics. A relatively small proportion of patients exhibit possibly intentional shopping behaviour with psychotropic drugs, in particular related to the heavy use of hypnotics and anxiolytics. Linking pharmacy computer systems will signal and hopefully prevent most problems related to pharmacy shopping behaviour. Communicating with the patient may already reduce unintentional problems.

INTRODUCTION

Transition of patients across health care settings (e.g. from hospital to long-term care, from hospital to primary care or vice versa) as well as physician shopping (among others defined as the use of a second physician without referral from the first for a single episode of illness) have been associated with discontinuity of care.[1] Discontinuity of care bears the risk of medication errors and poor clinical outcomes.[2-5] Conversely, continuity of care has been associated in most but not all studies with improved preventive care, reduced hospitalization and lower costs.[2,3,6-14]

Continuity of care has been addressed especially from the perspective of general medical practice.[15] Little is still known about the relation between continuity of care from a community pharmacy perspective and clinical outcomes. Some studies have described pharmacists' provision of continuity of care for special groups of patients (e.g. HIV patients) or the provision of structures that support continuity of care across health care settings (e.g. transfer of information about drug use).[16-20] Discontinuity of pharmacy care may put the patient at risk for drug therapy related problems, since pharmacy shopping hampers adequate medication surveillance. Examples of such unintentional problems include unwanted duplicate medications, drug-disease interactions, drug intolerabilities (including allergies) and drug-drug interactions, but also conflicting information about drug use from different pharmacies, confusion between brand and generic names and incorrect quantities.[5,21] Medicine users may also intentionally visit different pharmacies because of certain drug related problems, such as heavy use and addiction. Prescription claims from more than five pharmacies in one quarter of a year have been reported as indicators of potential abuse or misuse of prescription drugs.[22]

As continuity of pharmacy care can be considered an important prerequisite for the clinical risk management of drug therapy related problems, we studied the prevalence and determinants of pharmacy shopping behaviour. Since physician shopping, in some instances described as prescription shopping, has been mainly associated with the heavy use of benzodiazepines and opioids, we additionally aimed to describe the association between pharmacy shopping behaviour and heavy use of psychotropic drugs.[23,24]

METHODS

Setting, study population and data collection

Data were obtained from the pharmacy claims database of a Dutch health insurance company ('O.W.M. Zorgverzekeraar Zorg en Zekerheid u.a.') concerning the year 2001. This health insurance company mainly proceeds in the western region between The Hague and Amsterdam, and can be described as relatively small (on average 448 392 beneficiaries in 2001).

The data obtained were related to the beneficiaries who were insured under the Social Health Insurance Act comprising all employees earning less than about 33 000 Euro per year, social security recipients and certain old-age groups. In 2001, about 65% of the Dutch population was insured under this law, against 94.8% (on average 425 061) within this insurance company.

Of all Social Health Insurance Act beneficiaries, 338 423 (79.6%) had at least one pharmacy claim during 2001. Of these, all patients visiting[a] two or more pharmacies in 2001 – thus having received at least two prescriptions in 2001 – were identified from the pharmacy claims database (n=45 805). These patients, with a certain degree of discontinuity of pharmacy care, were indicated as 'shoppers'. From all other beneficiaries who received at least one prescription and visited only one pharmacy during 2001, a random, numerically equivalent, sample was taken (n=45 805). These patients were indicated as 'non shoppers'.

For shoppers as well as non shoppers, data were obtained comprising age and gender. For each patient a medication history was collected covering information about all dispensed and (partially) reimbursed drugs during 2001, such as name, Anatomical Therapeutic Chemical (ATC) code, date of dispensing, dispensed amount, dosage regimen, type of prescriber, and the community pharmacy (anonymous, unique code) where the drug had been dispensed.

Classification of data

Determinants of pharmacy shopping behaviour

Although several measurement techniques have been used in the literature to define and study (dis)continuity of care, especially in general medical practice, we used a method tailored to the pharmacy setting.[6,15] Shoppers were classified into three mutually exclusive categories based upon (a) the number of visits to one or more pharmacies other than the main dispensing pharmacy (='elsewhere'), (b)

[a] This means that a visit was made to a pharmacy concluded by a dispensing and a pharmacy claim to the health insurance company based upon the dispensing.

the proportion of prescriptions dispensed in pharmacies elsewhere, and (c) the total number of prescriptions dispensed in pharmacies elsewhere (Table 1). Several characteristics were investigated as determinants of shopping behaviour: gender, age (four categories: 0-25; 26-40; 41-60; >60), the number of different type of prescribers (general practitioner (GP), specialist or other), and the number of different drugs (active substances) dispensed in 2001 (based upon ATC code-level 7; three categories: 0-2; 3-5; >5). In addition, we studied whether any dispensing in 2001 of the therapeutic groups of drugs in accordance with the ATC classification of the WHO Collaborating Centre for Drug Statistics Methodology (level 1), as well as subclasses of the Nervous System drugs (N category), was associated with shopping behaviour.

Table 1: CLASSIFICATION OF SHOPPING BEHAVIOUR

Description	Definition[a]	Number	(% of all shoppers)
Non shopper	patients who visited only one pharmacy	45 805	-
Light shopper	all patients who visited more than one pharmacy at least once, except for patients defined as heavy or moderate shoppers	45 252	98.8%
Moderate shopper	- number of pharmacies visited 3 or 4 AND - proportion of prescriptions elsewhere >10% AND - number of prescriptions elsewhere >10	458	1.0%
Heavy shopper	- number of pharmacies visited ≥5 AND - proportion of prescriptions elsewhere >10% AND - number of prescriptions elsewhere >10	95	0.2%

a) 'visited' means that a visit was made to a pharmacy concluded by a dispensing and a pharmacy claim to the health insurance company based upon the dispensing (see the method section).

Shopping behaviour and heavy use of psychotropic drugs

Partly based upon literature and based upon data analysed and presented in this study concerning the association between any dispensing of an ATC-group and shopping behaviour, we examined the association between shopping behaviour and the heavy use of specific psychotropic drugs.[23,24] Psychotropics comprised hypnotics and anxiolytics (including all benzodiazepine hypnotics and anxiolytics as well as zolpidem, zopiclon, chloral hydrate, buspiron and hydroxyzine; excluding clonazepam), antidepressants, antipsychotics (excluding lithium salts and prochlorperazine) and opioids (excluding codeine). Clonazepam was

excluded from analyses because it is mainly prescribed for epilepsy and restless legs. The relation between shopping behaviour and heavy use of more than one category of psychotropic drugs (hypnotics and anxiolytics, antidepressants, antipsychotics, and opioids) was investigated as well. Heavy use was defined as the use of more than 365 Defined Daily Doses (DDDs) dispensed in 2001, implying an average use of more than one DDD per day.

Data analysis

Data were analysed using standard descriptive data analysis (SPSS version 12.0). Logistic regression analysis was used to estimate the strength of the association between characteristics and pharmacy shopping behaviour and of the association between pharmacy shopping behaviour and the heavy use of several psychotropic drugs and expressed as odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

Shopping behaviour

Of the Social Health Insurance Act beneficiaries of the health insurance company (on average n=425 061 in 2001), a total number of 45 805 patients (10.8%) were identified who had visited more than one pharmacy in 2001 on at least one occasion (Table 1). Of these, the vast majority (98.8%) could be described as 'light shoppers'. Most of these 'shopping' patients (86.4%) visited only one other pharmacy, 11.2% visited two and 2.4% three or more other pharmacies. Within the group of patients visiting only one other pharmacy, 63.4% visited the second pharmacy only once (data not shown). A small minority (0.2%) of the shoppers was classified as 'heavy shoppers'.

Table 2 shows the characteristics of the study population. Comparing all shoppers with non shoppers and adjusted for all included variables, female gender (OR_{adj} 1.2; 95%CI 1.1-1.2), younger age (≤40 yr) (OR_{adj} 1.7; 95%CI 1.7-1.8), the use of three or more different drugs (OR_{adj} 2.9; 95%CI 2.8-3.0) and different kind of prescribers (OR_{adj} 2.4; 95%CI 2.4-2.5) were associated with shopping behaviour.

Shoppers received more frequently at least one prescription for systemic anti-infectives (51.7% vs. 30.8%; OR 2.4; 95%CI 2.3-2.5) and for nervous system drugs (46.2% vs. 29.3%; OR 2.1; 95%CI 2.0-2.1) than non shoppers (Table 3). For the other ATC classes the differences were less clear. We especially found a strong association between any dispensing of nervous system drugs and heavy shopping (OR 16.7; 95%CI 9.1-30.5) as well as between any dispensing of

nervous system drugs and moderate shopping (OR 20.1; 95%CI 14.9-27.1). To some extent similar associations were also found for selected psychotropics, i.e. hypnotics and anxiolytics, antidepressants, antipsychotics and opioids.

Shopping behaviour and its relation with heavy use of psychotropic drugs

In the group of patients with any form of shopping behaviour, the prevalence of heavy use of hypnotics and anxiolytics was 2.8% compared to 1.4% in non shoppers (Table 4). The prevalence values concerning the heavy use of antidepressants were 2.6% and 1.2%, respectively. The prevalence of heavy use of antipsychotics was found to be relatively low both in non shoppers (0.2%) and in shoppers (0.3%). A low prevalence of heavy use was also found in the group of opioid users: 0.04% (non shoppers) versus 0.2% (shoppers).

Although the absolute prevalence of heavy use of the selected psychotropics was low, there was a clear association between the degree of shopping behaviour and heavy use of various psychotropic drugs. The association between heavy shopping behaviour and the heavy use of hypnotics and anxiolytics was OR_{adj} 17.3; 95%CI 10.4-28.9. A strong association was revealed between moderate and heavy shopping behaviour respectively and heavy use of opioids (OR_{adj} 14.9; 95%CI 7.0-31.7 and 19.4; 95%CI 4.3-87.8, respectively). Lower risks were found concerning the association between moderate shopping behaviour and heavy use of hypnotics and anxiolytics, moderate shopping behaviour or heavy shopping behaviour and heavy use antidepressants or antipsychotics.

In Table 5, patients with heavy use of either hypnotics and anxiolytics, antidepressants, antipsychotics or opioids (n=3507) are presented. Of this group 412 (11.7%) were overusing a combination of two or three of these groups of psychotropics. There was a clear association between the degree of shopping behaviour and heavy use of more than one category of these psychotropic drugs. For example, within the group of heavy shoppers 41.1% had heavy use of at least one of the defined categories of psychotropic drugs, whereas this was 2.5% in the group of non shoppers. After adjustment for all variables, the association between heavy shopping behaviour and the heavy use of two or three groups of psychotropic drugs was OR_{adj} 14.8; 95%CI 7.1-31.1, concerning moderate shopping behaviour it was OR_{adj} 7.4; 95%CI 4.7-11.8.

Table 2: CHARACTERISTICS OF THE STUDY POPULATION (n=91 610)

Characteristic	Number of patients (medicine users)			
	Non shoppers n=45 805 (100%)	Light shoppers n=45 252 (100%)	Moderate shoppers n=458 (100%)	Heavy shoppers n=95 (100%)
Female gender	28 116 (61.4%)	30 272 (66.9%)	322 (70.3%)	62 (65.3%)
Age (yr)				
mean (sd)	*41.8 (22.0)*	*41.1 (21.9)*	*57.6 (21.2)*	*39.6 (17.9)*
0–25	11 333 (24.7%)	10 803 (23.9%)	36 (7.9%)	18 (18.9%)
26–40	12 042 (26.3%)	14 362 (31.7%)	79 (17.2%)	40 (42.1%)
41–60	12 051 (26.3%)	10 543 (23.3%)	131 (28.6%)	25 (26.3%)
>60	10 379 (22.7%)	9 544 (21.1%)	212 (46.3%)	12 (12.6%)
Different type of prescribers (n)				
1	33 563 (73.3%)	21 431 (47.4%)	81 (17.7%)	16 (16.8%)
2	11 070 (24.2%)	19 835 (43.8%)	259 (56.6%)	46 (48.4%)
>2	1 172 (2.6%)	3 986 (8.8%)	118 (25.8%)	33 (34.7%)
Different drugs[a] (n)				
0–2	21 550 (47.0%)	9 444 (20.9%)	2 (0.4%)	4 (4.2%)
3–5	14 112 (30.8%)	16 973 (37.5%)	22 (4.8%)	14 (14.7%)
>5	10 143 (22.1%)	18 835 (41.6%)	434 (94.8%)	77 (81.1%)
Dispensed prescriptions (n)				
1–2	14 348 (31.3%)	3 161 (7.0%)	0 (0.0%)	0 (0.0%)
3–5	10 787 (23.5%)	10 747 (23.7%)	0 (0.0%)	0 (0.0%)
6–9	6 887 (15.0%)	9 138 (20.2%)	0 (0.0%)	0 (0.0%)
10–20	7 650 (16.7%)	11 105 (24.5%)	5 (1.1%)	7 (7.4%)
>20	6 133 (13.4%)	11 101 (24.5%)	453 (98.9%)	88 (92.6%)

a) active substances

Table 3: ASSOCIATION BETWEEN ANY DISPENSING OF GROUPS OF MEDICINES AND SHOPPING BEHAVIOUR

Group of medicines	Non shoppers n=45 805 (100%)	Light shoppers n=45 252 (100%)	Moderate shoppers n=458 (100%)	Heavy shoppers n=95 (100%)
Any dispensing of ATC-group				
Alimentary tract and metabolism (A)	10 787 (23.5%)	15 803 (34.9%)	329 (71.8%)	45 (47.4%)
Cardiovascular system (C)	9 939 (21.7%)	11 483 (25.4%)	268 (58.5%)	29 (30.5%)
Dermatologicals (D)	13 333 (29.1%)	17 050 (37.7%)	252 (55.0%)	45 (47.4%)
Genital-urinary system and sex hormones (G)	12 990 (28.4%)	16 831 (37.2%)	139 (30.3%)	40 (42.1%)
General anti-infectives for systemic use (J)	14 102 (30.8%)	23 330 (51.6%)	287 (62.7%)	60 (63.2%)
Musculoskeletal system (M)	11 988 (26.2%)	17 366 (38.4%)	220 (48.0%)	46 (48.4%)
Nervous system (N)	13 440 (29.3%)	20 690 (45.7%)	409 (89.3%)	83 (87.4%)
Respiratory system (R)	11 866 (25.9%)	16 160 (35.7%)	244 (53.3%)	55 (57.9%)
Any dispensing of specific psychotropic drugs				
Hypnotics and anxiolytics[a]	7 393 (16.1%)	12 156 (26.9%)	330 (72.1%)	72 (75.8%)
Antidepressants	2 968 (6.5%)	5 404 (11.9%)	165 (36.0%)	49 (51.6%)
Antipsychotics[b]	668 (1.5%)	1 446 (3.2%)	66 (14.4%)	23 (24.2%)
Opioids[c]	909 (2.0%)	2 669 (5.9%)	118 (25.8%)	22 (23.2%)

a) excluding clonazepam
b) excluding lithium and prochlorperazine
c) excluding codeine

Table 4: ASSOCIATION BETWEEN SHOPPING BEHAVIOUR AND HEAVY USE OF SELECTED PSYCHOTROPIC DRUGS

Category		No and normal use	Heavy use	OR (95%)	
		n (%)	n (%)	Crude	Adjusted[a]
Hypnotics and anxiolytics					
non shopper	n=45 805 (100%)	45 179 (98.6%)	626 (1.4%)	1 (reference)	1 (reference)
light shopper	n=45 252 (100%)	44 070 (97.4%)	1 182 (2.6%)	1.9 (1.8– 2.1)	1.4 (1.2– 1.5)
moderate shopper	n=458 (100%)	377 (82.3%)	81 (17.7%)	15.5 (12.0– 20.0)	4.7 (3.6– 6.1)
heavy shopper	n=95 (100%)	69 (72.6%)	26 (27.4%)	27.2 (17.2– 43.0)	17.3 (10.4–28.9)
Antidepressants					
non shopper	n=45 805 (100%)	45 266 (98.8%)	539 (1.2%)	1 (reference)	1 (reference)
light shopper	n=45 252 (100%)	44 141 (97.5%)	1 111 (2.5%)	2.1 (1.9– 2.3)	1.4 (1.2– 1.5)
moderate shopper	n=458 (100%)	415 (90.6%)	43 (9.4%)	8.7 (6.3– 12.0)	3.3 (2.4– 4.7)
heavy shopper	n=95 (100%)	76 (80.0%)	19 (20.0%)	21.0 (12.6– 35.0)	7.9 (4.7–13.4)
Antipsychotics					
non shopper	n=45 805 (100%)	45 735 (99.8%)	70 (0.2%)	1 (reference)	1 (reference)
light shopper	n=45 252 (100%)	45 127 (99.7%)	125 (0.3%)	1.8 (1.4– 2.4)	1.1 (0.8– 1.6)
moderate shopper	n=458 (100%)	451 (98.5%)	7 (1.5%)	10.1 (4.6– 22.2)	4.2 (1.8– 9.5)
heavy shopper	n=95 (100%)	93 (97.9%)	2 (2.1%)	14.1 (3.4– 58.1)	4.0 (0.9–17.2)
Opioids					
non shopper	n=45 805 (100%)	45 787 (100.0%)	18 (0.04%)	1 (reference)	1 (reference)
light shopper	n=45 252 (100%)	45 167 (99.8%)	85 (0.2%)	4.8 (2.9– 8.0)	2.8 (1.7– 4.8)
moderate shopper	n=458 (100%)	446 (97.4%)	12 (2.6%)	68.4 (32.8–142.9)	14.9 (7.0–31.7)
heavy shopper	n=95 (100%)	93 (97.9%)	2 (2.1%)	54.7 (12.5–239.1)	19.4 (4.3–87.8)

a) The association was adjusted for gender, age, number of different kind of prescribers, number of different drugs (ATC-level 7).

Table 5: RELATION BETWEEN SHOPPING BEHAVIOUR AND HEAVY USE OF ONE OR MORE CATEGORIES OF PSYCHOTROPIC DRUGS (HYPNOTICS AND ANXIOLYTICS, ANTIDEPRESSANTS, ANTIPSYCHOTICS AND OPIOIDS)

	Number	No heavy use	Heavy use of 1 category	Heavy use of 2 categories	Heavy use of 3 categories
Non shopper	45 805	44 654 (97.5%)	1 058 (2.3%)	84 (0.2%)	9 (0.02%)
Light shoppers	45 252	43 049 (95.1%)	1 919 (4.2%)	268 (0.6%)	16 (0.04%)
Moderate shoppers	458	344 (75.1%)	88 (19.2%)	23 (5.0%)	3 (0.7 %)
Heavy shoppers	95	56 (58.9%)	30 (31.6%)	8 (8.4%)	1 (1.1 %)

Heavy use of 4 categories of psychotropic drugs did not occur.

DISCUSSION

The prevalence of pharmacy shopping was rather low (10.8%) and occurred especially in women, younger people, people using a high number of different drugs and those having different kind of prescribers. The dispensing of any anti-infective drug was related to (light) shopping. Moderate and heavy shopping was clearly associated with the heavy use of one or more categories of psychotropic drugs.

This study confirms that Dutch patients are in general loyal to one pharmacy, leading to rather complete patient medication records.[25,26] This may be due to the fact that in the Dutch health care system, patients are historically closely linked to one pharmacist. This situation is different from several other countries, such as Canada, where 40% of elderly patients visit more than one pharmacy.[27] Our finding has been confirmed to some extent in a small Dutch survey in which less than 1% of the respondents stated to visit other pharmacies structurally.[28] In the same survey younger people reported to be more prone to pharmacy shopping, a confirmation of our finding as well. In the Netherlands, it is allowed to move around to seek medical treatment, especially outside office hours. Most shoppers visited only one other pharmacy. This 'light' shopping behaviour is probably at least partly related to required pharmaceutical (and medical) treatment outside office hours. Indicative for this explanation is our finding that there was a strong association between any dispensing of systemic antibiotics and antimycotics and shopping behaviour. These drugs are often needed in more or less acute situations occurring during evenings, nights and in the weekend.

Nevertheless, also light shopping behaviour may hamper adequate medication surveillance and put the patient at risk for unintentional drug therapy related problems, such as duplicate medications, drug-disease interactions and drug-drug interactions. Not surprisingly, it has already been reported that an increasing number of pharmacists involved in the dispensing of drugs, increases the risk of dispensing potentially inappropriate drug combinations.[21] In this respect, we may consider the strong association between any dispensing of systemic antibiotics and antimycotics and shopping behaviour as an indication for a possible high frequency of unintentional, but potentially harmful drug-drug interactions, in which antibiotics, particularly macrolides and fluoroquinolones, and several oral antimycotics, are involved.[29] This warrants further investigation in future studies.

A strong relation was found between pharmacy shopping behaviour, particularly moderate or heavy shopping behaviour, and heavy use of psychotropic drugs. To

our knowledge, the relation between shopping behaviour and heavy use of these medicines has been reported for physician shopping, but not yet for pharmacy shopping.[23,24]

We found a prevalence of 1.4% of patients with heavy use of hypnotics and anxiolytics in the non shopping category. Given the sampling strategy that we applied in our study design, this means that the prevalence of heavy use related to all non shopping beneficiaries was almost 1.1%. Assuming a similar prevalence for the other beneficiaries and extrapolating this figure to the average size of a Dutch pharmacy, each pharmacy would have about 88 non shopping patients with heavy use of hypnotics and anxiolytics. Although not the focus of our study, this considerable number has to be evaluated seriously by the responsible pharmacists and by community pharmacy in general. In the Netherlands, heavy use and addiction to medicines have especially been associated with the use of benzodiazepines.[30] We found a higher prevalence of heavy use of hypnotics and anxiolytics in patients with any form of shopping behaviour, on average 2.8%. For the Netherlands, this accounts for approximately 48 500 patients and 28 of such patients per pharmacy. For moderate and heavy shopping patients with heavy use of hypnotics and anxiolytics, the result is about 2.3 per pharmacy. Heavy shopping behaviour is a very strong determinant for heavy use of hypnotics and anxiolytics.

The prevalence of patients with heavy use of antidepressants was to some extent comparable to that of hypnotics and anxiolytics. Data from the Netherlands show that there has been a strong rise of antidepressant use from 1992 till 2004, among other things due to a longer duration of use.[31,32] In 2001 the total prevalence was found to be about 2.4%. Data of heavy use or misuse of antidepressants are unknown. The extent of shopping behaviour is a considerable determinant for the heavy use of antidepressants, and an even stronger one for the heavy use of hypnotics and anxiolytics.

The prevalence of antipsychotic use (excluding lithium) in the Netherlands increased 43% from 1994 till 2003, mainly based upon an increase of the duration of use of these agents. A prevalence of 0.47% was revealed.[33] Heavy use or misuse has not been described. In our study, data about heavy use of antipsychotics are presented for the first time. A less strong association was found between shopping behaviour categories and the heavy use of this group psychotropic drugs. Moreover, absolute numbers of shopping patients with heavy use of antipsychotics were low.

We found a strong association between the level of shopping behaviour and the heavy use of opioids. The absolute number, however, for moderate and heavy shopping patients with heavy use of opioids was low. Based upon our data, the extent of heavy use or misuse of opioid prescription medications in the Netherlands in general seems to be low. However, the use of opioids is strongly growing in the Netherlands, particularly concerning oxycodon prescriptions.[34] In the United States, there are multiple indicators that non-medical use of prescription opioids are on the rise. It is said, that these opioids, especially oxycodon, are abused to almost the same extent as cocaine, and perhaps heroin.[35,36] The growth of especially longitudinal use of these substances is understandable: people stay alive for a longer period of time since more cancer diseases are curable and, moreover, the use of opioids is not solely restricted to cancer therapy anymore.[37,38]

The first step to reduce discontinuity of care due to pharmacy shopping (which is frequently invisible in the pharmacy) is better detection. Asking the patient for actual medication use and diseases may help to detect unintentional drug therapy related problems, such as duplicate medications, drug-disease interactions and drug-drug interactions, for instance, those involving systemic antibiotics and antimycotics. In addition, patients should be encouraged to stick not only to a single primary care physician, but also to a single dispensing pharmacy. Tamblyn et al. found that the use of a single dispensing pharmacy lowered the risk of potentially inappropriate drug combinations.[21]

Intentional heavy use, however, such as the heavy use or misuse of psychotropic drugs, will probably not be found by communicating with these patients. To detect this type of problem, systems are needed which exchange information among pharmacists.[16] In the Netherlands, there is a tendency of locally and regionally clustering of pharmacy computer systems. The development of a nationwide system, coordinated by the Ministry of Health, is not expected to be finished within the next 2-3 years. In a recent Canadian study, primary care physicians believed that such an integrated system would improve continuity of care.[39]

Other more retrospective interventions may be added to these proactive interventions and prerequisites. Educational programmes designed to reduce inappropriate utilization of prescription drugs and aimed at patients and/or their physicians have shown some favourable impact.[22,40]

This study had several limitations. In studies like ours (over)dispensing claims are considered to be identical with the (over)use of medicines. It is known, however,

that psychotropic drugs are exchanged among drug abusers. Secondly, pharmacy shopping might have been underestimated. A prescription, in some instances, may not have been followed by a dispensing, because it was refused for some reasons, for instance, heavy use. Thirdly, pharmacy claims of a relatively small health insurance company were used. Although patients from rural as well as non-rural areas were included, over- or underestimation cannot be totally ruled out, because patients from the largest Dutch cities as well as those from areas with a low population density were underrepresented. In addition, we used only data from beneficiaries that were insured under the Social Health Insurance Act, which comprises a specific selection of the Dutch population with on average a lower socio-economic status. This could have led to overestimation. Moreover, we did not include the purchase of certain medications by the use of the Internet. This type of self-care could have occurred, but the extent to which Dutch people use Internet pharmacies is unknown. In the US, however, drug abusers of psychoactive prescription medications have turned increasingly to the Internet as community based efforts to curtail physician shopping have been expanded.[41] Over the counter drugs were not included in the database. Finally, our definition of heavy use was somewhat arbitrary but in line with definitions used in other studies.

CONCLUSIONS

Pharmacy shopping behaviour is still limited in the Netherlands. Female gender, younger age, using a high number of different drugs and having different kind of prescribers are the main determinants of pharmacy shopping behaviour. Even light shopping behaviour may put the patient at risk for intentional drug related problems (including heavy use which was the subject of our study) but also for unintentional drug therapy related problems, such as drug-drug interactions, for instance, with systemic antibiotics and antimycotics. Intentional shopping behaviour seems especially related to the heavy use of (several categories of) psychotropics. It was found that the higher the shopping category, the higher the chance of a heavy use of hypnotics and anxiolytics, opioids and to a lower extent antidepressants. Linking pharmacy computer systems, locally, regionally or preferably nationwide will signal and hopefully prevent most of the intentional and unintentional problems related to pharmacy shopping for prescription only medicines. Pending this development, communicating with the patient may

already reduce unintentional problems. Future research should focus on unintentional drug therapy related problems due to pharmacy shopping behaviour.

Acknowledgements. We would very much like to thank Prof Hubert G.M. Leufkens, PharmD, PhD, for his support concerning the methodology of this study. The health insurance company 'O.W.M. Zorgverzekeraar Zorg en Zekerheid u.a.', especially Ms Manon Goddijn MSc., who was closely involved in initiating the study, is acknowledged for providing the anonymous data.

REFERENCES

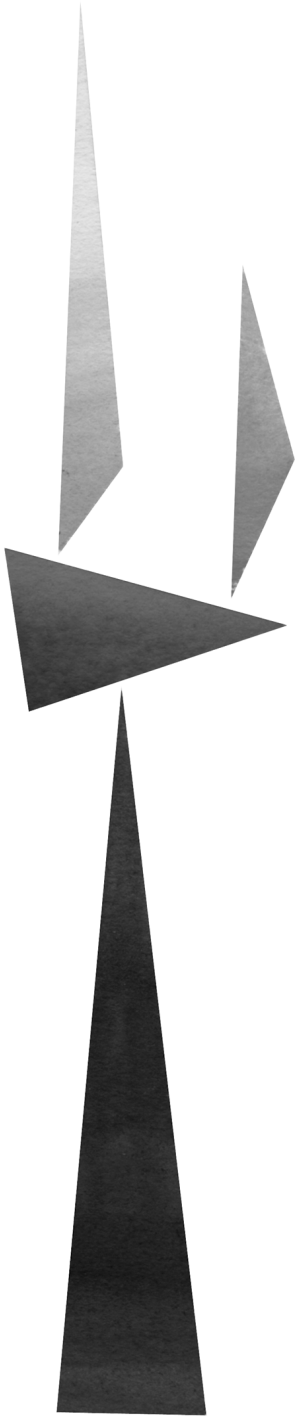
1. Macpherson AK, Kramer MS, Ducharme FM, Yang H, Bélanger FP. Doctor shopping before and after visit to a paediatric emergency department. Paediatrics & Child Health 2001;6:341-46.
2. Van Walraven C, Mamdani M, Fang J, Austin PC. Continuity of care and patient outcomes after hospital discharge. J Gen Intern Med 2004;19:624-31.
3. Moore C, Wisnivesky J, Williams S, McGinn T. Medical errors related to discontinuity of care from an inpatient to an outpatient setting. J Gen Intern Med 2003;18:646-51.
4. Paulino EI, Bouvy ML, Gastelurrutia MA, Guerreiro M, Buurma H. Drug related problems identified by European community pharmacists in patients discharged from hospital. Pharm World Sci 2004;26:353-60.
5. Coleman EA, Smith JD, Raha D, Min SJ. Posthospital medication discrepancies: prevalence and contributing factors. Arch Intern Med 2005;165:1842-7.
6. Gill JM, Mainous AG 3rd. The role of provider continuity in preventing hospitalizations. Arch Fam Med 1998;7:352-7.
7. Burge F, Lawson B, Johnston G. Family physician continuity of care and emergency department use in end-of-life cancer care. Med Care 2003;41:992-1001.
8. Christakis DA, Wright JA, Zimmerman FJ, Bassett AL, Connell FA. Continuity of care is associated with well-coordinated care. Ambul Pediatr 2003;3:82-6.
9. Tandeter HB, Vinson DC. Transient discontinuity of care. Others seeing what we have missed. J Fam Pract 1998;47:423-4.
10. De Maeseneer JM, De Prins L, Gosset C, Heyerick J. Provider continuity in family medicine: does it make a difference for total health care costs? Ann Fam Med 2003;1:144-8.
11. Saultz JW, Lochner J. Interpersonal continuity of care and care outcomes: a critical review. Ann Fam Med 2005;3:159-66.

12. Forster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW. The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med 2003;138:161-7.
13. Gill JM, Mainous AG, 3rd, Diamond JJ, Lenhard MJ. Impact of provider continuity on quality of care for persons with diabetes mellitus. Ann Fam Med 2003;1:162-70.
14. Nutting PA, Goodwin MA, Flocke SA, Zyzanski SJ, Stange KC. Continuity of primary care: to whom does it matter and when? Ann Fam Med 2003;1:149-55.
15. Saultz JW. Defining and measuring interpersonal continuity of care. Ann Fam Med 2003;1:134-43.
16. Kuehl AK, Chrischilles EA, Sorofman BA. System for exchanging information among pharmacists in different practice environments. Am J Health Syst Pharm 1998;55:1017-24.
17. Crotty M, Rowett D, Spurling L, Giles LC, Phillips PA. Does the addition of a pharmacist transition coordinator improve evidence-based medication management and health outcomes in older adults moving from the hospital to a long-term care facility? Results of a randomized, controlled trial. Am J Geriatr Pharmacother 2004;2:257-64.
18. Foisy MM, Tseng A, Blaikie N. Pharmacists' provision of continuity of care to patients with human immunodeficiency virus infection. Am J Health Syst Pharm 1996;53:1013-7.
19. Dvorak SR, McCoy RA, Voss GD. Continuity of care from acute to ambulatory care setting. Am J Health Syst Pharm 1998;55:2500-4.
20. Munday A, Kelly B, Forrester JW, Timoney A, McGovern E. Do general practitioners and community pharmacists want information on the reasons for drug therapy changes implemented by secondary care? Br J Gen Pract 1997;47:563-6.
21. Tamblyn RM, McLeod PJ, Abrahamowicz M, Laprise R. Do too many cooks spoil the broth? Multiple physician involvement in medical management of elderly patients and potentially inappropriate drug combinations. CMAJ 1996;154:1177-84.
22. Hoffman L, Enders JL, Pippins J, Segal R. Reducing claims for prescription drugs with a high potential for abuse. Am J Health Syst Pharm 2003;60:371-4.
23. Kamien M. 'Doctor shoppers': at risk by any other name. Med J Aust 2004;180:204-5.
24. Pradel V, Thirion X, Ronfle E, Masut A, Micallef J, Begaud B. Assessment of doctor-shopping for high dosage buprenorphine maintenance treatment in a French region: development of a new method for prescription database. Pharmacoepidemiol Drug Saf 2004;13:473-81.
25. Klungel OH, de Boer A, Paes AH, Herings RM, Seidell JC, Bakker A. Agreement between self-reported antihypertensive drug use and pharmacy records in a population-based study in the Netherlands. Pharm World Sci 1999;21:217-20.

26. Monster TB, Janssen WM, de Jong PE, de Jong-van den Berg LT. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. Pharmacoepidemiol Drug Saf 2002;11:379-84.
27. Tamblyn R, Huang A, Perreault R, Jacques A, Roy D, Hanley J, et al. The medical office of the 21st century (MOXXI): effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care. CMAJ 2003;169:549-56.
28. Van der Schee E, van Dijk L, Blom L, Lelie-van der Zande R, Broerse A. Consumentenpanel Gezondheidszorg peilt leemtes [*Panel of consumers in health care gauges gaps*]. Pharm Weekbl 2004;139:618-22.
29. Stockley IH. Drug Interactions. 6th edition. London: The Pharmaceutical Press; 2002.
30. Van Laar M. Afhankelijkheid van alcohol, drugs of andere middelen. In: Nationaal Kompas Volksgezondheid (version 3.3.1; 11 October 2005). Bilthoven, the Netherlands: RIVM; 2002.
31. Meijer WE, Heerdink ER, Leufkens HG, Herings RM, Egberts AC, Nolen WA. Incidence and determinants of long-term use of antidepressants. Eur J Clin Pharmacol 2004;60:57-61.
32. Stichting Farmaceutische Kengetallen [*Foundation for Pharmaceutical Statistics*]. Gebruik antidepressiva stijgt sterk [*Use of antidepressants strongly grows*]. Pharm Weekbl 2005:767.
33. Hugenholtz GW. Antipsychotics in daily practice: patterns, choices and consequences [dissertation]. Utrecht, the Netherlands: Utrecht University; 2005.
34. Stichting Farmaceutische Kengetallen [*Foundation for Pharmaceutical Statistics*]. Pijnbestrijding met opioiden [*Treatment of pain with opioids*]. Pharm Weekbl 2005;140:385.
35. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on problems of drug dependence taskforce on prescription opioid non-medical use and abuse: position statement. Drug Alcohol Depend 2003;69:215-32.
36. Hays LR. A profile of OxyContin addiction. J Addict Dis 2004;23:1-9.
37. Jarlbaek L, Andersen M, Hallas J, Engholm G, Kragstrup J. Use of opioids in a Danish population-based cohort of cancer patients. J Pain Symptom Manage 2005;29:336-43.
38. Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med 2002;17:173-9.
39. Tamblyn R, Huang A, Kawasumi Y, Bartlett G, Grad R, Jacques A, et al. The Development and Evaluation of an Integrated Electronic Prescribing and Drug Management System for Primary Care. J Am Med Inform Assoc 2006;13:148-59.

40. Gorgels WJ, Oude Voshaar RC, Mol AJ, van de Lisdonk EH, van Balkom AJ, Breteler MH, et al. Predictors of discontinuation of benzodiazepine prescription after sending a letter to long-term benzodiazepine users in family practice. Fam Pract 2006;23:65-72.
41. Lineberry TW, Bostwick JM. Taking the physician out of 'physician shopping': a case series of clinical problems associated with Internet purchases of medication. Mayo Clin Proc 2004;79:1031-4.

Chapter 5

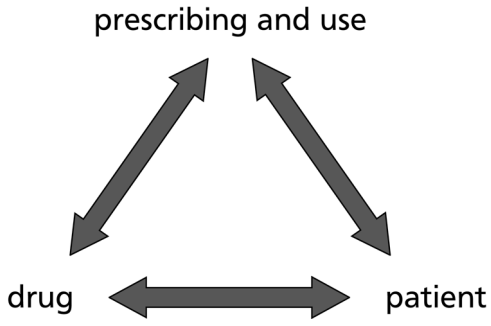


GENERAL DISCUSSION

INTRODUCTION

Despite extensive review of the evidence concerning efficacy and safety by regulatory authorities, and despite the strong development of methodologies and regulations since the Softenon drama to evaluate risks of new drugs before and after entering the market, several examples of drug withdrawals, such as rofecoxib, cerivastatin, mibefradil and cisapride, have shown that the handling of the drug by health professionals and patients is an important but rather unpredictable and uncontrollable modifier of the intrinsic risks of drugs.[1] The interaction in the triangle 'drug - patient - prescribing and use' is therefore a major determinant of the balance between efficacy and safety (Figure 1). In other words, an optimal choice and the appropriate use of a drug are the best guarantees for a safe and successful therapy.[2] The occurrence of several drug therapy related problems due to suboptimal or inappropriate prescribing and use has been subject of several studies and has been fuelled by the public debate on patient safety in general and medication errors in specific (and vice versa). One may conclude that redefining the role of (community) pharmacy practice from a drug orientation to a patient care orientation, is driven by the recognition that the benefit-risk balance of drug therapy goes beyond pharmacology and is determined by the prescribing, dispensing and usage processes as well (Chapter 1).

Figure 1: THE TRIANGLE DRUG, PATIENT, AND PRESCRIBING AND USE



Adapted from reference 2.

In this thesis, several studies have been presented providing information about frequency, nature and determinants of drug therapy related problems as they

occur in daily pharmaceutical practice, including unavailability, drug-drug interactions and heavy use of psychotropic medicines. These studies especially focused on the pharmacist and his contribution and quality to the 'solution' of these problems. Thereby, they add to our knowledge and understanding of pharmacists' contribution to patient care in the modern health care system. These include:

1. In 2001 Dutch community pharmacies still compound more than 13 000 medicines per day (2.3% of all prescriptions), mainly consisting of dermatological preparations. At least 1.2 compounded prescriptions per pharmacy per day (about 10%) have a specific pharmaceutical care reason according to the pharmacists, such as intolerance, contraindication, inconvenience to use and special dose needed. Thereby, compounding remains an important though 'niche' activity of community pharmacy. The compounding pharmacies did not use a standardized or semi-standardized protocol in 42% of the cases. Quality of compounding is an important issue as the relatively low rate of compounding in individual pharmacies could lead to insufficient experience among technicians. *(Chapter 2.1)*
2. Dutch community pharmacies modified 2.8 prescriptions for 'prescription only medicines' per pharmacy per working day, which could potentially have had clinical consequences if not altered. These interventions concerned an array of drug therapy related problems, but especially wrong doses. A multidisciplinary panel of reviewers unanimously rated almost 60% of these interventions as clinically relevant. By extrapolating these data, we estimated a daily occurrence of approximately 2700 clinically relevant interventions leading to a prescription modification in all Dutch pharmacies. *(Chapter 2.2 en 4.1)*
3. A high frequency of drug-drug interaction alerts was found: 6% of all prescriptions generated such an alert. Most concerned recurrent alerts. External action by pharmacists, mostly concerning a communication with the patient, took place in about 27%. A first alert was the main determinant for external action. The abundance of apparently non-relevant alerts, which implies the risk of overriding these, needs further study and policy making. *(Chapter 2.3)*
4. In the latter study, we also found some indicators that the management of drug-drug interaction alerts by pharmacies can be improved. In another study in this thesis, an overall adherence of approximately 70% to a national guideline was revealed concerning the management of drug-drug interaction

alerts. The degree of adherence varied with the nature of the drug-drug interaction, patient characteristics and the nature of the advised management actions in the guideline. Further research into underlying reasons for non-adherence is warranted to guide efforts to improve this situation. *(Chapter 2.3 and 3.2)*

5. In a selection of Dutch pharmacies at least one documented disease and/or intolerability was found in the electronic patient record of almost 60% of the patients. For some diseases, such as diabetes and hypothyroidism, the documentation was quite accurate, but for others the quality required further improvement, especially heart failure. *(Chapter 3.1)*
6. Community pharmacies are confronted with a modest, but clinically relevant level of heavy use of psychotropic drugs, especially of hypnotics and anxiolytics. Part of the problem will not be discovered because of pharmacy shopping behaviour of patients using these drugs. *(Chapter 4.2)*
7. Although pharmacy shopping behaviour in the Netherlands is (still) limited, unintentional shopping behaviour, for instance, because of required medical treatment outside office hours, could lead to unnoticed but potentially harmful drug-drug interactions. Linking pharmacy computer systems, preferably nationwide, will hopefully prevent intentional and unintentional problems related to pharmacy shopping behaviour. *(Chapter 4.2)*

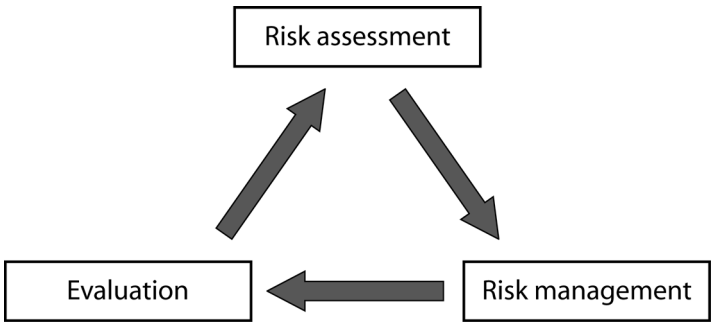
In this final chapter the presented studies will be put into a broader perspective of community pharmacy practice, clinical risk management and pharmacy practice research. For a discussion of the shortcomings and merits of the individual studies in this thesis we like to refer to the discussion in previous chapters.

EVALUATION OF THE CLINICAL RISK MANAGEMENT SYSTEM CONCERNING MEDICINES

Studies in this thesis aim to contribute to the knowledge on clinical risk management in community pharmacy practice. Clinical risk management can be defined as all the endeavours applied to the use of therapeutic products, such as medicines, that seek to assure that benefits to patients outweigh risks.[3] In the introductory chapter we added this concept of clinical risk management to the currently dominant concept of pharmaceutical care. The risk management model adds several essential issues to the problem finding, solving and preventing

activities of pharmaceutical care. By the accurate identification and relative assessment of risks of medicines, clinical risk management helps to prioritizing for and focusing on the drug therapy related problems and their management in daily patient care, which are most essential. This concept causes a system orientation considering the whole chain of drug distribution as well as the whole chain of health care with drugs.[4-6] Regulators request a risk management strategy from pharmaceutical industry,[1] but this needs to be complemented by risk management strategies by health care professionals including pharmacists, both in community and hospital. The concept of clinical risk management is a challenging model to describe community pharmacy as part of a system. In this system one has to define the role of community pharmacy: which management tools are deployed and which are functional barriers in minimizing risks?[7] A risk management system is never finished and should be seen as a continuous process that to some extent is comparable to models used in quality management, like the Deming cycle (Figure 2).

Figure 2: THE CLINICAL RISK MANAGEMENT CYCLE



The evaluation part of the risk management model is focusing on the other two parts of the same model, namely 1) problem identification and assessment of risks and 2) the management of risks. In this way, one may relate the evaluation of the risk management system, particularly in pharmacy, with the field of pharmacy practice research. We would like to comment on the evaluation of both parts of the model.

IDENTIFICATION AND ASSESSMENT OF RISKS

Since the early 1980s several instruments such as guidelines, standards, algorithms, protocols and formularies have been developed as outcomes of the process of identification, assessment and prioritizing of risks, mostly concerning the prescribing of medicines. These instruments are nowadays widely embraced as tools to improve quality of care.[8] Within the concept of risk management these instruments may also be nominated as management plans. These instruments not only describe the management of several issues concerning the prescribing of medicines, but also concerning the use of medicines, such as issues of the understanding of drug use and (non)compliance of patients. With the introduction of information technology, management tools as to drug-drug interactions, drug-disease interactions and so on were introduced. In the distribution chain in which pharmacies are naturally involved, a significant problem has been identified already for many years, i.e. the unavailability of drugs, particularly concerning specific groups of patients. The compounding of specific medicines in community pharmacies nowadays is to some extent solving that problem (see Chapter 2.1). Assessment of risks has brought us protocols concerning the process of compounding and, recently, a specific (Dutch) internet tool ('Farmanco') for the management of unavailability of drugs.

The process from problem identification to the development and accomplishment of instruments or management plans such as guidelines and protocols, has been subject to much research, especially with respect to general practice, hospital care and specific disease areas such as cancer care.[8] Several studies showed significant improvements in the process and outcomes of care following the introduction of such instruments.[8,9] Nevertheless, several problems have been encountered with some of these instruments as well. An important limitation of guidelines, for instance, was that recommendations turned out to be outdated or wrong.[8] The development process leading to these guidelines has been extensively investigated.[10] Five steps have been determined as critical to the development process: identifying and refining the subject area, convening and running guideline development groups, assessing the evidence about the clinical question or condition, translating the evidence into recommendations and reviewing the guideline externally.[8,11]

With respect to the development of guidelines used in Dutch community pharmacies, this process and the defined five steps have hardly been investigated. However, such instruments have already been used for many years, such as those

concerning the management of drug-drug interactions, drug-disease interactions and drug dosing control. A beginning has been made to give more transparency about the development method used in the assessment of drug-drug interactions by one of the guideline committees.[12] In this thesis, some information was collected and analysed that can be used as feedback information for the guideline development group when reviewing the content of the guidelines. In Chapter 3.2, for instance, we found differences between management actions of pharmacies and the proposed management by the guideline of different potentially hazardous drug-drug interactions. Also concerning compounding, we found considerable non-adherence to the use of standardized protocols (Chapter 2.1). Not all very surprising, as we know that there is evidence that guidelines are not always widely implemented into practice.[8]

Implementation of management plans

Implementation research is important and will often reveal obstacles connected to either the level of the individual health care professional or the social or the organizational context of provision of care.[13] Implementation research will provide information about the execution of, for instance, guidelines and its determinants, but also necessary feed-back for the further development and adaptation of these guidelines. Moreover, implementation research can help to incorporate guidelines in (pharmacy) information systems. Implementation research will not only focus on process outcomes, as was done in this thesis concerning the adherence to a guideline on the management of drug-drug interaction alerts (Chapter 3.2). It will also pay attention to prerequisites for a successful implementation, so-called structural factors. In Chapter 3.1 an example can be found concerning a good quality of disease documentation. Linking the data of the latter two studies (Chapter 3.1 and 3.2) to the results of Chapter 2.2 in which a process outcome, i.e. the modification of a prescription, was investigated, one may conclude that more of such prescription modifications are possible. However, according to Seligman, to achieve best practices, we need "better messages (specific, evidence-based), better delivery of information (education, reminder systems), and better assurance over how recommended practices are promoted and adhered to".[14]

Finally, prioritizing is an elementary issue in the assessment phase of the clinical risk management model, for instance, prioritizing between drug-drug interaction alerts which was an important message in Chapter 2.3. As the editor of the Journal of Clinical Pharmacy and Therapeutics, Dr Li Wan Po, stated in his

editorial in 2005: "We need to do better and put up bollards and flashing lights only when necessary."[15] Leape et al. add the problem of effective, but costly interventions to the issue of prioritizing between interventions. Methods for prioritizing safety practices should be a key area for future research, according to them.[16] The application of evidence based guidelines as well as the principle of prioritizing between interventions, however, may in some instances be critical to improving individual care.[17] In this way, this touches the difference between a system orientation, such as the clinical risk management model, and a patient centred orientation, that is reflected by the pharmaceutical care model.

Formal and informal identification and assessment of risks

Assessment of risks, as described above, concerning medicines and the system in which they are provided and used, is based upon evidence that is provided by clinical trials, pharmacoepidemiological studies and health services research. It is a formal assessment by institutions, working groups et cetera, leading to (national) guidelines and directives. However, in a continuous flow of scientific articles, reports, editorials and opinions (new) drug therapy related risks are identified and described and more or less informal solutions are thought of. Health care professionals may use these developing assessments in daily practice, for instance, by discussing them with colleagues in pharmacotherapeutic consulting groups of pharmacists and general practitioners (GPs). Concerning pharmacy, these more or less informal assessments may help to propose a number of areas where pharmacists could have greater involvement, such as the management of (repeatedly) prescribed medicines, chronic disease management, discharge medication and health promotion. The development of medication surveillance since the 1970s in community pharmacies in the Netherlands can partly be attributed to these informal assessments in daily practice (see Chapter 1). In this way, pharmacy practice is continuously changing and new possibilities may be built into the risk management system, at first on a local level. One may reveal several developments of newly generated care in parts of (Dutch) pharmacy practice, such as shared information concerning clinical data. Interesting examples may also be found between the nominees for the Dutch 'Pharmaceutical Care Award' which is granted each year since 1998. Based upon formal and more or less informal assessments of risks and probably several external factors, also strong changes may be expected in the near future concerning the internal system of pharmacies, such as a differentiation in personnel profiles, another infrastructure, and the use of robots.

This dynamic and challenging process of identification and assessment of risks and the implementation of new interventions in daily pharmacy practice, which can also be described as the development of pharmaceutical care, has to be anticipated and evaluated by formal institutions and working groups and by pharmacy practice research as well. It is known that many - not only Dutch - implementation projects are not really evaluated well.[18] Some outcomes of newly developed interventions, however, may be unexpected or surprising, such as the impact of nurse practitioners on the workload of GPs.[19]

THE MANAGEMENT OF DRUG THERAPY RELATED RISKS IN PHARMACY

The evaluation of pharmacy practice, i.e. the management in community pharmacy of certain risks of medicines, was the main topic of this thesis, thereby exploring the second phase of the risk management process. This thesis presents a picture about the frequency and nature of certain interventions of community pharmacy. Most Dutch studies in pharmacy practice are dealing with such outcomes of community pharmacy. A growing number of studies is presented in scientific and professional journals, for instance, about communication interventions,[20,21] or about collaborative services among community pharmacies.[22-24]

We would like to mention two areas of research that has been underestimated in the Netherlands until now. The first one, already described in the United Kingdom, concerns the risk management system of the pharmacy itself with questions about dispensing errors, the influence of workload on the performance of pharmacies and the nature of safety culture in community pharmacies.[25,26] The second area concerns new interventions, such as the structured way of communication with patients in case they receive a medicine for the first time or for the second time. Newly developed interventions have hardly been accompanied by formal research into the effects of such interventions, i.e. randomized controlled trials. Only a few Dutch peer-reviewed studies have been published presenting an intervention, in which the Dutch pharmacist was involved,[18,27] but there is more ongoing research. Similar conclusions can be made with respect to comparable areas of research. Public health research in the UK, for instance, is dealing in only 4% with interventions, of which only 10% (0.4% of the total) focuses on the outcomes of the these interventions.[28] There is

little information on several therapeutic risk management interventions, newly introduced by the FDA, available in the published domain. When available, effectiveness evaluations of these programmes are process oriented rather than outcome oriented.[1]

It is recognised, that randomized controlled trials on the effects of professional interventions, such as specific pharmacists' care, are complicated, time-consuming and expensive.[18,29] Moreover, not all new interventions or new practices should wait for incontrovertible proof, because this would mean inaction and an abdication of responsibility (see also above). Leape et al. propose to make reasonable judgements based on the best available evidence combined with successful experiences in health care, such as from practices based on human factors principles and accepted practices in other industries.[16] Once interventions have been implemented structurally in daily practice, a randomized controlled trial cannot be executed easily for ethical and/or practical reasons. In addition to observational studies, one may value interventions of pharmacies already constituted in daily practice by using the method of evaluation by clinical experts, a less strong level of evidence. This thesis gives an example of rating pharmacists' interventions (Chapter 4.1).

Variability between pharmacy practices

Risk management of medicines requires a system orientation. Consequently, one may consider the entire pharmacy profession as well as each pharmacy separately as part of a system. Studies in this thesis were merely population based, and some of them concerned a specific selection of pharmacies. Little attention was given to pharmacy characteristics as potential determinants of the investigated outcomes. Future research should be more focused on these probably important variables, because they can have major relevance concerning quality outcomes. Some studies have underlined the importance of pharmacy related determinants.[30,31] Further research into the variability of risk management between individual pharmacies is warranted. Where studies presented in this thesis show aspects of the performance of the whole group of community pharmacies, individual pharmacies may find general outcomes and recommendations applicable to their own practice, such as the low adherence to the guideline of some important drug-drug interactions, and the low rate of documentation of certain diseases (e.g. heart failure) in the electronic patient record. Nevertheless, mirror information on an individual pharmacy level will present specific information, which may also involve benchmark data from other

pharmacies. It is interesting to observe a development internationally towards pharmacy practice research using performance indicators.[32] In the Netherlands, this type of research concerning community pharmacy got a strong impetus by a series of projects initiated by the Health Inspectorate.[33] In our study concerning drug-disease interactions (Chapter 3.1) we used different types of drug-morbidity pairing, of which three had an almost unambiguous relation between disease and currently used medication: diabetes, hypothyroidism and benign prostatic hyperplasia. These diseases could be used as performance indicators of individual pharmacies concerning the documentation of diseases in the electronic patient records. Nevertheless, there is discussion on such performance indicators and problems related to these, such as chance variation and lack of clear predefined benchmarks.[34]

Other types of research focusing on individual pharmacy performance are, for instance, pseudo customer research concerning information giving and over the counter distribution, and case series research or risk management analysis concerning errors in community pharmacies.[18,35] In Dutch hospital pharmacies, a system of documentation of errors and near misses is gradually introduced, but in several instances not well implemented.[36] In the context of risk management, we would stress the importance of such a system of continuous and blame free documentation of errors and near misses in the distribution chain as well as the health care chain concerning community pharmacy. One could start with a relatively small group of sentinel pharmacies, which is also proposed for other purposes in the following paragraph of this chapter.

Finally, it would be interesting to search for other possibilities to investigate pharmacies on an individual level in order to provide feedback information on their relative performance. In the Netherlands, there is long-lasting experience concerning a central examination by the Laboratory of Dutch Pharmacists of test preparations compounded by pharmacies, of which the results are presented in a series of anonymous results from other pharmacies. A comparable system has been described for clinical pathology concerning the quality control of laboratory testing.[37] In this way, one could imagine the introduction of test patients with an attached medication history in community pharmacies' information systems with which test prescriptions containing drug therapy related problems could be investigated.

Longitudinal studies or timely surveys

In most of the studies presented in this thesis, a random or selected group of pharmacies was enrolled to perform the study protocol just for one day (e.g. Chapter 2.2). In these studies the necessary effort for these pharmacies was limited. This is of great advantage since one may expect fewer problems concerning selection bias (participation, selection of cases). In our study concerning the adherence to the drug-drug interaction management guideline, which was held over a much longer period of three months, we saw more problems in this respect. In other studies, prolonged participation has created unintended differences in recording between pharmacies and differences over time.[18,38] Because pharmacists have to be well motivated over a long period of time, differences in, for instance, coding may be expected, unless there is a continuous feedback. Opposite to Dutch community pharmacy as well as hospital pharmacy, longitudinal research and data collection in primary care is well-known, in the Netherlands as well as abroad. Primary care practices based research networks have emerged as the infrastructure for research in family practice. These networks extend the time window of timely research projects and among others their content consists of more detailed information as well as outcomes of care.[39] Since it is possible for pharmacies in the Netherlands to register care activities, problems as well as their management, there is a discussion how to reliably aggregate these data to a national level. One may conclude that only a small well equipped and motivated group – which is also the case for GP practices in these networks - of pharmacies with sufficient incentives are able to maintain a rigorous regime of data registration and delivery during months or even years. It would be valuable when clinically relevant endpoints were included in or linked to these pharmacy databases. In all other cases, it is preferable to conduct a research project with as little effort of pharmacies as possible.

In this respect, it would be interesting to search for cross-links between these practices based research networks and the concept of academization of pharmacy practice. A specific start of this model concerning pharmacy was made in 1985 in the health care centre Stevenshof in Leiden, involving a community pharmacy, which still has a close linkage with the pharmacy faculty of Utrecht University concerning practice research and education.[40] More recently, other relations between academia and pharmacy practice were initiated, such as 'Interaction' in Groningen and 'UPPER' in Utrecht. In a report in 2000 of the Dutch Council for Health Research about the academic working place, suggestions were made

about further development of this concept in medical curricula, although regrettably not for others. According to the Council, these working places 'in real practice' should be actively involved in patient bound education and research, there should be a strong cooperation between faculty and working places, the care given should be an example to others and the working place should offer opportunities for innovation of care.[41] Where funding for medical faculties is available, although not always sufficient, we would like to support this for pharmacy as well.

SOME FINAL CHORDS

Pharmacy practice research as part of health services research

In this final chapter, we positioned pharmacy practice research as the evaluation part of the clinical risk management system. Pharmacy practice research, however, can also be defined as part of health services research. Several definitions and classifications of health services research have been proposed. Recently, a definition and a domain description were formulated in the Netherlands to be used in the funding process of the Netherlands Organization for Health Research and Development (ZonMW).[29] For the domain description we refer to Box 1. There are several relationships between the areas of observation, which are the subject of research as well. The authors discriminate in their report between health services research and health research, in which the association between health and aetiological factors is the main issue (Figure 3). The magnitude of health services research is probably still limited. For the UK, it had been assessed that health services research accounts for 2-3% of the money spent on health research each year.[42] Pharmacy practice research in the Netherlands is a growing, but still limited area of research, especially when compared to the larger area of health services research and that of general medical practice in particular. Limited research and under funding has been described for other professions in health care as well, such as nursing, midwifery and allied professions.[43] These represent two thirds of the staff responsible for direct care for patients in the UK, yet little is known of their clinical or cost effectiveness.

Studies in this thesis fit well in this description of domains of health services research. They particularly deal with pharmacy service interventions and the performance (process outcomes, quality) of pharmacists, which are the providers of these interventions. In several of these studies, relations have been investigated

with characteristics of users of the interventions, in other words the patients to which medicines were dispensed. On the other hand, it is also obvious which questions were not put forward in the context of this thesis, such as those concerning politics related to pharmacy services, the funding of it and the ultimate outcome of pharmacy service interventions, i.e. the health status of the patient. In Chapter 4, however, patient and outcome related issues were addressed.

Box 1: DOMAIN DESCRIPTION OF HEALTH SERVICES RESEARCH

The domain of Health Services Research constitutes of the following areas of observation:

1. Health service interventions
2. Issues that are influencing health service interventions
   a) Performance and characteristics of users of health service interventions
   b) Performance and characteristics of providers of health service interventions
   c) Politics concerning health services
   d) Funding of health services
3. Issues that are influenced by health service interventions
   Health status

Adapted from reference 29.

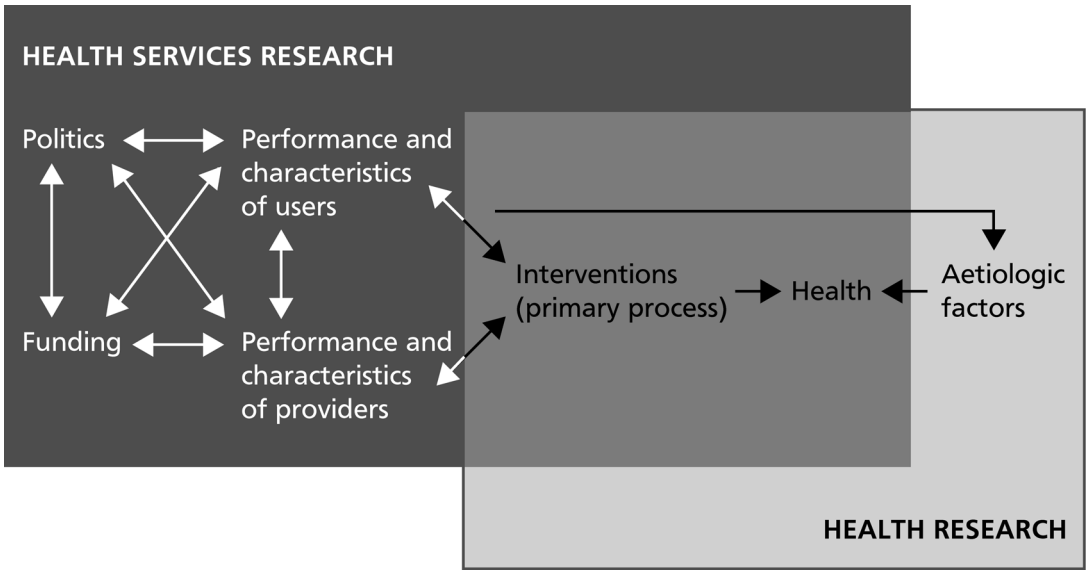
It is interesting to observe discussions on the domain of pharmacy practice research in the Netherlands, which relate to the distinction between health services research and health research. Pharmacy practice research and pharmacoepidemiology can be considered as a part of the domain of health services research and health research, respectively (Figure 3). The borderline between pharmacy practice research and pharmacoepidemiology is somewhat indistinct as well, partly because pharmacoepidemiology has further expanded since pharmacies also serve as a tool, source or place through which data are collected.[44]

Cooperation and coordination

In its report in 2000, the Dutch 'PRISMA' Foundation (Practice Research in Cooperation with Pharmacists) summarized, by its first president Prof Albert Bakker, some obstacles for further developing of pharmacy practice research. In the meanwhile, some positive changes have occurred, such as more cooperation with academic complementary disciplines, including pharmacoepidemiology (Utrecht, Groningen) and research into the quality of medical care (Nijmegen).

A more or less strong linkage with these types of institutions will be beneficial for the output of pharmacy practice research, but also for methodological developments. In the same report, methodological flaws were described concerning pharmacy practice research. Since the start of the 'PRISMA' foundation, however, several pharmacy practice research studies have been published in peer-reviewed international journals, although only a few were randomized controlled intervention studies. Since its start more cooperation between research institutions of different backgrounds has been developed as well, although still little coordination of research and prioritization have been observed. The same applies for pharmacy practice research programmes within and between faculties of pharmacy. In Australia, a Community Pharmacy Research Support Centre has been established by nine academic pharmacy units in order to "develop and support community pharmacy practice research expertise and capacity".[45]

Figure 3: AREAS OF OBSERVATION AND THEIR MUTUAL RELATIONSHIPS



Reproduced with permission from Juttmann et al. (reference 29).

Limited funding is probably one reason for the relatively small research workforce in this area. This suggests a reinforcement of this area of research, as was done in the UK in 1996 by four representative pharmaceutical bodies by

establishing the Community Pharmacy Research Consortium and in 1999 by the Royal Pharmaceutical Society by establishing the Pharmacy Practice Research Trust.[13,46] Similar examples from abroad may be found in Canada and Australia.[45,47] Since pharmacy practice research is on the edge of academia and practice, it is not surprising that representative pharmaceutical bodies should be involved in the development of pharmacy practice research.

Dissemination of results of pharmacy practice research

An important challenge to cope with is the dissemination of results, which may contribute positively to changes of policy and practice. An essential characteristic of health services research is that the information produced should add to service improvement and planning.[42] A UK research report concluded, however, that such research is still not optimally contributing to health service improvement, for instance, because of unclear responsibilities for communication of the results of research to users.[42] Policy should be developed using pharmacy practice research data, for instance, for the development and evaluation of management plans (guidelines, protocols), strategies to implement these and to evaluate their use in daily practice. The state of the art based upon research data, may help individual pharmacists and groups of pharmacies/pharmacists (e.g. the national society of pharmacists, chains or formulas of pharmacists) to formulate what goals they have for the (near) future. In this respect it is interesting to refer to the web-site of the American Society of Health System Pharmacists (www.ashp.2015.org), where an overview is given of ambitious performance indicators concerning the process, prerequisites and outcomes to fulfil before 2015 based upon up-to-date survey results of the state of the art of this sector in pharmacy.

Finally, by describing and analysing pharmacy practice, the information will serve as an evidence base, necessary to make clear to society (politics, patient groups, other health care professionals) what the role is of community pharmacy in the management of risks related to medicines, i.e. the balance between efficacy and safety, and thereby to patient care.[48]

CONCLUSIONS

In this final chapter, we synthesized the main results of the studies captured in this thesis and we made some suggestions concerning the evaluation of pharmacy practice, underlining the necessity of evaluations within the clinical risk management cycle. Linking this with pharmacy practice research, we suggested

more research into the assessment phase and its relation with the management phase (implementation, quality). Research concerning the management phase has to continue, but in a higher acceleration. Because pharmacies are also part of the production and distribution chain, risk management studies are also warranted concerning compounding and (newly introduced) distribution systems. Some suggestions were made with respect to methodology, such as more accent on controlled trials concerning new interventions, studies emphasizing the variability between pharmacies and the development of a Dutch pharmacy care practices based research (and education) network. Informal assessment of risks and the implementation of new interventions based thereon will continue at local and other decentralized levels. This is important for the development of pharmaceutical care and clinical risk management, but formal institutions and working groups, including research related ones, should have a proactive, anticipating role. The evaluation of the clinical risk management system, in other words pharmacy practice research, has to be developed further taking into account its relationship with other fields of health services research and health research including pharmacoepidemiology. There is a necessity of newly developed and well-coordinated programmes and of more generous funding. In addition, more effort is needed to promote the diffusion of results from evaluations into pharmacy practice.

REFERENCES

1. Andrews E, Gilsenan A, Cook S. Therapeutic risk management interventions: feasibility and effectiveness. J Am Pharm Assoc (Wash DC) 2004;44:491-500.
2. Egberts ACG, Leufkens HGM. Ongewenste, onbedoelde en sub-optimale effecten van geneesmiddelen. In: Van den Berg Jeths A, editor. Volksgezondheid Toekomst Verkenning 2002, geneesmiddelen nu en in de toekomst. Houten (the Netherlands): Bohn Stafleu Van Loghum; 2002. p. 521-33.
3. Kramer JM. Managing the risks of therapeutic products: proceedings of a workshop. Pharmacoepidemiol Drug Saf 2005;14:619-28.
4. Nolan TW. System changes to improve patient safety. BMJ 2000;320:771-3.
5. Madar J. Clinical risk management in newborn and neonatal resuscitation. Semin Fetal Neonatal Med 2005;10:45-61.
6. Helmreich RL. On error management: lessons from aviation. BMJ 2000;320:781-5.
7. Guchelaar HJ, Colen HB, Kalmeijer MD, Hudson PT, Teepe-Twiss IM. Medication errors: hospital pharmacist perspective. Drugs 2005;65:1735-46.

8. Andrews EJ, Redmond HP. A review of clinical guidelines. Br J Surg 2004;91:956-64.
9. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. Lancet 1993;342:1317-22.
10. Jackson R, Feder G. Guidelines for clinical guidelines. BMJ 1998;317:427-8.
11. Shekelle PG, Woolf SH, Eccles M, Grimshaw J. Clinical guidelines: developing guidelines. BMJ 1999;318:593-6.
12. Van Roon EN, Flikweert S, le Comte M, Langendijk PN, Kwee-Zuiderwijk WJ, Smits P, et al. Clinical relevance of drug-drug interactions: a structured assessment procedure. Drug Saf 2005;28:1131-9.
13. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet 2003;362:1225-30.
14. Seligman PJ. Thinking outside the (black) box: a new research agenda. Pharmacoepidemiol Drug Saf 2006;15:387-9.
15. Li Wan Po A. Drug-drug interactions and adverse drug reactions: the bollards and flashing lights syndrome. J Clin Pharm Ther 2005;30:97-9.
16. Leape LL, Berwick DM, Bates DW. What practices will most improve safety? Evidence-based medicine meets patient safety. Jama 2002;288:501-7.
17. Boyd CM, Darer J, Boult C, Fried LP, Boult L, Wu AW. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases: implications for pay for performance. JAMA 2005;294:716-24.
18. Van Mil JW, Schulz M, Tromp TF. Pharmaceutical care, European developments in concepts, implementation, teaching, and research: a review. Pharm World Sci 2004;26:303-11.
19. Laurant MG, Hermens RP, Braspenning JC, Sibbald B, Grol RP. Impact of nurse practitioners on workload of general practitioners: randomised controlled trial. BMJ 2004;328:927-32.
20. Hugtenburg JG, Blom AT, Gopie CT, Beckeringh JJ. Communicating with patients the second time they present their prescription at the pharmacy. Discovering patients' drug-related problems. Pharm World Sci 2004;26:328-32.
21. Pronk MC, Blom LT, Jonkers R, Rogers EM, Bakker A, de Blaey KJ. Patient oriented activities in Dutch community pharmacy: diffusion of innovations. Pharm World Sci 2002;24:154-61.
22. Kwint HF, Luchtman T, Krijger-Dijkema JM, Eekhof J, de Kanter J. Arts en apotheker houden samen toezicht. Controle van herhaalreceptuur op geneesmiddelgerelateerde problemen *[Physician and pharmacist cooperate in supervision of repeat prescribing]*. Pharm Weekbl 2003;138:1732-37.
23. Muijrers PE, Knottnerus JA, Sijbrandij J, Janknegt R, Grol RP. Changing relationships: attitudes and opinions of general practitioners and pharmacists

regarding the role of the community pharmacist. Pharm World Sci 2003;25:235-41.

24. Storimans MJ, Klungel OH, Talsma H, Bouvy ML, de Blaey CJ. Collaborative services among community pharmacies for patients with diabetes. Ann Pharmacother 2005;39:1647-53.
25. Ashcroft DM, Quinlan P, Blenkinsopp A. Prospective study of the incidence, nature and causes of dispensing errors in community pharmacies. Pharmacoepidemiol Drug Saf 2005;14:327-32.
26. Ashcroft DM, Morecroft C, Parker D, Noyce PR. Safety culture assessment in community pharmacy: development, face validity, and feasibility of the Manchester Patient Safety Assessment Framework. Qual Saf Health Care 2005;14:417-21.
27. Bouvy ML, Heerdink ER, Urquhart J, Grobbee DE, Hoes AW, Leufkens HG. Effect of a pharmacist-led intervention on diuretic compliance in heart failure patients: a randomized controlled study. J Card Fail 2003;9:404-11.
28. Macintyre S. Evidence based policy making. BMJ 2003;326:5-6.
29. Juttmann R, Klazinga N, Mackenbach J. Wetenschappelijke kwaliteit van het gezondheidszorgonderzoek. Erasmus MC, Universitair Medisch Centrum Rotterdam, afdeling Maatschappelijke Gezondheidszorg; 2004.
30. Muijrers PE, Knottnerus JA, Sijbrandij J, Janknegt R, Grol RP. Pharmacists in primary care. Determinants of the care-providing function of Dutch community pharmacists in primary care. Pharm World Sci 2004;26:256-62.
31. Becker ML, Kallewaard M, Caspers PW, Schalekamp T, Stricker BH. Potential determinants of drug-drug interaction associated dispensing in community pharmacies. Drug Saf 2005;28:371-8.
32. Morris CJ, Cantrill JA, Hepler CD, Noyce PR. Preventing drug-related morbidity--determining valid indicators. Int J Qual Health Care 2002;14:183-98.
33. Mulder J. "Overdosering methotrexaat komt nog veel te vaak voor" *["Overdose of methotrexate occurs too often"]*. Pharm Weekbl 2006;141:42-3.
34. Giard RW. Prestatie-indicatoren als maat voor de kwaliteit van medische zorg: retoriek en realiteit *[Performance indicators as a measure of the quality of medical care: rhetoric and reality]*. Ned Tijdschr Geneeskd 2005;149:2715-9.
35. Van Leeuwen JF, Bleumink GS, Hansen JMM, Blom ATG, Stricker BHC. Waar mensen werken ... Fouten in de openbare apotheek *[Where people work … Errors in community pharmacy]*. Pharm Weekbl 2001;136:1911-14.
36. Van Haga-Lakhi SA, Vulto AG, van der Pol WS, van der Schaaf WF. Invloed op foutcultuur en aantal meldingen *[Inluence on error culture and number of reports]*. Pharm Weekbl 2005;140:921-4.
37. Westgard JO, Westgard SA. The quality of laboratory testing today: an assessment of sigma metrics for analytic quality using performance data from proficiency testing

surveys and the CLIA criteria for acceptable performance. Am J Clin Pathol 2006;125:343-54.

38. Van Mil JW, Dudok van Heel MC, Boersma M, Tromp TF. Interventions and documentation for drug-related problems in Dutch community pharmacies. Am J Health Syst Pharm 2001;58:1428-31.
39. Van Weel C. Longitudinal research and data collection in primary care. Ann Fam Med 2005;3 Suppl 1:S46-51.
40. Buurma H, Leufkens HGM. Academische Apotheek Stevenshof bestaat 15 jaar. Van poldergeploeter tot volwassen instituut. Pharm Weekbl 2000;135:1400-2.
41. Anonymous. Werkplaatsfunctie buiten het academisch ziekenhuis *[Working place outside the academic hospital]*. The Hague: Raad voor Gezondheidsonderzoek; 2000.
42. Dash P, Gowman N, Traynor M. Increasing the impact of health services research. BMJ 2003;327:1339-41.
43. Rafferty AM, Traynor M, Thompson DR, Ilott I, White E. Research in nursing, midwifery, and the allied health professions. BMJ 2003;326:833-4.
44. Leufkens HG, Buurma H, Bakker A. 'Pharmacy practice research': na tien jaar nog steeds prominent op de agenda. Pharm Weekbl 1996;131:730-2.
45. Benrimoj SI, Roberts AS. Providing patient care in community pharmacies in Australia. Ann Pharmacother 2005;39:1911-7.
46. Anonymous. Medicines and People. Turning knowledge into know-how. London (United Kingdom): Pharmacy Practice Research Trust; 2004.
47. Canadian Pharmacists Association. Pharmacy practice research in Canada. http://www.pharmacists.ca/content/hcp/resource_centre/pharmacy_practice_research/index.cfm. (assessed June 2006)
48. Traulsen JM, Almarsdottir AB. Pharmaceutical policy and the pharmacy profession. Pharm World Sci 2005;27:359-63.

SUMMARY

This thesis starts with an introduction (*Chapter 1*) in which an overview of the recent history of community pharmacy practice is presented, and in which we elaborate on the evolving role of community pharmacists. We concluded that during recent years the concept of pharmaceutical care has changed the way of thinking and acting of pharmacists. The focus of pharmacists' care has shifted from the drug to its user. Pharmaceutical care has become important in the education of pharmacists, thereby dramatically altering the competencies of pharmacists compared to those thirty years ago. The question is, however, whether this concept gives the most appropriate response to the systematic problem of medication errors and drug therapy related problems in general. We proposed to involve the concept of clinical risk management in the description and evaluation of pharmacy practice. This systematic approach adds several essential items that are underexposed in the current pharmaceutical care concept, such as the assessment of risks of medicines, the management of risks in daily practice and ultimately the evaluation of (parts of) the risk management system.

The objective of this thesis is to increase our knowledge and understanding of pharmacists' contribution to patient care in the modern healthcare system. The presented studies in this thesis can be divided into three parts.
The first part (*Chapter 2*) focuses on the frequency and nature of drug therapy related problems encountered in Dutch community pharmacies, in other words the outcomes of the daily primary processes in community pharmacy. In *Chapter 3* we were interested in two preconditions for the quality of risk management by pharmacies. In the third part (*Chapter 4*) of the thesis, we focused on patient outcomes of clinical risk management by community pharmacies.

In *Chapter 2.1* we studied the nature and frequency of compounded medicines in a sample of 79 Dutch community pharmacies. By comparing prescriptions for compounded medicines with non-compounded medicines, randomly selected on the same day, we assessed several patient, drug and prescriber related determinants for compounding medicines. In addition, some organizational characteristics, like compounding site and use of protocols, were investigated. Also, the value of compounded medicines in terms of the availability of an industrially compounded equivalent and patient specific reasons, as perceived by the participating pharmacists, were evaluated. We found that the overall frequency of prescriptions for pharmacy compounded medicines in relation to the total number of dispensed prescriptions was 3.4%. This means 12.5

compounded medicines per pharmacy per day on average, with a large variation between pharmacies. Excluding the products purchased from specialized compounding companies (28.4%) and the small part of medicines coming from other pharmacies, such as hospital pharmacies (5.2%), we found a frequency of 2.3% of actual compounding in the pharmacy itself. Almost half of the latter was prepared extemporaneously. Compared to non-compounded medicines we found a huge share of dermatological dosage forms among compounded medicines (62.1% versus 5.3%). Oral solutions and ear-nose-throat products were also found relatively often. The dermatologist was a very strong determinant of compounded medicines compared to GPs. Patients of 12 years or younger received a significantly higher rate of compounded medicines than persons older than 12 years of age. Compounding occurred almost twice as often when a medicine was prescribed for the first time compared to a repeat prescription meaning that they were less chronically prescribed. For 58% of the products manufactured in the pharmacy itself or coming from other pharmacies a (semi-)standardized protocol was used. This part of *Chapter 2.1* connects well with Chapter 3, in which the quality of risk management by pharmacies is the central issue. In about 63% of compounded medicines, the pharmacist judged that an industrially produced medicine could not substitute for the compounded medicine. In about 33% of the compounded products, pharmacists indicated a patient specific reason for compounding; in about 10% this reason concerned a strictly defined pharmaceutical care issue, such as an intolerability or contraindication, inconvenience to use or special dose needed. This means that at least 1.2 compounded prescriptions per pharmacy per day have a specific pharmaceutical care reason, according to the pharmacists.

A specific outcome of the daily primary process in community pharmacy of medication surveillance is a modification of a prescription, resulting from an intervention executed by the pharmacy. In a sample of 141 community pharmacies, the frequency and nature of various drug therapy related problems were investigated using modified prescriptions as the study set. The results are presented in *Chapter 2.2*. By comparing modified prescriptions (n=2014) with randomly selected non-modified prescriptions (n=2581), we assessed patient, drug and prescriber related determinants for a modified prescription. These prescriptions were collected on a predetermined day in the first quarter of 1999. The overall incidence of prescription modifications was 4.3%, with a mean of 14.3 modifications per pharmacy per day. For prescription only medicines

(POM) the incidence was 4.9%. The majority (71.8%) of POM prescription modifications concerned a clarification of an insufficiently specified prescription, e.g. dose not specified, insufficient patient data or strength not specified. In 22.2% a prescription could potentially have had clinical consequences if dispensed unaltered. More than half of the latter concerned a dose error (13.7% of all cases). Drug-drug interactions, contraindications and duplicate medications were other, but less frequent, reasons for a prescription modification. POM prescriptions of patients aged 40-65 years had a significantly lower chance of modification compared to those of younger people. With respect to drug class, we found a higher chance of POM prescription modifications in the respiratory domain and a decreased chance for nervous system prescriptions. With regard to prescriber related determinants modifications were found three times more often in non-printed prescriptions than in printed ones. Compared to prescriptions by the patient's own general practitioner (GP), prescriptions of specialists, other GPs and other prescribers such as dentists and midwives gave a higher probability of prescription modifications. When a GP had no on-line access to the computer of the pharmacy, the chance of a modification was also higher. Multivariate analysis revealed that a non-printed prescription was the strongest independent determinant of prescription modifications.

Chapter 2.3 focuses on one specific type of drug therapy related problems, namely drug-drug interactions. We measured the frequency and nature of drug-drug interaction alerts as well as their management in the daily practice of Dutch community pharmacy. Based upon data collected in 63 pharmacies on 2.4 days per pharmacy on average, we found a high frequency of drug-drug interaction alerts: about 6% of all prescriptions generated such an alert. Of all alerts (n=2572), 31.1% occurred for the first time and in 21% of the cases two different prescribers were involved. The twenty most frequently occurring drug-drug interaction alerts accounted for about 76% of all alerts. Cardiovascular drugs, NSAIDs, oral contraceptives and antibacterials were most frequently involved. External action took place in 27.3% of the alerts, meaning either a modification of one of the concerned prescriptions (n=65; 9.3%), communication with the prescriber or anticoagulation clinic (n=90; 12.8%), or communication with the patient or relative (n=547; 77.9%). When there was no external action (n=1860; 72.3%), pharmacists concluded in about 76% that the drug-drug interaction alert had been managed in the past. Other reasons not to intervene externally were, for instance, incorrect alert, acceptable drug-drug interaction, or drug-drug

interaction considered irrelevant. A first alert was by far the most important determinant for external action. Because of the high number of alerts, we advise that alerting for drug-drug interactions with no or low evidence/relevance should be reconsidered. The opportunity to actively suppress alerts for a certain period of time could be an important tool to reduce the number of alerts, but should be studied in more detail. We found some indicators in this study that the management by pharmacies can be improved concerning patient oriented advices and the consistent management of recurrent and first alerts.

In *Chapter 3* we were interested in two preconditions for the quality of risk management by pharmacies. One important precondition for managing drug-disease interactions and drug-intolerability interactions is the documentation of diseases and intolerabilities. Such documentation in electronic patient records in pharmacies is needed to produce an alert in case a contraindicated medicine is prescribed. Limited research is available concerning electronic patient records in pharmacies. In *Chapter 3.1* a study on the prevalence and quality of this documentation in electronic patient records in a specific sample of 79 Dutch community pharmacies is presented. Each participating pharmacy collected data on one day in 2003 for each patient enrolled into the study (n=687). In 57.4% of the electronic patient records, at least one disease and in 7.9% at least one intolerability was documented. Higher age, number of drugs used and chronic disease score were associated with any documentation of a disease/intolerability in the electronic patient record. Certain diseases were documented to a relatively high degree; others had poorer levels of documentation: the highest sensitivity scores (completeness) were found for diabetes (84.7%), asthma/COPD (strict definition; 75.9%) and hypothyroidism (75.0%). Rather low values were found for prostatic hyperplasia (55.6%) and heart failure (29.4%). The positive predictive value (reliability) was high for hypothyroidism (100%) and diabetes (87.1%). We concluded that, for optimal surveillance of drug-disease interactions in Dutch pharmacies, the frequency and quality of disease documentation needs further improvement.

A precondition considered to be important for clinical practice is the utilization of evidence-based guidelines. Contrary to (general) medical practice, little is known about adherence of pharmacies to practice guidelines, e.g. those concerning the management of drug-drug interaction alerts, which play an important role in daily pharmacy practice. In the Netherlands, these guidelines

have been developed and kept up to date by working groups on the basis of published evidence of drug-drug interactions. In *Chapter 3.2* we measured the (non)adherence of community pharmacies to a Dutch guideline for the management of drug-drug interactions as well as patient and prescriber related determinants for non-adherence. Sixteen clinically relevant drug-drug interactions were included in the study. During a specific time frame in 2005, Dutch pharmacists (n=149) collected alerts for these interactions occurring in daily patient care as well as information related to the patient, the alert itself, the prescriber and the management of the alert. The overall adherence to the guideline amounted to 69.3% (423 of 610) with large differences between the various drug-drug interactions. A high adherence was found for two interactions involving coumarin anticoagulants (92.3% and 95.8%). Adherence was also relatively high for tricyclic antidepressants – terbinafine (90.9%), statins – macrolides (89.8%), statins – antimycotics (82.2%) and PDE-5 inhibitors – CYP3A4 inhibitors (75.0%). A relatively low adherence was found for two types of interactions involving theophylline (45.0% and 21.6%), digoxin – macrolides (8.9%) and PDE-5 inhibitors – nitrates (2.8%). The degree of adherence varied not only with the nature of the drug-drug interaction, but also with its management characteristics. For those alerts for which substitution was the only proposed management option, we found a low adherence (9.2%) to the guideline. For those alerts for which a clear alternative option was possible in addition to substitution, the adherence amounted to 82.2%. Substitution of one of the involved agents, recommended for most of the drug-drug interactions, was only executed in a small minority of cases. A substitution, a dose reduction, or a temporary stop of one of the agents as a result of interaction management was frequently not consistent with the guideline. Adjusted for all other variables male gender, the highest age category (>75 yr) and current use of more than seven medications were associated with a higher probability for non-adherence to the guideline by pharmacies. Prescriber related variables had no influence on non-adherent management.

In *Chapter 4*, we focused on patient outcomes of clinical risk management by community pharmacies. In *Chapter 4.1*, we examined the clinical value of pharmacists' interventions to correct prescription errors. This study was based upon data gathered in the second study presented in this thesis (Chapter 2.2). We reviewed a random sample of 144 modifications of prescription errors. Each prescription modification was evaluated by a robust panel of reviewers (mostly 9

or 10), comprising of representatives of five groups of healthcare professionals (community pharmacists, hospital pharmacists, general practitioners, specialists for internal diseases, and non-practising medical/pharmaceutical experts). After generally rating each modification as positive, negative, or neutral as to the pharmacotherapy of the patient, the reviewers assessed its outcome (in terms of prevention of an adverse drug reaction (ADR), an improvement in effectiveness, both, or other), the probability and importance of improvements in effectiveness and/or the probability and seriousness of an ADR in case of a non-intervention. Our analysis concerning the first general assessment included 144 interventions. After this, the analysis concerned a selection of 90 interventions that were consistently rated 'positive'. On average, one in 200 prescriptions (0.49%) was found to have been positively modified by Dutch community pharmacists. By extrapolating these data, we estimated a daily occurrence of approximately 2700 positive interventions leading to a modification of the prescription in all Dutch pharmacies (1.6 per pharmacy per day). About half of these interventions (49.8%) were aimed at preventing ADRs, 29.2% at the effectiveness of pharmacotherapy and 8.6% at both effectiveness and ADR. Reviewers' ratings varied widely between different categories of drug related problems (wrong dose, wrong medicine, drug-drug interaction, drug-disease interaction (contraindication) medicine obsolete, double medication and duration of use). The impact of individual interventions (n=83) varied and for 53% of these interventions, it was estimated to be relatively high.

In a second study within *Chapter 4*, we were interested in the issue of continuity of care, of which little is known concerning community pharmacies. Discontinuity of care carries the risk of medication errors and poor clinical outcomes. The objective of the study, presented in *Chapter 4.2*, was to explore the prevalence and determinants of pharmacy shopping behaviour and, in addition, the association between shopping behaviour and heavy use of psychotropic drugs. We used a Dutch health insurance pharmacy claims database for this study. All beneficiaries visiting two or more pharmacies in 2001 were indicated as 'shoppers' (n=45 805). From all others having received at least one prescription, a random sample was taken and indicated as 'non shoppers' (n=45 805). Shoppers were classified into three mutually exclusive categories (light, moderate and heavy shoppers). We investigated variables as determinants of shopping behaviour. The association between shopping behaviour and the heavy use of (a combination of) categories of psychotropic drugs (hypnotics and

anxiolytics, antidepressants, antipsychotics and opioids) was examined. Of all beneficiaries, 10.8% were identified as shoppers, of which the vast majority (98.8%) could be described as 'light shoppers' and a small minority (0.2%) as 'heavy shoppers'. In addition, we found that female gender, younger age (≤40 yr), the use of three or more different drugs and visiting different kinds of prescribers were associated with shopping behaviour. Shoppers more frequently received at least one prescription for systemic anti-infectives (51.7% vs. 30.8%). This finding suggests that these patients are at risk for (unintentional) problems, such as drug-drug interactions, which occur regularly with these agents. Communicating with the patient may already reduce these unintentional problems. Shoppers also more frequently received at least one prescription for nervous system drugs (46.2% vs. 29.3%). There was a clear association between the degree of shopping behaviour and heavy use (≥ 365 Defined Daily Doses dispensed in 2001) of one or more categories of the psychotropic drugs, for example, between heavy shopping behaviour and the heavy use of hypnotics and anxiolytics (OR_{adj} 17.3; 95%CI 10.4–28.9). We may conclude that a relatively small proportion of patients exhibit possibly intentional shopping behaviour with psychotropic drugs, in particular related to the heavy use of hypnotics and anxiolytics. Linking pharmacy computer systems will signal and hopefully prevent most problems related to pharmacy shopping behaviour.

In the final *Chapter 5*, we synthesized the main results of the studies in this thesis and deduced some suggestions concerning the evaluation of pharmacy practice, underlining the necessity of evaluations within the clinical risk management cycle. Linking this with pharmacy practice research we suggested more research into the assessment phase and the management phase as well as the relation between both (implementation, quality). We suggested some areas of research, such as: the development of guidelines used in pharmacies; the issue of prioritising between drug therapy related problems; the process of implementation of such guidelines; the adherence to pharmacy guidelines in daily pharmacy practice; the process of identification and assessment of risks leading to new interventions in pharmacies; the value or effectiveness of newly introduced pharmacy interventions; the risk management system of the pharmacy itself (e.g. dispensing errors, the influence of the workload, nature of safety culture); and the variability between pharmacy practices (e.g. pharmacy characteristics as potential determinants of quality outcomes; quality indicators). In addition, we made some suggestions concerning the methodology such as more accent on

randomized controlled trials concerning new interventions and the development of a Dutch pharmacy care practices-based research (and education) network. Finally, we discussed the development of pharmacy practice research taking into account its relationship with other fields, such as health services research and pharmacoepidemiology. There is a necessity for newly developed and well coordinated programmes and for more generous funding. More thought has to be given to possibilities to disseminate results from evaluations into pharmacy practice and policy.

SAMENVATTING

Dit proefschrift begint met een inleiding (*Hoofdstuk 1*), waarin we een overzicht geven van de recente geschiedenis van de openbare farmacie. Tevens gaan we in op de veranderingen in de taken en positie van de openbare apotheker. We concludeerden dat het farmaceutische patiëntenzorg concept de manier van denken en doen van apothekers recentelijk heeft veranderd. De essentie van de zorg van apothekers is verschoven van het geneesmiddel naar de gebruiker ervan en zijn therapie. Farmaceutische patiëntenzorg heeft grote invloed gehad op de opleiding van apothekers, waardoor de competenties van apothekers wezenlijk zijn veranderd vergeleken met die van dertig jaar geleden. De vraag is echter of dit concept het meest geschikte antwoord geeft op het systematische probleem van medicatiefouten en geneesmiddeltherapie gerelateerde problemen in het algemeen. Daarom stellen we in de inleiding voor om het concept van risicomanagement te betrekken bij de beschrijving en evaluatie van de apotheekpraktijk. Het concept van risicomanagement voegt diverse belangrijke aspecten toe, die bij het concept van farmaceutische patiëntenzorg onderbelicht zijn, zoals de beoordeling van risico's van geneesmiddelen, het management van risico's van geneesmiddelen in de dagelijkse praktijk en tot slot de evaluatie van (delen van) het risicomanagement systeem.

Na de inleiding op dit proefschrift wordt een aantal onderzoeken gepresenteerd, die alle als doel hebben om de kennis en het begrip over de bijdrage van de apotheker aan de patiëntenzorg in onze moderne gezondheidszorg te vergroten. De gepresenteerde onderzoeken in dit proefschrift vallen globaal genomen in drie delen uiteen. Het eerste deel (*Hoofdstuk 2*) richt zich vooral op de aard en omvang van geneesmiddeltherapie gerelateerde problemen, zoals deze zich voordoen in Nederlandse openbare apotheken, oftewel de uitkomsten van dagelijkse primaire processen in de openbare apotheek. In *Hoofdstuk 3* zijn we geïnteresseerd in twee randvoorwaarden voor goede kwaliteit van risicomanagement in apotheken. In het derde deel (*Hoofdstuk 4*) van het proefschrift richten we ons vooral op patiëntuitkomsten van het risicomanagement in de zorgpraktijk van openbare apotheken.

In *Hoofdstuk 2.1* presenteren we een onderzoek naar de aard en omvang van bereidingen in een steekproef van 79 openbare apotheken in Nederland. Eeuwenlang was de bereiding een elementaire taak van apotheken, maar sinds de Tweede Wereldoorlog is deze sterk veranderd. Door recepten van bereide geneesmiddelen te vergelijken met een even grote steekproef van recepten van

niet bereide geneesmiddelen onderzochten we welke patiënt, geneesmiddel en voorschrijver gerelateerde factoren geassocieerd zijn met recepten voor bereide geneesmiddelen. Daarnaast wilden we weten waar de huidige bereidingen vandaan komen en in welke mate er gebruik gemaakt wordt van protocollen voor de bereiding. Tot slot vroegen we ons af welke inschatting de betrokken apothekers konden maken over de beschikbaarheid van een industrieel geneesmiddel voor de betrokken bereide geneesmiddelen en of er naar hun mening patiënt gerelateerde redenen waren voor de bereiding. Beide laatste vragen geven een indruk over de waarde van bereidingen in de apotheek. Het percentage recepten voor bereidingen was 3,4%, gerelateerd aan het totaal aantal recepten in de betrokken apotheken. Dit betekent gemiddeld 12,5 bereidingen per apotheek per dag, waarbij we wel een grote spreiding tussen de apotheken waarnamen. Niet al deze bereidingen kwamen uit de apotheek zelf: 28,4% was afkomstig van gespecialiseerde bereidingsbedrijven en 5,2% van andere apotheken, zoals ziekenhuisapotheken. De werkelijke omvang van de bereiding in de openbare apotheek zelf kwam daarmee op 2,3%, waarvan circa de helft in voorraad werd gehouden. Het merendeel van de bereidingen betrof doseervormen voor op de huid, veel meer dan bij de niet bereide producten (62,1% versus 5,3%). Ook dranken en middelen voor toepassing in de keel, neus of het oor kwamen relatief vaak voor. De dermatoloog was een sterke determinant voor bereide geneesmiddelen, vergeleken met de huisarts. Jonge patiënten (≤12 jaar) ontvingen vaker een bereid geneesmiddel dan patiënten die ouder waren. Recepten voor bereidingen, die voor het eerst werden voorgeschreven, kwamen twee keer zo vaak voor als herhaalrecepten voor deze middelen, hetgeen betekent dat bereide middelen minder chronisch worden voorgeschreven. We ontdekten dat bij 58% van de in de apotheek bereide middelen een (semi)gestandaardiseerd protocol werd gebruikt. Dit deel van het onderzoek past overigens goed bij Hoofdstuk 3, waarin de kwaliteit van het risicomanagement van apotheken centraal staat. Tot slot vonden de deelnemende apothekers dat ongeveer 63% van de bereide middelen niet vervangen kon worden door een industrieel geproduceerd geneesmiddel. Ze waren verder van mening dat er in ongeveer een derde van de gevallen een patiënt gerelateerde reden voor de bereiding was te geven. In ongeveer 10% van de gevallen gaf men typische farmaceutische patiëntenzorg redenen aan, zoals intolerantie of contra-indicatie, gebruiksgemak of een speciaal benodigde doseringseenheid. Dit betekent dat er tenminste 1,2 geneesmiddel per apotheek per dag met zo'n specifieke patiëntenreden wordt bereid.

De wijziging van een recept vanwege een interventie door de apotheek is een specifieke uitkomst van de dagelijkse primaire procesgang in de openbare apotheek. In een grote steekproef van 141 apotheken in Nederland onderzochten we de aard en omvang van de geneesmiddeltherapie gerelateerde problemen die aan deze wijzigingen zijn verbonden. De resultaten worden gepresenteerd in *Hoofdstuk 2.2*. Door gewijzigde recepten te vergelijken met een willekeurige steekproef van niet gewijzigde recepten konden we vaststellen welke patiënt, geneesmiddel en voorschrijver gerelateerde factoren van invloed waren op deze wijzigingen. De recepten werden op een door ons vastgestelde dag tijdens het eerste kwartaal van 1999 verzameld. We vonden dat 4,3% van alle recepten op de onderzoeksdag was gewijzigd, met een gemiddelde van 14,3 wijzigingen per apotheek per dag. Voor recepten met 'uitsluitend recept geneesmiddelen' was de incidentie 4,9%. De meerderheid (71,8%) van de wijzigingen van dit soort recepten betrof een min of meer administratieve wijziging, veelal vanwege onvolledige gegevens op het recept (bijvoorbeeld niet gespecificeerde dosering of sterkte, of onvolledige patiëntgegevens). Bij 22,2% van de wijzigingen ging het om recepten die bij ongewijzigde aflevering wellicht vervelende consequenties voor de patiënt hadden betekend. Het belangrijkste probleem was de dosering, meer dan de helft. Andere, minder vaak voorkomende problemen waren onder andere geneesmiddeleninteracties, contra-indicaties en dubbelmedicaties. De kans op een wijziging was significant groter als het recept bedoeld was voor iemand jonger dan 40 jaar, vergeleken met iemand in de leeftijd tussen 40 en 65. Een hogere kans op een wijziging werd ook gevonden voor recepten voor geneesmiddelen voor ademhalingsproblemen. Vergeleken met recepten van de eigen huisarts bleken recepten van specialisten en andere voorschrijvers een hogere wijzigingskans te hebben. Geschreven recepten hadden een driemaal zo grote wijzigingskans in vergelijking met geprinte recepten. Het geschreven recept bleek de sterkste onafhankelijke determinant te zijn in een multivariate analyse.

In *Hoofdstuk 2.3* gaan we specifiek in op een van de geneesmiddeltherapie gerelateerde problemen, namelijk de geneesmiddeleninteracties. We onderzochten de omvang en de aard van interactiesignalen in de openbare apotheek en de wijze waarop apotheken deze afhandelden. In 63 apotheken werden hierover gegevens verzameld (gemiddeld gedurende 2,4 dag per apotheek). We vonden een hoog percentage signalen: ongeveer 6% van alle recepten genereerde zo'n signaal. Bij een minderheid (31,1%) van de signalen (n=2572) ging het om een

interactie die voor het eerst voorkwam bij de betreffende patiënt, bij 21% van de signalen waren twee voorschrijvers betrokken. De 20 meest voorkomende interacties zorgden voor ongeveer 76% van alle signalen. Geneesmiddelen voor hart- en vaataandoeningen, NSAIDs (een soort pijnstillers), orale anticonceptiva (de pil) en antibiotica waren het meest bij deze interacties betrokken. De betrokken apotheken gingen over tot een zogenoemde externe actie in 27,3% van de signalen. Dat betekende een wijziging van een van de geneesmiddelen (n=65; 9,3%), communicatie met de voorschrijver of de trombosedienst (n=90; 12,8%) of communicatie met de patiënt (n=547; 77,9%). Als er geen externe actie plaats vond (n=1860; 72,3%), hadden de apothekers in de meeste gevallen (circa 76%) geconcludeerd dat de geneesmiddeleninteractie al in het verleden was afgehandeld. Andere redenen om uiteindelijk niet te interveniëren waren bijvoorbeeld onterecht signaal, acceptabele geneesmiddeleninteractie, of geneesmiddeleninteractie niet als relevant beschouwd. De kans op externe actie van de apotheek was veel groter bij interacties die voor het eerst bij de betrokken patiënt voorkwamen. Vanwege het grote aantal meldingen voor geneesmiddeleninteracties per apotheek per dag adviseren we de deskundigen om nog eens na te gaan welke interacties werkelijk bewaakt moeten worden. Het onderdrukken van signalen voor een zekere tijd nadat het signaal eenmaal is afgehandeld, is een interessante mogelijkheid om dit probleem aan te pakken, maar zal nader onderzocht moeten worden. De kwaliteit van de signaalafhandeling verdient ons inziens nadere aandacht, omdat er aanwijzingen uit dit onderzoek naar voren kwamen dat deze verbeterd kan worden.

In *Hoofdstuk 3* gaan we in op een tweetal randvoorwaarden voor de kwaliteit van risicomanagement in openbare apotheken. Een belangrijke randvoorwaarde voor de afhandeling van zogenoemde contra-indicaties is de documentatie van ziekten en intoleranties in het elektronisch farmaceutisch dossier van de patiënt. Bij een contra-indicatie is er sprake van een negatieve wisselwerking tussen een ziekte en een voorgeschreven geneesmiddel of van een intolerantie, waaronder allergie, voor het voorgeschreven geneesmiddel. Dergelijke vastlegging in elektronische patiëntendossiers in apotheken is noodzakelijk om een signaal te genereren op het moment dat een voorgeschreven gecontra-indiceerd geneesmiddel wordt ingevoerd in de computer van de apotheek. Het is opvallend dat er nauwelijks onderzoek beschikbaar is over elektronische patiëntendossiers in apotheken. In *Hoofdstuk 3.1* wordt een onderzoek gepresenteerd naar het voorkomen en de kwaliteit van deze vorm van documentatie in elektronische patiëntendossiers in

een specifieke groep van 79 apotheken. Deze apotheken verzamelden gedurende één dag in 2003 documentatiegegevens van iedere geselecteerde patiënt (n=687). In 57,4% van de dossiers werd tenminste één geregistreerde ziekte aangetroffen en in 7,9% ervan tenminste één intolerantie. Hoe hoger de leeftijd, het aantal in gebruik zijnde geneesmiddelen en de ziektelast (de zogenaamde 'chronic disease score') des te groter de kans op een dergelijke documentatie in het elektronische dossier van de patiënt. We vonden echter dat bepaalde ziekten in relatief hoge mate waren gedocumenteerd, zoals diabetes (84,7%), astma/COPD (strikte definitie; 75,9%) en hypothyroïdie (75,0%), terwijl andere slechts beperkt (prostaathyperplasie; 55,6%) of heel beperkt (hartfalen; 29,4%) waren vastgelegd. De betrouwbaarheid van de documentatie van de ziekten was hoog voor hypothyroïdie (100%) en diabetes (87,1%). We mogen concluderen dat door een verbetering van de besproken documentatie de bewaking van contra-indicaties in Nederlandse openbare apotheken verder geoptimaliseerd kan worden.

Voor een goede medische praktijk wordt het gebruik van richtlijnen, die gebaseerd zijn op resultaten uit wetenschappelijk onderzoek, belangrijk gevonden. Deze richtlijnen zijn al vaak onderwerp van onderzoek geweest. Er is echter maar weinig bekend hoe apotheken zich houden aan de richtlijnen die bedoeld zijn voor de afhandeling van signalen die zich in apotheken voordoen, zoals die ten gevolge van een geneesmiddeleninteractie. In *Hoofdstuk 3.2* presenteren we de resultaten van een onderzoek hiernaar. We keken daarbij ook naar de relatie tussen het zich niet houden aan de richtlijn en bepaalde patiënt en voorschrijver gerelateerde factoren. Voor dit onderzoek werden 16 klinisch relevante interacties geselecteerd. Tussen juni en augustus 2005 verzamelden 149 apotheken signalen voor deze interacties, zoals ze in de dagelijkse praktijk voorkomen. Bovendien werd informatie over de betreffende patiënt verzameld, alsmede over het signaal zelf, de voorschrijver en de wijze van afhandelen. Er werd in 69,3% (423 van 610) conform de richtlijn gehandeld, waarbij er grote verschillen waren tussen de 16 geselecteerde interacties. Hoge waarden werden gevonden bij twee interacties met coumarines (92,3% en 95,8%) en relatief hoge waarden bij tricyclische antidepressiva – terbinafine (90,9%), statines – macroliden (89,8%), statines – antimycotica (82,2%) en PDE-5 remmers – CYP3A4 remmers (75,0%). (Aanzienlijk) lagere waarden werden gevonden bij de twee interacties met theophylline (45,0% and 21,6%), digoxine – macroliden (8,9%) and PDE-5 remmers – nitraten (2,8%). Voor die signalen waarvoor vervanging van één der middelen de enige afhandelingsoptie was, werd in een

minderheid van de gevallen (9,2%) volgens de richtlijn gehandeld. Voor die signalen met een duidelijke alternatieve optie was dit veel vaker (82,2%) het geval. Vervanging van één der betrokken geneesmiddelen, door de richtlijn geadviseerd voor de meeste interacties, werd slechts in een minderheid van de gevallen uitgevoerd. Een vervanging, een dosisreductie of een tijdelijke stopzetting van één der geneesmiddelen als uitkomst van de afhandeling van het signaal, kwam regelmatig niet overeen met de richtlijn. De kans op inconsistentie met de richtlijn was groter bij mannen, de hoogste leeftijdscategorie (>75 jaar) en bij gelijktijdig gebruik van meer dan zeven medicijnen. Deze laatste bevinding vereist nader onderzoek. Aan de voorschrijver gerelateerde variabelen hadden geen invloed op de inconsistentie, ook betrokkenheid van meerdere voorschrijvers bij een interactiesignaal niet.

In *Hoofdstuk 4* beschrijven we de onderzoeken die vooral gaan over patiëntuitkomsten gerelateerd aan het werk van apothekers. In de eerste studie, die u terugvindt in *Hoofdstuk 4.1*, onderzochten we de betekenis voor de patiënt van de apotheekinterventies die leiden tot een receptwijziging. De receptwijzigingen, die voor dit onderzoek werden gebruikt, kwamen eerder aan de orde in Hoofdstuk 2.2. In het onderzoek beschreven in *Hoofdstuk 4.1* hebben we gebruik gemaakt van een steekproef van 144 gewijzigde recepten met fouten. Iedere receptwijziging werd beoordeeld door een panel van deskundigen (meestal 9 of 10), die afkomstig waren uit vijf groepen van gezondheids-zorgprofessionals (openbare apothekers, ziekenhuisapothekers, huisartsen, internisten en medisch/ farmaceutische deskundigen, die elders maar niet in de gezondheidszorgpraktijk werkzaam waren). In de eerste plaats moest men iedere receptwijziging beoordelen als positief, negatief of neutraal voor de behandeling van de patiënt. Vervolgens werd gevraagd de uitkomst van de interventie van de apotheek te scoren: preventie van bijwerkingen, verbetering van de werkzaamheid of beide. Tot slot werd gevraagd naar de waarschijnlijkheid en het belang van de verbetering van de werkzaamheid en/of de waarschijnlijkheid en ernst van een bijwerking in geval de apotheek geen interventie had ondernomen. De eerste stap omvatte in totaal 144 receptwijzigingen, waarna werd doorgegaan met 90 nagenoeg unaniem positief beoordeelde interventies. Dit laatste betekent dat er gemiddeld 1 op de 200 recepten (0,49%) in positieve zin gewijzigd werden door Nederlandse openbare apothekers. Voor heel Nederland zou dit betekenen dat er elke dag circa 2700 positieve interventies plaats vinden die leiden tot een wijziging van het recept (1,6 per apotheek per dag). Ongeveer de helft (49,8%)

waren gericht op de preventie van bijwerkingen, 29,2% op de verbetering van de effectiviteit van de geneesmiddelentherapie en 8,6% op beide. De beoordeling van de deskundigen van de diverse categorieën van problemen (verkeerd geneesmiddel, verkeerde dosering, geneesmiddeleninteractie, obsoleet geneesmiddel, dubbelmedicatie en gebruiksduur) varieerde sterk. De geschatte impact van 83 (van 90) interventies varieerde flink, maar voor 53% hiervan was de schatting relatief hoog.

In een tweede onderzoek in dit deel van het proefschrift waren we geïnteresseerd in het thema van de continuïteit van zorg, waarover weinig bekend is waar het apotheken betreft. Discontinuïteit van zorg houdt risico's in, zoals medicatiefouten en negatieve gezondheidsuitkomsten. Het doel van het onderzoek gepresenteerd in *Hoofdstuk 4.2* was in de eerste plaats om het voorkomen van apotheek-shopgedrag te onderzoeken alsmede de factoren die daarop van invloed zijn. In de tweede plaats waren we geïnteresseerd in de relatie tussen apotheek-shopgedrag en meer dan normaal chronisch gebruik van psychotrope geneesmiddelen (hypnotica en anxiolytica, antidepressiva, antipsychotica en opioïden). Voor ons onderzoek konden we gebruik maken van een gegevensbestand uit 2001 van een regionale zorgverzekeraar, waarin gegevens over de aflevering van geneesmiddelen door apotheken aan verzekerden waren opgenomen alsmede allerlei andere relevante variabelen. Alle verzekerden die twee of meer apotheken in 2001 hadden bezocht, werden gekarakteriseerd als 'shoppers' (n=45 805). Van alle andere verzekerden die tenminste één recept in dat jaar verstrekt hadden gekregen, werd een even grote steekproef genomen. Zij werden aangeduid als 'non-shoppers'. Op deze wijze konden we onderzoek doen naar factoren die van invloed zijn op het shopgedrag. De shoppers werden verder onderverdeeld in lichte shoppers, matige shoppers en zware shoppers. Van alle verzekerden bleek 10,8% shopper te zijn, waarvan echter de overgrote meerderheid (98,8%) lichte shoppers waren en slechts een kleine minderheid zware shoppers (0,2%). We vonden verder dat vrouwen, jonge mensen (≤40 jaar), mensen die drie of meer verschillende middelen gebruiken en zij die gebruik maken van verschillende soorten artsen een grotere kans hebben op shopgedrag. Shoppers ontvingen vaker tenminste een recept voor een antibioticum (51,7% versus 30,8%). Dit wijst erop dat deze patiënten risico lopen op onbedoelde risico's, zoals geneesmiddelinteracties, die met deze middelen regelmatig voorkomen. Communicatie met de patiënt tijdens het bezoek aan de apotheek kan de kans op deze onbedoelde problemen wellicht

reduceren. Shoppers ontvingen ook vaker tenminste een recept voor een psychotroop geneesmiddel (46,2% versus 29,3%). Er bleek een duidelijke associatie te bestaan tussen de mate van shopgedrag en meer dan normaal chronisch gebruik van een of meer van deze middelen (≥365 standaard dagdoseringen afgeleverd in 2001). Zo vonden we bijvoorbeeld dat de kans op meer dan normaal chronisch gebruik van hypnotica en anxiolytica meer dan 17 keer groter is bij heavy shoppers dan bij non-shoppers. Op basis van dit onderzoek mogen we concluderen dat een relatief klein aantal patiënten vermoedelijk bedoeld shopgedrag met psychotrope middelen aan de dag legt, in het bijzonder van hypnotica en anxiolytica. Door apotheekcomputersystemen met elkaar te verbinden zullen dit soort en andere problemen makkelijker aan het licht komen en voorkomen kunnen worden.

Na de beschrijving van de belangrijkste resultaten van dit proefschrift in *Hoofdstuk 5*, benadrukken we in dit slothoofdstuk nog eens het belang van evaluatie van het systeem van risicomanagement in de zorgpraktijk, van de apotheek en daarbuiten. We maken een verbinding met het terrein van het farmaceutisch praktijkonderzoek. We doen enige suggesties voor onderzoeksgebieden, zoals de ontwikkeling van apotheekrichtlijnen, het thema van prioritering tussen geneesmiddeltherapie gerelateerde problemen, het proces van implementatie van zulke richtlijnen, de toepassing van apotheekrichtlijnen in de dagelijkse praktijk, het proces van identificatie en beoordeling van risico's dat leidt tot nieuwe interventies in apotheken, de waarde of de effectiviteit van nieuw geïntroduceerde apotheekinterventies, het systeem van risicomanagement van de apotheek zelf (bijvoorbeeld afleverfouten, de invloed van werklast, de veiligheidscultuur) en de variatie tussen apotheekpraktijken (bijvoorbeeld apotheekkarakteristieken als determinanten van uitkomsten, kwaliteitsindicatoren). Daarnaast doen we enige voostellen over de methodologie, zoals de ruimere toepassing van gerandomiseerde en gecontroleerde onderzoeken bij de beoordeling van nieuwe interventies en de ontwikkeling van een onderzoeksnetwerk van Nederlands apotheken. Tot slot gaan we in op de verdere ontwikkeling van het farmaceutisch praktijkonderzoek, waarbij men zich rekenschap moet geven van de relatie met andere terreinen van onderzoek, zoals het gezondheidszorgonderzoek en de farmacoepidemiologie. Nieuw ontwikkelde en goed gecoördineerde praktijkonderzoekprogramma's zijn noodzakelijk alsmede ruimere financiering daarvan. Tevens moet nagedacht

worden over mogelijkheden om de resultaten van onderzoek te vertalen naar de farmaceutische praktijk en naar het beleid.

EEN WOORD VAN DANK...

Doe geen afstand van uw illusies.
Wanneer zij verdwenen zijn, bestaat u nog steeds,
maar dan hebt u opgehouden te leven.
(Mark Twain)

Geachte lezer,

Het zal u bij het doorbladeren van het boekje zijn opgevallen dat velen hebben meegewerkt. U kwam allerlei namen tegen als medeauteurs van hoofdstukken of in de dankbetuiging aan het einde daarvan. "Je kunt het niet alleen" was de titel van de oratie van mijn promotor Peter de Smet. Dat geldt ook voor dit promotietraject en een woord van dank is dan ook op zijn plaats.
Een dankwoord schrijven is echter moeilijk. Het is proza van een andere orde. Je moet het gevoel van dankbaarheid of erkentelijkheid omzetten in woorden. En woorden schieten vaak te kort, zoals u weet. Maar ik sta in het krijt bij velen en bij enkelen in het bijzonder, dus het moet. Zonder hun hulp immers, en zonder hun bemoediging, steun en vriendschap zou het werkelijk onbegonnen werk zijn geweest.

Allereerst wil ik u mijn promotoren voorstellen. Ik heb werkelijk geboft met hun inspirerende, maar ook nauwkeurige en kritische begeleiding. Iedere vergadering was weer een exercitie in het 'to-the-point' formuleren van doelstellingen, de insteek, de belangrijkste resultaten, de vertaling naar de praktijk. Jammer eigenlijk, dat we aan het einde van dit traject zijn aangeland! Mijn eerste promotor, prof. Toine Egberts, hoogleraar te Utrecht en ook ziekenhuisapotheker, is een formidabele onderzoeker en onderwijsgever, en niet in de laatste plaats een voortreffelijke apotheker. Bruggenbouwer tussen eerste en tweede lijn, tussen de openbare farmacie en de ziekenhuisfarmacie. Het was daarom heel logisch dat hij mij, als openbaar apotheker, al die jaren heeft begeleid. Eigenlijk moet ik zeggen, aan de hand genomen. Eerst rustig aan, voetje voor voetje, en dan langzamerhand steeds sneller. Ik heb veel van hem geleerd, zoals het systematisch werken aan een onderzoek en aan een artikel. Terwijl hij heel doelgericht bezig was, heb ik nooit druk ervaren. Altijd vriendschappelijk, tot en met een prachtige tocht in de bergen! Ook daar herkende ik zijn zorg en zijn perfectie. Prof. Peter de Smet, hoogleraar in Nijmegen, is één van de mensen die mij stimuleerde toch nog te promoveren. Door de SIR Masterclass, waarover ik later nog iets meer zal vertellen, zijn we nauw in het onderzoek gaan samenwerken. Een boeiende samenwerking. Het logische gevolg daarvan was dat hij mijn tweede promotor werd. Ik heb veel aan hem gehad vanwege zijn enorme kennis van de (openbare) farmacie en van de literatuur. Hij heeft een kritische houding en hij is precies, waardoor we regelmatig discussieerden over de betekenis van resultaten en – dichter als hij is –

over de betekenis van woorden. Ik zal die regelmatige discussies met hem, een denker over de farmacie, missen.

Beste lezer, vanzelfsprekend zijn mijn promotoren voor het proefschrift zelf het belangrijkst geweest. Maar u zult begrijpen dat op mijn leeftijd en in mijn setting, ontstaan na zoveel jaren, veel meer mensen van groot belang zijn geweest voor dit resultaat. Laat ik beginnen op de plek waar ik - in Leiden - werk.
Zonder het succes van het academiseringsproject in de Stevenshof in Leiden, zou er geen proefschrift zijn verschenen. En dat project zou er niet zijn geweest zonder prof. Bert Leufkens, hoofd van de afdeling farmaco-epidemiologie en farmacotherapie van de Universiteit in Utrecht. Hij is al jaren, dat wil zeggen vanaf het begin in 1985, van grote betekenis voor de ontwikkelingen in de Stevenshof, voor mijn ontwikkeling en voor het plezier dat ik in de farmacie beleef. Weinigen zijn zo innoverend en stimulerend, en zijn zo belangrijk in het scheppen van randvoorwaarden als hij. Ik hoop hem nog lang in beeld te houden. Bert Leufkens is ook, al die jaren, voorzitter geweest van de stichting die verantwoordelijk was voor de apotheek- en onderzoekspraktijk in de Stevenshof. Het welslagen is mede te danken aan de inspanningen van het bestuur van de stichting. De bestuursvergaderingen, vol ideeën, fungeerden gedurende al die jaren veeleer als denktanksessies. Met goede adviezen en honderd procent vertrouwen heb ik kunnen groeien en heeft het project kunnen groeien naar wat het nu is. Voortreffelijke apothekers en academici, misschien wel het 'crème de la crème' van de Nederlandse farmacie, hadden al die jaren zitting in het bestuur. Ik prijs me gelukkig.

Ik ga al jaren met veel plezier naar mijn werk! De voortreffelijke en gemotiveerde collega's en assistenten in apotheek Stevenshof en bij het SIR Institute for Pharmacy Practice and Policy zijn daar verantwoordelijk voor. Fijne, enthousiaste en hardwerkende mensen. Een goed functionerende thuisbasis dus, van groot belang voor het welslagen van mijn proefschriftproject. Ik had steeds het volste vertrouwen dat de zorg van alledag goed verliep, maar ook dat de basisgedachten achter het academiseringsproject in het vizier bleven: een werkplaats in de praktijk met een nauwe samenwerking met de academie, een voorbeeld voor anderen en innovatief. Ik zou ze u allen wel willen voorstellen. Maar zonder anderen tekort te willen doen wil ik met name twee mensen in de Stevenshof noemen. Met hen eer ik allen. Allereerst Marcel Bouvy: hij was nauw betrokken bij één onderzoek in dit proefschrift, maar ook bij de inleiding en het

slothoofdstuk. Marcel Bouvy is eigenlijk het kloppend hart van ons onderzoeksinstituut; hij is een prima wetenschapper, maar ook een bijzonder mens, waarmee ik heel graag samenwerk. Dat laatste hoop ik nog een tijdje te doen, ondanks de nieuwe uitdagingen die zich zullen aandienen. Dat zullen bijzondere uitdagingen voor hem zijn, maar ze zullen ook van belang zijn voor het Stevenshof project en - ik weet het zeker - ook voor de farmacie. Ik zal hem daarbij – indien nodig - graag helpen. Een klein beetje terugdoen, als het ware. Henk-Frans Kwint is de andere, die ik op de voorgrond zet. Hij is beherend apotheker van apotheek Stevenshof, de teamleider met andere woorden. Hij begeleidt met overgave de alledaagse zorg in de apotheek, daarbij samenwerkend met enthousiaste tweede apothekers en met zorggerichte assistenten, waarvan ik sommige al zo lang ken. Onder zijn leiding is 'ons project' niet stil blijven staan, integendeel! De samenwerking met een bijzondere groep van huisartsen in de wijk groeit nog steeds en is gestoeld op vertrouwen en gericht op het welzijn van patiënten.

Geachte lezer, de werksituatie noemde ik als thuisbasis. Mijn echte thuisbasis is echter mijn gezin. Zoals u wellicht hebt gezien, heb ik aan hen mijn boekje opgedragen. Ik voel me met hen zeer verbonden. Heleen Swart, mijn bijzondere partner, gaf mij steun zoals alleen zij dat kan. Bovendien ook heel concreet bij het ontwerp voor de buitenkant van het proefschrift. Het geeft een heel goed gevoel dat ze zelfs tijdens de verdediging, als paranimf, vlakbij me is. Natuurlijk draag ik het boekje ook op aan mijn twee lieve dochters, Marleen en Jorien. Zij waren wel enigszins gewend aan mijn fascinatie voor de farmacie en mijn meer dan normaal werken, maar het laatste jaar was toch wel een beetje 'heavy'. Gelukkig konden ze me iets beter begrijpen toen ze zelf betrokken raakten bij het project door bijvoorbeeld het intikken van onderzoeksgegevens en het opbergen van al die formulieren! Het is dus ook een beetje hun boekje.

En waarom Martine Kruijtbosch dan als tweede paranimf? Zij verenigt heel verschillende werelden in één persoon. Na jaren van hard werken tegen kinderarbeid in India onder zeer eenvoudige omstandigheden kwam ze per toeval bij de SIR terecht. Ze werd een belangrijke steun bij mijn onderzoek. Ik bedank haar voor de collegialiteit, haar enthousiasme en vriendschap. Het (Groningse) hart zit bij haar aan de goede kant: "We bliev'n der veur goan!"
En toen het bijna af was, was daar Francis te Nijenhuis voor een prachtige vormgeving van het binnenwerk van het boekje! Ze begeleidde mij heel precies

langs de diverse hobbels aan het einde van het traject. Haar toewijding en kritische instelling, maar vooral haar vriendelijkheid zal ik niet vergeten.

Beste lezer, een promotieproject is een soort reis. Niet altijd luxueus, soms is het een beetje afzien. Op die reis kom je allerlei mensen tegen. Je leert ze kennen, je werkt ermee samen. Vaak aardige, enthousiaste, bijzondere mensen. Van de afdeling farmaco-epidemiologie en farmacotherapie van de Universiteit in Utrecht bijvoorbeeld, zoals Svetlana Belitser, die aardige Russische vrouw (met een klein beetje heimwee en) met die fenomenale kennis van de statistiek; Patrick Souverein, waarmee ik nog graag dat 'Tsjechische interactieonderzoek' wil afronden; die lieve (en soms een beetje strenge) Addy, die gemoedelijke gastvrouw Ineke en die aardige Suzanne, de dames van het secretariaat, die me jarenlang 's ochtends ontvingen, weer een plekje voor me zochten, maar me nooit het gevoel gaven dat iets teveel was. Min of meer per toeval ontstond er een nauwe samenwerking met Tom Schalekamp, één van de senior medewerkers van de afdeling en bovendien voortreffelijk apotheker. Ik heb zijn toewijding en zijn uitgebreide kennis van de farmacotherapie en van geneesmiddeleninteracties in het bijzonder zeer gewaardeerd. Ik zou nog graag een project over geneesmiddeleninteracties met hem willen uitwerken. Op deze afdeling reisde ik langs nagenoeg alle kamers, die de afdeling heeft, waar velen me gastvrij ontvingen. Een genoegen was het om er te werken, zoals bijvoorbeeld bij Lyda (wat kennen we elkaar al lang; worden we oud?), bij Kees (altijd belangstellend), bij Jan (wat een aanstekelijk enthousiasme), bij Willem Rump van Upper (gemoedelijk smedend aan de relatie tussen academie en praktijk), en al die anderen. Vanaf de achtste etage heb ik op deze manier in alle richtingen de Utrechtse omgeving mogen bewonderen. Overigens, niet alleen in Utrecht liep ik mensen tegen het lijf. Door mijn onderzoeken kwam ik in contact met Olga van den Hoff, toen nog werkzaam bij het WINAp in Den Haag, die de eerste twee studies logistiek voortreffelijk begeleid heeft, en met Yvonne Bouwman-Boer, vanwege haar uitmuntende kennis over de bereidingstaak van apothekers. Bij Stichting Health Base, ook een omgeving waar praktijkonderzoek leeft, met Eric Hiddink en Martijn Nieuwhof; bij de regionale zorgverzekeraar Zorg en Zekerheid met Manon Goddijn, die zo voortreffelijk de data voor het laatste onderzoek aanleverde; en met studenten, zoals de hardwerkende en heel precieze Rohini van Exel.

Het merendeel van de gegevens komt uit de praktijk van alledag, aldaar verzameld door apothekers of hun assistentes. Misschien had ik mijn woord van dank wel met deze passage moeten beginnen. Geachte lezer, ik wil heel graag benadrukken hoe belangrijk de apothekers, werkend in de praktijk van alledag, voor mijn onderzoeken zijn geweest. Zij hebben belangeloos de gegevens verzameld, geanonimiseerd, genoteerd, gefaxt, gemaild of wat dan ook. Soms moesten ze meerdere dagen gegevens verzamelen, terwijl het soms heel druk kan zijn in de apotheek. Afgemeten aan de grote belangstelling en inzet van apothekers om aan mijn onderzoeken mee te doen, zijn er veel fantastische collega's in de praktijk werkzaam.

Fantastische collega's kom ik ook ieder jaar tegen in de zogenaamde SIR Masterclass Farmaceutisch Praktijkonderzoek, die ons SIR Instituut ieder jaar organiseert. Ongeveer 10 tot 15 apothekers doen een jaar lang onderzoek in de praktijk, wat gelardeerd wordt met onderwijs. Die apothekers, maar ook wijzelf, beleven daar erg veel plezier aan. Maar behalve dat, slagen we er regelmatig in het onderzoek te publiceren. Een drietal van deze Masterclass onderzoeken vormde de basis voor een hoofdstuk in dit proefschrift. Bij het hoofdstuk over bereidingen waren de apothekers Henrieke Sysling-van Unen, Michiel Storimans, Antoinette van Yperenburg en Matthijs Engering betrokken; aan het onderzoek naar de documentatie in elektronische patiëntenkaarten in de apotheek werkten Jeroen Kappe, Esther Roebert-Reitsma, Magda Tuijn en Gudy Meyvis-de Jongh (zeer gewaardeerde apothekersassistente) mee; terwijl bij het onderzoek naar receptwijzigingen Els Dik, Monique Martens-van Motman, Taco van Witsen en Annemieke Floor-Schreudering (senior SIR medewerker en ook al in de startblokken voor een promotietraject) betrokken waren.

Tot slot vertel ik u graag dat er een commissie van enige hoogleraren is geweest die dit proefschrift heeft beoordeeld. Daarvoor wil ik de commissie graag bedanken.

Beste lezer, ik wil u danken voor de belangstelling voor dit boekwerk. Wilt u met mij over de inhoud van gedachten wisselen dan nodig ik u graag uit om met mij contact te zoeken.

Henk Buurma

LIST OF CO-AUTHORS

Marcel L Bouvy
SIR Institute for Pharmacy Practice and Policy, Leiden.
Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht.

Antoine CG Egberts
Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht.
Department of Clinical Pharmacy, TweeSteden Hospital and St Elisabeth Hospital, Tilburg.

Annemieke Floor-Schreudering
SIR Institute for Pharmacy Practice and Policy, Leiden.

Olga P van den Hoff
Scientific Institute of Dutch Pharmacists (WINAp), The Hague.

Martine Kruijtbosch
SIR Institute for Pharmacy Practice and Policy, Leiden.

Hubert GM Leufkens
Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht.

Peter AGM de Smet
Scientific Institute of Dutch Pharmacists (WINAp), The Hague.
Department of Clinical Pharmacy, University Medical Centre, Radboud University Nijmegen, Nijmegen.

Tom Schalekamp
Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht.

Co-authors

Michiel Storimans
Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, Utrecht.

Henrieke Sysling-van Unen
SIR Institute for Pharmacy Practice and Policy, Leiden.

Affiliations during the conductance of the research

LIST OF PUBLICATIONS
since 1996

PUBLICATIONS RELATED TO THE THESIS

1. Buurma H, de Smet PA, van den Hoff OP, Egberts AC. Nature, frequency and determinants of prescription modifications in Dutch community pharmacies. Br J Clin Pharmacol 2001;52:85-91.
2. Buurma H, de Smet PA, van den Hoff OP, Sysling H, Storimans M, Egberts AC. Frequency, nature and determinants of pharmacy compounded medicines in Dutch community pharmacies. Pharm World Sci 2003;25:280-7.
3. Buurma H, De Smet PA, Leufkens HG, Egberts AC. Evaluation of the clinical value of pharmacists' modifications of prescription errors. Br J Clin Pharmacol 2004;58:503-11.
4. Buurma H, De Smet PA, Kruijtbosch M, Egberts AC. Disease and intolerability documentation in electronic patient records. Ann Pharmacother 2005;39:1640-6.
5. Buurma H, De Smet PA, Egberts AC. Clinical risk management in Dutch community pharmacies: the case of drug-drug interactions. Drug Saf (in press).

OTHER INTERNATIONAL PUBLICATIONS

1. Rahimtoola H, Egberts AC, Buurma H, Tijssen CC, Leufkens HG. Reduction in the intensity of abortive migraine drug use during coumarin therapy. Headache 2001;41:768-73.
2. Rahimtoola H, Egberts AC, Buurma H, Tijssen CC, Leufkens HG. Patterns of ergotamine and sumatriptan use in the Netherlands from 1991 to 1997. Cephalalgia 2001;21:596-603.
3. Bouvy ML, Buurma H, Egberts TC. Laxative prescribing in relation to opioid use and the influence of pharmacy-based intervention. J Clin Pharm Ther 2002;27:107-10.
4. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Incidence and determinants of migraine prophylactic medication in the Netherlands. Eur J Clin Pharmacol 2002;58:149-55.
5. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Migraine prophylactic medication usage patterns in The Netherlands. Cephalalgia 2003;23:293-301.

6. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Single use of sumatriptan: a patient interview study. Headache 2003;43:109-16.
7. Van der Elst ME, Cisneros-Gonzalez N, de Blaey CJ, Buurma H, de Boer A. Oral antithrombotic use among myocardial infarction patients. Ann Pharmacother 2003;37:143-6.
8. Bouvy ML, Buurma H, Egberts AC. Determinants for successful smoking cessation with bupropion in daily practice. Pharm World Sci 2003;25:207-11.
9. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts AC. Incidence and determinants of antidepressant drug use in migraine patients. Int Clin Psychopharmacol 2003;18:331-9.
10. Van der Elst ME, Buurma H, Bouvy ML, de Boer A. Drug therapy for prevention of recurrent myocardial infarction. Ann Pharmacother 2003;37:1465-77.
11. Rahimtoola H, Buurma H, Tijssen CC, Leufkens HG, Egberts ACG. Reduction in the therapeutic intensity of abortive migraine drug use during ACE inhibition therapy - a pilot study. Pharmacoepidemiol Drug Saf 2004;13: 41-47.
12. Paulino EI, Bouvy ML, Gastelurrutia MA, Guerreiro M, Buurma H. Drug related problems identified by European community pharmacists in patients discharged from hospital. Pharm World Sci 2004;26:353-60.

OTHER PUBLICATIONS (DUTCH LANGUAGE)

1. Leufkens HG, Buurma H, Bakker A. 'Pharmacy practice research': na tien jaar nog steeds prominent op de agenda. Pharm Weekbl 1996;131:730-2.
2. Bouvy M, Buurma H. Maatregel zelfzorg zal niet lang stand houden. Pharm Weekbl 1999;134:1022-3.
3. Bouvy ML, Buurma H, Kwint HF, Rahimtoola H. Het nut van begeleiding bij staken van medicatie. Pharm Weekbl 1999;134:1380-1.
4. Van Akkerveeken HM, Kelder O, Stuijt CCM, van der Wolf JW, Buurma H, Gerrits CMJM. Een gewenste combinatie. Pharm Weekbl 2000;135:911-4.
5. Buurma H, Naaykens MMS, Kwint HF. Eenduidige geneesmiddelinformatie noodzakelijk. Overheid gedoogt grote verschillen tussen patiëntenbijsluiters. Pharm Weekbl 2000;135:1250-3.

6. Buurma H, Leufkens HGM. Academische Apotheek Stevenshof bestaat 15 jaar. Van poldergeploeter tot volwassen instituut. Pharm Weekbl 2000;135:1400-2.
7. Geers H, Pot HM, Overmars-van der Weij WCK, Gerrits CMJM, Buurma H. De standaard en de praktijk. Gebruik van inhalatiecorticosteroïden bij chronische astma. Pharm Weekbl 2001;136:266-70.
8. Buurma H, de Smet PAGM, van den Hoff OP, Egberts ACG. Prescriptiewijzigingen door openbare apotheken. Aard, frequentie en determinanten. Pharm Weekbl 2001;136:1159-60.
9. Bouvy ML, Buurma H. Vragen aan de geneesmiddelinfolijn. Actiever voorlichten over slaap- en kalmeermiddelen. Pharm Weekbl 2001;136:1850-2.
10. Floor-Schreudering A, Schoenmakers T, Septer ARW, Toemen MPH, Zon EME, Buurma H. Bevordering doelmatig geneesmiddelengebruik slaat aan. Doelmatigheidsprojecten in Nederlandse openbare apotheken in 2001. Pharm Weekbl 2003;138:1361-6.
11. Sysling-van Unen H, Buurma H. De registratie van zorghandelingen. Leiden & The Hague: SIR Institute for Pharmacy Practice and Policy & WINAp; 2003.
12. Buurma H, Meijvis-de Jongh GHBM, Kappe J, Roebert-Reitsma EN, Tuijn MM, De Smet PAGM. Inhoud valt mee, maar kan nog beter. Elektronische patiëntenkaart in de openbare apotheek. Pharm Weekbl 2005;140:1604-5.

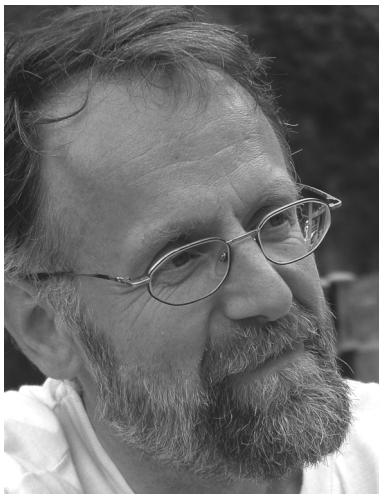
BOOKS (DUTCH LANGUAGE)

1. Reijnders L, Bouvy M, Buurma H, de Jong-van den Berg L, Vulto A, redactie. Geneesmiddelen in Nederland. 17e editie. Amsterdam: Van Gennep; 2004.
2. Buurma H, Beudeker HJ, de Jong-van den Berg LTW, Leufkens HGM, redactie. Het Geneesmiddel. 4e editie. Maarssen: Elsevier Gezondheidszorg; 2005.
3. Henk Buurma, redactie. Het Juiste Medicijn. Editie 2004. Den Haag: Consumentenbond; 2004.

PUBLICATIONS IN DUTCH NEWSPAPERS

1. Bouvy M, Buurma H. Een bezuiniging die geld kan kosten. De Volkskrant, 3 augustus 1999.
2. Bouvy M, Buurma H. Aspirine liever zonder airmiles. De Volkskrant, 9 september 2000.
3. Noach EL, Buurma H. Paracetamol hoort niet bij benzinepomp. Trouw, 7 oktober 2000.
4. Leufkens HGM, Buurma H, Bouvy ML. De apotheker is onmisbaar. Trouw, 14 februari 2006.

ABOUT THE AUTHOR



Henk Buurma was born on 3 November 1950 in Groningen, the Netherlands.
He lives in Leiden together with his wife, Heleen Swart, and his two daughters, Marleen and Jorien.
He studied pharmacy in the city of Groningen, where he obtained his pharmacy degree in 1978.

Main positions:

- researcher at the Department of Social Pharmacy and Pharmacoepidemiology (formerly called 'Farmacie en Samenleving' (Pharmacy and Society)) at Groningen University, 1978-1985;
- pharmacist at 'Apotheek Jansen' in Hoogeveen (1978-1980);
- director of 'Apotheek Stevenshof' / SIR Institute for Pharmacy Practice and Policy in Leiden (from 1985 onwards);
- researcher at the Division of Pharmacoepidemiology and Pharmacotherapy (chair: Prof.dr. Bert Leufkens), Utrecht Institute for Pharmaceutical Sciences, Utrecht University (from 1989 onwards).

Other activities and positions:

- co-author of different books (see list of publications);
- editor ad interim of the 'Geneesmiddelenbulletin';
- member of the editorial board of the 'Geneesmiddelenbulletin';
- member of the editorial board of the 'Pharmaceutisch Weekblad';
- freelance activities, e.g. for the 'Consumentenbond' (Dutch consumer organization);
- co-founder of the 'Wetenschapswinkel voor Geneesmiddelen' (science shop for medicines) at Groningen University and Utrecht University;
- co-founder of the 'PRISMA' Foundation (Practice Research in Cooperation with Pharmacists).