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THE PRESCRIPTION DRUG HISTORY
IN PHARMACOEPIDEMOLOGY

THE PRESCRIPTION DRUG HISTORY IN PHARMACOEPIDEMOLOGY

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Rijksuniversiteit Limburg te Maastricht,
op gezag van de Rector Magnificus, Prof. Mr. M.J. Cohen,
volgens het besluit van het College van Dekanen,
in het openbaar te verdedigen
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ABBREVIATIONS

ACE	angiotensin-converting enzyme
ATC	anatomic-therapeutic-chemical
ADR	adverse drug reaction
CI	confidence interval
DDD	defined daily dose
MAO	monoamine-oxidase
MEMS	medical event monitoring system
NZAMS	New Zealand Asthma Mortality Study
OTC	over-the counter
PSA	prescription sequence analysis
TCA	tricyclic antidepressant
WHO	World Health Organization

Chapter 1

INTRODUCTION

After introduction of a new drug for general medical use it is often not well known how the drug is used, by whom, and what its effects are in the group of users. Development and registration of a new drug occurs in a more or less standardized stepwise process, but what happens after market introduction is often known only in a fragmentary way. Questions remain about the reasons the drug is actually used for, what kind of people get the drug and what are the benefits and hazards of using the drug for these patients.

Pharmacoepidemiology seeks to answer these questions. Knowledge in this field has implications for pharmacotherapy in individual patients: expected benefits from use of a drug should be set against potential side-effects. Knowledge of these intended and unintended effects in the heterogeneous group of users in the population at large can only come from observational studies.

The adoption of a new medicine by prescribing physicians and its use in specific groups of patients depend on the perceived characteristics of the drug, marketing forces, and the availability of other drugs with a similar therapeutic indication. Effects of drugs can be expected to vary between groups of users with different age distribution, disease stage, or co-morbidity. Without specifically directed research, little is known about these differences. Also, the use of a drug has a time component: it is initiated and stopped at a certain time and may be followed by other therapy. These consumption patterns are usually not known at population level. Recognizing that the prescription drug history is an essential tool in pharmacoepidemiology we focussed our work on developing methods to collect, analyze and interpret such drug histories.

STRUCTURE OF THIS THESIS

The studies presented have a specific source of information on drug consumption in common: automated records in Dutch community pharmacies. An introductory chapter gives an overview of approaches in epidemiology to study drug use and drug effects, as far as they are relevant for this thesis (Chapter 2); the text is partly based on two earlier publications.^{1,2} Chapter 3 describes the various ways with which data on drug use can be collected, with emphasis on automated records in Dutch pharmacies. The main purpose of this thesis is to show three ways in which such records are useful in pharmacoepidemiology:

- 1) The analysis of collections of drug histories to look for patterns of dispensing that are suggestive of prescribing to counter side effects of another drug. (Prescription Sequence Analysis).

The approach is intended as a fast screening method when there is an urgent need for more information about the reality of possible side-effects after case reports; the approach is restricted to the subgroup of adverse reactions for which a specific medical therapy exists. Analyses are presented of drug histories of persons who received the anti-vertigo/anti-migraine drug flunarizine (chapter 4) and inhalational anti-asthmatic steroids (chapter 5).

- 2) The detection of differences of recipients of pharmacologically closely related drugs (channeling).

Concomitantly prescribed medication can point to differences in disease severity. Higher dosages of treatment and drugs intended for more severe stages of a disease are especially suggestive of such differences. More severe medical problems can be expected to be seen in patients with markers of more severe or difficult-to-treat disease.

This "channeling" can occur as selective prescribing due to differences in drug labelling, but also as a consequence of less obvious factors, such as time of market introduction, the availability of other drugs, and promotional activities. Channeling and its consequences are discussed in chapter 6. A comparison of users of three pharmacologically related asthma drugs for markers of disease severity is presented in chapter 7. In chapter 8, users of ten antidepressant drugs are compared for differences in prevalence of cardiovascular conditions.

3) The study of drug use before and after hospital admission.

Cessation of therapy at hospital admission may or may not have been purposeful. The juxtaposition of drug histories from community and hospital pharmacies reveals such cessations of therapy. Chapter 9 presents the results of such a comparison. The comparison is completed with a study of medical files in the hospital to assess whether the stopping was inadvertent or purposeful.

In order to assess the quality of drug histories from pharmacy data bases we compared results from a patient questionnaire with pharmacy data on drug use. In chapter 10 the results of this comparison are presented.

An epilogue, chapter 11, gives an overview of the work and the ideas presented in thesis, with some of their implications. Also, suggestions for work in the future are made.

There is some repetition in the description of methods in chapters 4-10, due to the fact that the material has been published in the form of articles. An advantage should be that these chapters can be read separately.

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Chapter 2

EPIDEMIOLOGY AND DRUGS: BACKGROUND OF THE WORK

Before a drug is registered for general use, its benefits and degree of safety must be shown in one or more controlled clinical trials. Clinical trials to test for therapeutic effect of a drug rarely cover more than 3000 patients. Yet, severe adverse reactions with a low incidence, between 1 in 5000 and 1 in 30,000 users, have forced withdrawal of drugs. Detection of a much more common adverse reaction needs a large clinical trial if the condition has a sizeable background incidence (table 1). Apart from being very costly and impractical, studies to determine the incidence of serious adverse reactions would take a prohibitively long time to perform. Thus, one can say that methods other than controlled clinical trials are needed for the assessment of rare adverse drug reactions.

Also, controlled trials often include a rather limited diversity of patients. After introduction for general use, the drug may be prescribed for a more vulnerable group of patients with other concomitant conditions and other medication. Also, the indications for prescribing the drug may change in time, in the direction to conditions not included in premarket studies. Further, groups of patients kept out of trials because of exclusion criteria, e.g. pregnancy, may become exposed to the drug after market introduction. Thus, while homogeneity of a trial population makes the interpretation of the results of a study more straightforward, it may flaw the relevance of the trial for the more heterogeneous population of actual users of the drug.

Complementary to controlled clinical trials are studies in existing populations of users of drugs. In population-based studies of drug use and drug effects, epidemiological methods have an obvious place. Epidemiology is mainly concerned with such factors as the determinants, occurrence, and prognosis of disease in different groups of people. Drug use, both as a consequence and a determinant of disease, thus is a valid subject for population-directed study methods. Pharmacology and epidemiology also are linked by subjects other than rare adverse reactions, e.g. the study of initially unrecognized beneficial effects, many of which are recognized only after years of general use.¹⁻³

The approaches to study an adverse reaction to a specific drug depend on both frequency of use of the drug concerned and the incidence of the ADR in a group of users (tables 2 and 3). In a methodological sense table 2 gives a hierarchy of the strength of evidence that can be provided by the different approaches, with the controlled clinical trial at top and case reports on the bottom. The choice of the approach to study a specific problem is a trade-off between feasibility and the strength of evidence that can be achieved.

Case reports

First reports of adverse reactions are often published in medical journals as case reports or case series. Case reports have proven their value especially in the early recognition of possible adverse reactions; historically, initial alerting has almost always occurred by publication of case reports.⁴⁻⁷

In a more systematic way, case reports are collected and analyzed in a regional^{8,9} or national^{7,10} setting. The approach was initiated in Britain after the thalidomide catastrophe in the early 1960s. In this approach, physicians are encouraged to report on a standard form the adverse reactions they recognized. The background idea is that a set of reports of a suspected adverse reaction, submitted independently by many physicians, are stronger evidence than isolated reports. The quality and plausibility of the reports are assessed by the staff of the centers. If questions arise, contact is sought

with the reporting physician. Reports are mostly based on the relative frequency of reports on a problem with one drug as compared with other drugs with a similar indication. Publication often occurs in a collaboration of several national monitoring centers, sometimes with data of an international registry under the aegis of the W.H.O.^{10,11}

Table 1. *Size of clinical trial needed to detect an adverse drug reaction (ADR)**

Rate of ADR in control group	N** control group	N** exposed group
1 : 100	3,000	3,000
1 : 500	16,000	16,000

* based on a significance level α of .05, a power of .90 and a relative risk of 2.
** number of persons needed

Table 2. *Approaches to study adverse drug reactions*

- Controlled clinical trial
- Cohort study
- Case-control study
- Case series
- Case reports

Table 3. *Preference of approach for the study of adverse drug reactions*

Use of drug	Adverse reaction	
	rare	frequent
rare	case reports	cohort study
frequent	case-control study	cohort- or case-control study

Case-control and cohort studies

Compared to the collection of case reports, case-control and cohort studies provide a stronger kind of evidence on the relation between drug use and outcomes.

In pharmacoepidemiology, cohort studies generally are more drug-oriented than case-control studies. In a cohort study, a group of persons that uses a certain drug is followed and the subsequent occurrence of conditions is monitored. Thus, the cohort is defined on basis of exposure to the drug under investigation. The outcome is compared with that of a reference group not using the drug.

An example of a large cohort study from the past is the study of consequences of use of oral contraceptives by the British Royal College of General Practitioners.¹² Typically for cohort studies, it was initiated after the publication of case reports and case-control studies^{13,14} that suggested the existence of detrimental effects from this class of drugs.

A specific type of cohort study in the field of pharmacoepidemiology is Prescription Event Monitoring.^{15,16} In this monitoring system, copies of prescriptions for specific drugs are collected via the prescription pricing authority in Britain. Prescribers thus identified are asked to provide information on all medical events before, during, and after use of the drug by the patient for whom the drug under investigation was prescribed. Up to 40,000 users of a drug are covered in this way,¹⁷ i.e. much more than in clinical trials.

In a case-control study, the primary selection criterion is the presence of a specific condition. Drug use and other determinants are ascertained after selection of the case and control groups. If several other determinants, in addition to a specific drug are thought to be relevant for the disease, this approach will be more efficient than a cohort study. The case-control approach has been used on a relatively large scale in studies on adverse drug effects. Sometimes case-control studies have been definitive, even when they were rather small. The classic study on the relation of adenocarcinoma of the vagina with exposure in *utero* to diethylstilbestrol consisted of 8 cases and 40 controls.¹⁸ While the case-control studies generally take less time and effort to conduct than cohort studies they are more subject to biases, as will be discussed in the second half of this chapter.

Finally the "nested case-control" approach tries to combine the strength of cohort approach with the efficiency of case-control studies. In a defined population with registered exposure, controls are sampled at random. The control patients thus are sampled in the population from which the cases originated. Automated databases, with a limited array of information but covering defined large groups of patients, may be the framework to do more of such studies in the future.

Choice of approach

Frequent side-effects of drugs generally will be detected by pre-registration clinical trials. However, they may be overlooked when the symptoms are common in the general population. In order to detect an increased incidence of these common symptoms, questionnaires may be used in the different treatment groups. Clinical trials are not suitable to study more rare drug reactions, as the numbers needed would be too large. Table 1 shows that a very large trial would be needed if a reaction also occurs in the control group of persons who do not use the drug under investigation; the example is for an adverse reaction that is not rare (1 in 500 users). Apart of logistical constraints, ethical considerations may preclude trials where safety of the drug is a serious issue.

The case-control and cohort approaches each have their advantages and drawbacks for studies on drugs. Case-control studies need usually less time than cohort studies. This is especially true if one wants to study long-term effects of drugs. Further,

a cohort study generally needs a larger study population, especially in the case of relatively rare adverse reactions (table 3). However, if the drug under investigation is prescribed relatively infrequently, a cohort approach can be more efficient if the adverse reaction has a high incidence; in this case, adverse reactions are more readily detected within the group of users of the drug that is identified in advance. If use of the drug and the occurrence of the adverse reaction with the users are common, both the case-reference and the cohort approach are practical. If one wants to investigate a specific suspected adverse drug reaction, the case-control approach has the advantage that one knows which patients have to be selected. To study a rare reaction to a commonly used drug, the case-control approach is also more efficient than a cohort study. Case-control studies generally are completed in a shorter time than cohort studies. A drawback is caused by the interpretation problems that the results of many case-control studies on drugs have generated; we will discuss this issue later in this chapter.

If both the use of the drug and the adverse reaction are rare, the association generally has to be uncovered by case reports. A very large study population would be needed to show such a relationship with a more formal approach. Thus, the detection of these rare reactions will remain dependent on the individual observant physician. This detection and reporting, however, can be promoted by a national or regional institute that monitors drug safety.

Problems of interpretation in observational studies on drug effects

Historically, case recognition and observational studies have been the means to detect adverse drug reactions in the general population. As in all observational studies drug monitoring is subject to several types of bias. We will discuss here the three main forms of bias and subsequently will show examples in the field of drug studies:

Selection bias occurs when the persons selected for a study differ in a systematic way from those who were eligible but not selected. Selection bias can take many forms, common is that the persons who are included in a study differ from those who are not with respect to the relation between exposure and disease.

Observational bias occurs when there are flaws in the measurement of exposure or outcome in the groups to be compared. In studies on possible adverse drug reactions the problem frequently occurs in the form of a higher likelihood of detection of use of the imputed drug in the case group than in a control group.

Confounding bias is present when the apparent effect of an exposure is an artifact caused by the association of both the exposure parameter and outcome to a third, extraneous, factor. In pharmacoepidemiology problems associated with use of a drug have been confounded with the disease that was the reason for the therapy.

Observational studies on drug effects are perhaps even more susceptible to these forms of bias than other subjects in epidemiology: use of a drug is likely to be associated with use of other drugs, other morbidity, and specific, not well recognized, behavioral covariates. Compared to a field such as occupational health, pharmacoepidemiological studies generally will cover populations which are older and which have a more diverse and complex morbidity.

Biases in the different types of study

Case recognition, with spontaneous reporting, or in the more organized form of a national monitoring scheme, will not reveal the actual frequency of an adverse reaction, as only a minority of the problems are recognized to be drug-related, and only a minority of those recognized problems will be reported. Observational bias is likely to occur if a drug had some publicity about a purported adverse reaction: the drug will get more attention and the reported association between the drug and a problem is seen and reported more frequently.^{19,20} Comparison of the frequency of reports in a national monitoring scheme of two drugs is often hindered by lack of knowledge of the numbers of patients treated with the drugs. Thus, both the numerator (number of ADRs) and the denominator (number of users) required to establish a useful frequency parameter is not known. Even if the size of the treated population is known, a comparison is dubious, for the drugs may be used by patients with different health status, which may happen even with drugs in one therapeutic class. The weaknesses of the case approach are obvious; however, it should be recognized that case reports have often brought to attention previously unrecognized problems, initiating more formal studies. As we pointed out earlier in this chapter, some types of ADRs can only come to light when recognized and reported by an individual perceptive physician.

Case-control studies have been performed on a considerable scale in pharmacoepidemiology. Often the studies were initiated after the publication of a series of case reports. While relatively easy to perform, the results of case-control studies often have lead to considerable interpretation problems. Several times carefully designed case-control studies, partly very large and expensive resulted in controversy about the interpretation of results.²¹⁻²⁸

An example of the interpretative problems of a case-control study is the New Zealand asthma mortality study (NZAMS).²⁹ This study stimulated us to study characteristics of users of some asthma drugs in the Netherlands (Chapter 7).

As discussed by Miettinen,³⁰ basically a control group should come from the same source population as the cases; thus if cases have an asthma history controls should have one too. In the NZAMS indeed a group of asthmatics was chosen as controls, patients with a hospital discharge diagnosis of asthma. The association with mortality was ascertained for the different asthma drugs, both for pooled data and in subgroups defined by markers of asthma severity. The overall relative risk of asthma death in patients prescribed fenoterol by metered dose inhaler was 1.55 (95% confidence interval 1.04-2.33). The risk was higher in subgroups with a marker of more severe asthma. This elevated risk was not found for inhaled salbutamol, with fenoterol the only drug of the beta agonist class in New Zealand.

The relationship is especially difficult to study because an effect of the drug can easily be confounded with an effect of the disease. In this case, the purported fatal adverse reaction may be a consequence of asthma, the reason for therapy. Further, as in most other case-control studies, the choice of a reference group is not easy. In the NZAMS the reference group consisted of people admitted to hospital with the primary diagnosis of asthma. In order to compare the association of mortality to the use of different drugs, the degree of severity of asthma in the treatment groups should be similar. Obviously, degree of severity is hard to assess *after* the moment a patient was admitted to hospital or died. Also, the drug use before admission or death has to be

established. A small bias could result in the modestly elevated relative risk that was found in the NZAMS for patients prescribed fenoterol.

The collection of data on both disease severity and drug use is subject to observational bias: the different outcome may influence the quality of the data about the past of the patient. Information on drug use concerned the regularly prescribed medication and medication newly prescribed during the final attack. The NZAMS was criticized for not taking into account whether the imputed drugs were used in the hours preceding a fatal attack;³¹ this criticism does not seem reasonable as this information generally is not available. Retrospective studies on causes of mortality have their limitations, but there hardly seems any alternative in the case of asthma mortality in younger persons, an uncommon event even in groups of patients with more severe stages of the disease.

The recent introduction of accessible databases in health care makes case-control and historic cohort studies more convenient to perform. Databases can be linked to each other to provide the information about both exposure to drugs and disease in large numbers of patients.³²⁻³⁵ While the new information technology has promise for studies on larger groups of patients, caution is indicated with the use of these databases. Most databases were collected to accomplish billing and to have some information on drug consumption and use of medical services of individual patients. Procedures, interventions and other cost-linked aspects are better recorded than diagnoses.³⁶⁻³⁷ The present databases are largely hospital-bound, missing large parts of morbidity and giving little insight into the long-term changing condition of the patient.

Cohort studies are less susceptible to bias than case-control studies, but mostly impractical when the adverse reaction is rather rare. The selection of a suitable reference group is essential but is generally less difficult than the selection of a reference group in case-control studies. Unlike blinded clinical trials, exposure to drugs is known by the patients in cohort studies, a fact which may lead to observational bias. The baseline condition of patients in cohort studies remains crucial for the outcome of whatever exposure. An example where baseline condition clearly had a big role was the big mortality difference between two concomitantly run studies in the U.K. on users of enalapril.³⁸⁻⁴⁰ The mortality was 8% for a group of users of enalapril in Inman's Prescription Event Monitoring Study.³⁸⁻³⁹ In the other study⁴⁰ fewer than 0.5% of the users of enalapril died. The latter study excluded patients with congestive cardiac failure, renovascular disease, or other complications of hypertension. This study essentially included the relatively healthy persons, leaving Inman's study with many patients with a poor prognosis.

The last example shows how differences in patient characteristics can confound the comparison of outcome in therapy between treated groups. This common problem in pharmacoepidemiology made us to look for ways to characterize larger populations for the presence and severity of certain conditions.

Much of the work which will be presented in this thesis is focussed on the drug history as a marker of morbidity. Another impetus for us to focus on the drug history is that both case-control and historic cohort studies are vulnerable to observational bias as concerns the ascertainment of drug use. Thus, reliable sources on medication are needed. We will describe how pharmacy databases can be useful in this respect. Further, we will use drug databases in order to describe changes in therapy as a

possible marker of changes in the condition of individual persons. The drug histories will also be used to study cessation of therapy at hospital admission.

These different subjects are studied with the same type of community pharmacy-based drug histories. The fact that these data are readily analyzable as they are stored on magnetic medium is relevant in the light of the need for speed which is often felt when a problem with a drug arises. We hope that the availability of these data can help to cope with some of the problems in pharmacoepidemiologic studies described in this chapter.

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Chapter 3

PHARMACY DATA IN THE ESTIMATION OF DRUG USE IN POPULATIONS

In order to estimate consumption of a drug many approaches are available, ranging from the measurement of plasma levels in individual patients to the study of gross national sales data.

Consumption data can be divided in two types:

- 1) data aggregated on the level of a region or a group of persons
- 2) information on the level of individual persons

1) encompasses sales data from manufacturers and wholesalers. Further insurers often retrieve gross data on reimbursed drugs.

Gross data on the sale of units of a certain drug can be transformed in standard units, for interregional or international comparisons. The Defined Daily Dose (DDD) method of the Nordic Council^{1,2} is one approach, in which the daily dose for the main therapeutic indication is chosen as measurement unit. The gross sales and reimbursement data give an indication of the degree of exposure of a population to a drug. The DDD method provides an estimate of the number of patient-treatment days. Neither duration of therapy nor the actual number of treated patients is known. These drug utilization studies have been a kind of forerunner of pharmacoepidemiological studies that aim to be more explanatory. Inevitably, data on the level of the individual person are needed for such explanatory studies. For a more extensive discussion of the DDD approach, see Lee² and Leufkens.³

2) Consumption of drugs on the level of the individual patient can be assessed by several methods. Four approaches are to be compared with the pharmacy data:

- A) medical records
- B) patient questionnaires
- C) external monitoring of drug use
- D) biological monitoring of drug use

A) *Medical records* exist in a variety of forms: they can cover patient contacts in the general practice setting, hospitalized patients, or outpatient clinic care.

While medical records often are indispensable for finding relevant diagnostic information, they seem less suitable for getting reliable drug histories. Patients often receive medication prescribed by more than one physician. In the situation of a hospital admission, generally a drug history is taken, but the quality and format of this history is variable^{4,5} and the written files are hardly usable for larger-scale surveys.

B) *Patient questionnaires* on past use of specific drugs have showed a varying sensitivity, depending on the type and duration of use of the medication involved.^{6,7} The recall of current medication in the outpatient setting has been shown also to be a problem.^{8,9} The value of patient questionnaires in relation to other sources of information on drug use is discussed further in chapter 10 of this thesis, in the context of a study that compared drug histories from a questionnaire with information from a pharmacy data base.

C) *External monitoring* of drug use. Prescription or dispensing of a drug is not synonymous with use of the drug. Noncompliance is a substantial problem in

therapeutics and in clinical trials.¹⁰⁻¹² As a consequence of this, in clinical trials generally some form of monitoring of the patient's adherence to therapy is included. Most often this is done in the form of counts of the patient's residual number of tablets at clinic visits. The approach is valid as concerns the aspect that tablets brought back point to noncompliance. However, from pill counts the time pattern of non-use cannot be inferred. Even more important is that patients share their drugs with other persons or throw away unused dosage forms before the clinic visit.^{13,14}

Information on the time-dimension of non-compliance is provided by electronic monitoring.¹⁵ An electronic device in the cap of the drug vial registers the time of opening and closing of the vial. Direct consumption is not measured with this method, but regular opening and closing of the vial without actual use of the drug seems unlikely.

External monitoring is done in clinical trials or with selected persons in patient care. The results add to the insight gained from more extensive type of data on prescribing or dispensing.

D) *Biological monitoring* of the levels of a drug is done in samples of a body fluid as blood, urine or saliva. Sometimes instead of the drug a marker substance is used.¹⁶⁻¹⁹ These measurements often are used as a way to monitor compliance in clinical trials. Depending on the plasma half-life of the drug, a plasma level will give an indication of compliance in the hours or days before the clinic visit. This assessment at clinic visits has been shown to introduce a transient compliant behavior just before the visit.¹³ Urine and saliva measurements are more convenient for the patient, but here too measurements cannot give insight in the long-term use of the drug. Changes in this field may come from the wider use of easy-to-perform urine or saliva "dipstick" tests.

For studies on large populations the described approach of external monitoring is practical only for pre-defined groups of patients with a selected drug. To do this however, pharmacy databases can be a useful source to find a group of documented recipients of the subject drug.

Biological monitoring, the other way to monitor use of a drug, is not practical to use on a large scale; apart from this, as we stated earlier, its outcomes are dubious as concerns long-term compliance.

For the studies presented in this work, drug histories of up to 1200 users of a specific drug in a specific formulation were collected (chapter 4b). In order to get this number, a source population of 120,000 people was needed, as the subject drug was used by about one percent of the general population in a time span of a few years. Thus even when one percent implies a relatively much-used drug, a large reference population is still required. The listed methods of reviewing medical records, interviewing patients, or offering them a questionnaire are impractical for this purpose.

For information on outpatient drug use, pharmacies seem to be a natural source as all prescription drugs are dispensed via the pharmacy. However, to be practical, the data have to be stored in a readily accessible way. Further, in order to get a reliable history of drug dispensing on the level of individual persons, patients have to patronize one pharmacy. The use of computers in pharmacies recently has increased in many countries. In spite of this surge of the use of computers in the U.S., drug records there have been described as "...rarely in a format that is of any help to epidemiologists".²⁰ Indeed, in the U.S., insurers do not require patients to utilize one pharmacy. The relatively high density of pharmacies in the U.S. and the mobility of the population is likely to impair the completeness of the data on the patient level. There are

exceptions, however, notably in health maintenance organizations, which have proven their value for research.²¹⁻²³ In the U.S. the common pharmacies however have proven their value for prospective drug monitoring as a location where product users can be recruited when prescriptions are presented for filling.^{24,25}

In the Netherlands, the public insurers (*ziekenfonds*) require patients to patronize one pharmacy for their reimbursable drugs. About 65% of the population is publicly insured.²⁶ For the remaining patients, privately insured, this obligation does not exist. The *ziekenfonds* pays the pharmacist for drugs dispensed and are entitled to audit the claims; for this complete records for reimbursable drugs are required in the pharmacy. For the publicly insured patients the pharmacy databases can be said to be virtually complete for outpatient drugs. Exceptions are drugs dispensed at other pharmacies during weekends or when the patient is on holiday. Dutch pharmacies tend to serve a larger population than American pharmacies; the fewer number of pharmacies can be expected to lead to higher likelihood for individual patients to patronize one pharmacy.

The use of computers in Dutch pharmacies increased greatly in the last years: in 1991 computers were operative in 85% of the pharmacies.²⁷ Computers were first introduced for the purpose of billing; later the use was broadened to the control for dosing, double medication, and interaction of drugs prescribed to individual patients.

Besides the community pharmacy, there exists in the Netherlands one other channel for prescription drugs for non-hospitalized patients: the dispensing general practitioners. This channel exists in rural areas. About 15% of patients receive their drugs from the dispensing physicians.²⁶ For our analyses we have not used data from this group in patients; it should be kept in mind that this subgroup of people has a somewhat different, notably lower, drug consumption than the rest of the Dutch population.²⁸

For non-prescription drugs there exists in the Netherlands the channel of the "drogist" (druggist), where over the counter (OTC) drugs are sold. OTC drugs are also sold in pharmacies; when these non-reimbursed drugs are dispensed, in general no personalized data are stored in the computer database.

Summarizing, the features of Dutch community pharmacies are:

- virtually complete prescription drug histories of publicly insured patients.
- for the minority of privately insured patients the information is less complete, especially in towns.
- about 70% of pharmacies have a computer that stores individual drug histories.

At the same time it should be kept in mind that, while data on large numbers of patients can be collected via the pharmacies, the data have their limitations. First, there is the lack of information about the dispensing of OTC drugs. Secondly, there is the aspect that pharmacy data inherently cover dispensing, not use, of drugs. Undoubtedly, some portion of the drugs dispensed are not consumed, or at a lower rate than prescribed.

With respect to the drug histories from pharmacies, the question remains on the relation of dispense with use. The term "drug use" in context of our studies should be interpreted as use inferred from dispensing data. Certainty about compliance cannot be deduced from individual drug histories. Compliance is doubtful for the case of an isolated dispensing of a drug which is prescribed normally for chronic use. Compliance

to the prescribed therapy is more likely when the patient returns in time for refills of chronic medication. In chapter 4b this issue is discussed in relation to a possible adverse reaction to a drug meant for prophylactic chronic therapy; a separate analysis is done for incidental and chronic users of the drug. While the compliance problem is clearly present in the interpretation of pharmacy data, it can be expected to be smaller when the histories show regular refills of a drug.

The actual database used was somewhat different among the studies presented in chapters 4-10. In the method sections of these chapters a description is given of the source of the data, the size of the source population and the time period covered.

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INTRODUCTORY NOTE TO CHAPTER 4

The two articles in this chapter are both analyses of drug histories of recipients of the anti-vertigo/anti-migraine drug flunarizine. Material in section 4a was also used for the later work presented in section 4b. The work presented in this last section covers a larger set of data. In both articles, and also in chapter 5, the technique of prescription sequence analysis is used. The three articles reflect that our approach to analyze the data evolved in time. The technique presented in chapter 5, developed the last, should in general be the most versatile and best applicable for prescription sequence analysis (see also chapter 5, appendix).

PRESCRIPTION SEQUENCE ANALYSIS: A NEW AND FAST METHOD FOR ASSESSING CERTAIN ADVERSE REACTIONS OF PRESCRIPTION DRUGS IN LARGE POPULATIONS

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SUMMARY

Prescription sequence analysis (PSA) uses pharmacy-based prescription drug histories to detect a subset of drug effects: those that are themselves indications for changes in the prescribing of another drug. Dutch pharmacy practice ensures virtually complete drug histories. With a database of 25,000 patients, we used PSA to test an alleged link between the use of the anti-vertigo drug flunarizine and mental depression. The temporal sequence of anti-depressant use among flunarizine users shows no clustering that would suggest a causal link. PSA can be run within a few days, which may make it helpful in resolving certain of the periodic controversies about adverse drug reactions.

KEY WORDS Prescription sequence analysis Flunarizine Anti-depressants Adverse drug reactions
Prescription drugs Pharmacy records

INTRODUCTION

New drugs are registered on the basis of data from clinical trials usually involving less than 3000 patients. Economic and practical reasons set this limit. A consequence is that newly introduced drugs have a defined safety of less than 3.0 safety-degree units,¹ that is a per-treatment risk of serious adverse drug reaction of more than 1 in 10³ patients.

The only way to achieve a higher degree of safety (or its complement, a lower level of risk) is to monitor the use of the new drug in a larger number of treated patients than is possible in pre-market trials. Yet the history of forced withdrawals of prescription drugs for serious adverse reactions suggests that drugs not offering unique life-saving advantages need to have a defined safety greater than 4.7 safety-degree units, that is a per-treatment risk of serious adverse reaction of 1 in more than 50 000 patients. To attain this level of safety from spontaneous case-reporting requires that at least 1.5 million patients receive the drug, and perhaps many more. The number must be large because the denominator for risk definition is effectively divided by at least 10, as fewer than 10 per cent of adverse reactions are reported,^{2,3} and even the most simple statistic for interpreting non-occurrence divides the denominator again by at least 3.⁴

Spontaneous case reporting is sometimes complicated by sensational news media coverage, provoking clustered case reporting that tends to create overestimates of the actual risk. This leads to even more sensational reporting, and a vicious circle that creates a perceived crisis in risk management. When such an unstable situation develops, none of the conventional methods for

gathering relevant new information about prescription drugs can be initiated and completed fast enough to provide reassurance within the limited time period of a few weeks that society appears to demand for resolution of a perceived crisis in pharmaceutical risk management.

During the past two decades, one new pharmaceutical product in about 40 has become embroiled in such a crisis;¹ with about 20 new drugs entering the market annually, crises in pharmaceutical risk management occur biennially.

The vulnerability of a new prescription drug to a crisis in risk management depends upon its rate of adoption in the marketplace. When adoption is rapid in the U.S. or U.K., vulnerability appears to peak at about 9 months after introduction, because by then drug usage will have passed through an important risk zone of one serious adverse reaction in 5000–10000 treatment cycles. This has been the range of risk exhibited by tienilic acid and most of the withdrawn anti-depressant and nonsteroidal anti-inflammatory drugs.¹ If this risk zone is passed through without event, vulnerability then gradually declines as the drug gains a wider range of use, provided no substantially untoward events occur. However, vulnerability never ends, as illustrated by the anti-diarrheal drug, clioquinol, which was used widely for about 40 years without serious problems until the sudden occurrence of the SMON (sub-acute myelo-optic neuropathy) catastrophe in the 1970's.

There are two remedies when a crisis in risk management is perceived:

- (a) analyse ongoing postmarket studies
- (b) initiate and complete new studies.

However, to be effective, one or the other must be concluded within a fortnight. Both are important challenges to clinical research methodology and statistics. This paper describes Prescription Sequence Analysis as one approach to the second remedy.

RATIONALE AND MECHANICS OF PRESCRIPTION SEQUENCE ANALYSIS (PSA)

Prescription Sequence Analysis is based on the observation that some adverse drug reactions are conditions that themselves are indications for the use of prescription drugs. In such situations patients' drug histories should reveal an unusual frequency of some particular drug sequence:

drug *A* → drug *B*,

where *A* is the drug prescribed originally whose side-effect is the indication for the prescription of drug *B*, or more aptly one of the class of drugs represented by *B*. Obviously, PSA cannot detect adverse reactions that do not constitute or create specific indications for a change in the prescription of a particular drug or class of drugs. Also, PSA requires reliable and complete prescription drug histories.

A variant of PSA that should be mentioned, although we did not study it, is to look for post-treatment cessation or other changes in the pattern of drug use.

Uniqueness of Dutch pharmacy practice for PSA

About 70 per cent of the Dutch population is enrolled in the Sickfunds insurance system, which requires each patient to designate a single pharmacy from which they receive all reimbursed prescription drugs. This administrative requirement ensures that virtually complete information about each patient's prescription drug history is contained within one pharmacy's records. Without some such mechanism to ensure the pharmacy's exclusive use by the patient, pharmacy records cannot be relied on to show the sequence of medicines taken by the patient. Geographical location may in some instances be another basis for patients' exclusive use of a pharmacy and we

have used this as a qualifier of privately insured Dutch patients who, though they do not have an administrative requirement for single-pharmacy dispensing, live in a village with a single pharmacy, far enough from competing pharmacies to ensure exclusive use.

'Repeat' prescriptions give evidence of continuing use of both the drug and the pharmacy. Compliance may be gauged from the directions recorded on the prescription and the interval between visits.

A further essential feature of Dutch pharmacy practice is that about 75 per cent of all 1300 pharmacies operate with fully computerized dispensing records. Most Dutch pharmacies serve between 8000 and 14000 patients, which implies 4 to 8 general practitioners per pharmacy. In urban areas, the patients of any one doctor are served by many pharmacies, whereas in rural areas one doctor's patients are usually served by a single pharmacy.

What does a prescription drug history reveal?

A prescription is a functional summary of the physician's decision about the patient's medical needs at the time of writing. There are inevitable differences between academic and prevailing standards of diagnosis and between labelled and prevailing indications for drug use. Understanding those differences is obviously important to the interpretation of PSA. The problem of idiosyncratic prescribing is best dealt with by studying large numbers of pharmacies, physicians and patients.

When a doctor prescribes a drug indicated for the prevention and management of depression, it signifies the doctor's conclusion that the patient is depressed. When a large, geographically dispersed sample of Dutch physicians are seen writing prescriptions for anti-depressant drugs in a certain temporal sequence related to the patient's use of another drug, it is an early, and possibly first, warning of an epidemic of a drug-induced abnormal mental state. It may or may not be depression, but it is in any event a serious condition because non-trivial drugs have been prescribed for it.

A prescription that has been dispensed by a pharmacy shows that the patient has accepted the principle of treatment with the drug, for there is a minimum fee that the patient must pay to collect the prescribed drug. A prescription that has been repeated within a time period consistent with drug use according to the instructions on the earlier prescription is *prima facie* evidence of drug use by the patient. A drug used in the treatment of chronic disease that has been dispensed once and never repeated is an ambiguous indicator of use.

Operation of PSA

We applied PSA to test the validity of case reports that the anti-vertigo/anti-migraine drug, flunarizine, causes mental depression.⁵⁻⁹ From computerized pharmacy records, we selected all patients with a drug history recording use of flunarizine. For each patient, a plot was made of the periods of prescription of flunarizine and anti-depressant drugs. Under the null hypothesis, assuming no association between the use of these drugs the chance of starting anti-depressant drug treatment during or just after use of flunarizine is directly proportional to the duration of use of flunarizine relative to the total period of observation. The statistical analysis is based on a Monte Carlo simulation model which predicts the number of times that an anti-depressant drug is started within a defined period of use of flunarizine. Specifically we assumed that flunarizine-induced events would have occurred within the interval from the first dispensing of flunarizine to 30 days after the last prescribed dose of flunarizine should have been consumed. In the simulation the 'starts' of anti-depressant drug treatment are allocated randomly over the total period of observation assuming a uniform distribution; the number of starts allocated to each individual

history is equal to the observed number of 'starts' in the original patient medication history. The allocation process is repeated 1000 or more times for each history to generate a distribution of the number of expected starts of anti-depressant drug treatment within periods of flunarizine use.

Medication histories that contain a record of anti-depressant use in the first 90 days of the observation period are excluded, as previous flunarizine prescriptions cannot be ruled out. Imipramine, an anti-depressant which is used in low dosage to treat enuresis, was included only if prescribed at doses normal for anti-depressant use.

Pilot study

Two pharmacies participated in the pilot study; they served a total of 25 000 patients, among whom 274 received flunarizine during the 2½ to 3½ year period covered by computerized pharmacy records. Of these 274 patients, 16 per cent (44) were also prescribed an anti-depressant drug within the same interval. By contrast, only 5 per cent of age- and sex-matched patients who were not prescribed flunarizine received prescriptions for anti-depressant drugs in the same interval.

We need to know when in relation to the start of flunarizine use was an anti-depressant drug first prescribed.

Temporal sequence of flunarizine and anti-depressant drug dispensing

The number of 'starts' of anti-depressant drug use observed during or within 30 days after flunarizine use was 5 out of a total of 34 histories. Ten of the original 44 histories were excluded because of anti-depressant use in the first 90 days of the observation period.

With only 5 patients for whom an anti-depressant drug was prescribed within the interval for flunarizine-induced events, we can estimate that the maximum per-treatment risk of serious depression appears to be less than 1 in 274/5 or 1 in 55 flunarizine-treated patients.

But how much less? We can hazard a rough estimate, based on the results of the Monte Carlo simulation analysis, which show that the generated number of 'starts' of anti-depressant drugs in the periods during and 30 days after flunarizine use was about 20 per cent more than the number observed in the medication histories. Thus, whatever risk there may be of flunarizine-induced depression, it would appear at least an order of magnitude lower than the background risk. To give better precision to such risk estimates, we are presently endeavouring to expand the coverage of the PSA method to one million pharmacy patients.

The relatively high rate of anti-depressant prescribing in patients dispensed flunarizine suggests that this group of patients, if not having mental depression in a narrow sense, are at least prone to receive anti-depressant drugs for mood disturbances. That association deserves further study. Perhaps it accounts in some way for the spate of case reports suggesting an association of flunarizine with depression.

Time required to complete a PSA study

The first phase of this study was performed by hand and was completed within 3 working days. It included data from a single pharmacy with 100 recipients of flunarizine during a 3 year period. However additional time was required to write the general program that assembles complete drug histories of users of a specified drug or group of drugs from the pharmacy computer system. With such a general program, one can search a large database of dispensing records from multiple pharmacies, and within a few hours compile drug histories of hundreds or thousands of recipients of any specified combination of drugs. The Monte Carlo simulation analysis to search for unusual temporal clustering of prescriptions takes less than 1 hour of machine time on a desktop computer for several dozen patients if about one thousand runs of the simulation are made per patient history.

It is therefore evident that, with access established to a large archive of pharmacy dispensing records, a PSA study could be defined and executed within a fortnight. Thus, PSA can be a practical tool with which to develop information during a period of perceived crisis in risk management of a pharmaceutical product.

Confidentiality

Anonymity of patient records is ensured by the algorithm that transfers dispensing data from the pharmacy records to the database. Individual sets of data are identified only but adequately by birthdate, sex and pharmacy.

CONCLUSION

PSA is an inexpensive, fast method for assessing certain kinds of drug reactions, specifically those that are indications for change in the use of other prescription drugs. The simplest change is the commencement of another drug, but in principle, one could look for changes in prescribed dose or cessation of use of a drug prescribed already. Dutch pharmacy practice virtually ensures that prescription drug histories are complete. However, PSA should be validated; one way would be to detect a recognized prescribing pattern linking drug reaction and subsequent prescription, for example potassium supplementation after use of a diuretic drug.

PSA can serve by providing both a qualitative alert and a measure of the evident risk of drug use. It seems possible to obtain a risk measurement within a two-week period, once a database of pharmacy dispensing records is available. A risk measurement may have great value at a time of crisis in the perception of the risk of using a widely prescribed pharmaceutical product.

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RAPID METHOD FOR ESTIMATING THE RISK OF ACUTELY CONTROVERSIAL SIDE EFFECTS OF PRESCRIPTION DRUGS*

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Abstract—When controversy suddenly erupts about the risk of using a prescription drug, there is an urgent need for fast methods of risk estimation. Some unexpected side-effects of prescription drugs are indications for the prescribing of another kind of drug. If the risk of such a side-effect is high, it should be reflected in clustered prescribing of the side-effect-alleviating drug in sequence with the side-effect-causing drug. The risk of drug-attributable side-effects can be estimated by comparing average incidences of initial prescriptions for the side-effect-alleviating drug before, during, and long after the dispensing of the presumed side-effect-causing drug. We monitored computerized, complete drug dispensing records of anonymous outpatients for use of flunarizine, an anti-vertigo/anti-migraine drug that case reports had suggested causes mental depression and/or Parkinsonism. Among 1284 patients who eventually got flunarizine during a 31 month period, 1 in 7 was started on an anti-depressant before or long after flunarizine; only 1 in 82 might be said to have been started on an anti-depressant because of flunarizine. There was no evidence that anti-Parkinson drugs were started because of flunarizine, though the numbers are small. The analysis takes only a few days, and can help set bounds on risks of the subset of adverse drug reactions that are themselves indications for use of other drugs.

Adverse drug reactions Prescription sequence analysis Pharmacy records
Flunarizine Anti-depressant drugs Anti-Parkinson drugs Mental depression
Parkinsonism Vertigo Migraine Pharmaco-epidemiology

INTRODUCTION

Premarket trials of new drugs have well-recognized limitations on size and patient selection criteria. Consequently, certain adverse drug reactions only become apparent after market introduction, as general use expands both

numbers and diversity of patients receiving the drug. When first case reports of possible adverse reactions appear, there is strong desire but usually no capability for urgently gathering more information to estimate risk by defining incidence and probable causality. Confusion and usually exaggerated fears tend to prevail at such times, precipitating regulatory action on incomplete data. These actions taken in the name of risk reduction, are not without the potential to create risk to patients who are subjected to hasty and sometimes unwarranted changes in therapy [1, 2].

*A preliminary report on a portion of this work has been published [1].

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Thus, there is a need for methods of analyzing market-experience data within a few days to assist in risk estimation. The objective of this study was to identify and apply one such method, based on drug dispensing data from retail pharmacies.

The study analyzed an episode of reported adverse reactions involving flunarizine, an anti-migraine and anti-vertigo drug. This fluorinated derivative of cinnarizine entered European markets in 1983 with known side-effects of sedation and epigastric discomfort [3]. In 1986, several reports linked mental depression to flunarizine use. Table 1 summarizes these reports, showing major gaps in information that, though unique to this episode, are representative of the quality of information that usually prevails in the immediate aftermath of first reports on a previously unsuspected adverse reaction.

Adverse drug reactions can be divided into two classes: those that do and do not have a specific pharmacotherapy. Both depression and Parkinsonism belong to former class, because they are indications for the prescribing, respectively, of anti-depressants and anti-Parkinson agents. If flunarizine indeed has a high risk of causing either or both depression or Parkinsonism, one would expect to see a clustering of initial prescriptions for anti-depressant or anti-Parkinson drugs during the period of flunarizine use and for a certain time afterwards. Consequently, we analyzed the sequences in which anti-depressants and anti-Parkinson drugs were first prescribed and dispensed to a sizeable population of flunarizine recipients. We compared incidences of first prescriptions of anti-depressants or anti-Parkinson drugs before, during, and a relatively long time after the initial prescriptions for flunarizine.

METHODS

Collaborating community pharmacists identified ever-recipients of flunarizine in their computer files and supplied us with anonymous drug dispensing histories, in which patients were identifiable only by sex and birthdate. Each pharmacist used one of three different computer systems, two of which were flexible enough to provide complete drug dispensing histories on all ever-recipients of flunarizine. One system posed difficulties that made it economically feasible only to gather a count of ever-recipients of flunarizine and the dispensing details of flunarizine only, and any anti-depressant drugs they received. For several reasons, computerized dispensing records are held to a high standard of accuracy, not least because they are the audited basis on which pharmacies are paid by the State insurance system.

The drug dispensing histories spanned a mean period of 31 months (range 10–40 months). The database we created from these histories began at the start of the complete computerized data file of drug dispensing in each pharmacy. Our database ran through 30 August 1987. In five urban pharmacies only data from patients insured by the Sickfund (Zielfonds) were studied. Sickfund-insured patients, who comprise about 70% of the population, are required to designate a single pharmacy for all reimbursed prescription drugs, which include all drugs involved in this study. Privately insured patients might have used a second pharmacy for some prescription drugs, thus permitting some prescriptions to escape our analysis. In two rural towns, each served by a single pharmacy, and in one town where all four pharmacies share a common patient data bank, both Sickfund

Table 1. Number of flunarizine treated* patients with and without adverse reactions

With				Without	Ref.
Depression only	Parkinsonism† only	Both	Either or both‡		
0	1	11	—	?	[4]
21	0	1	—	?	[5]
2	0	7	—	21	[6]
—	6	—	—	?	[7]
—	—	—	17	3250	[8]

*Dosage varied, with some patients receiving a higher dosage than the recommended 10 mg/day.

†The terminology of the case reports differs: 'Parkinsonism' refers to a heterogeneous group of reported motor problems.

‡Not tabulated separately in the report.

"—". The category was not considered in the report.

"?". No numerical value was given in the report.

Table 2. Anti-depressant drugs used by patients who also received flunarizine

Anti-depressant	Number of users
Amitriptyline	60
Maprotiline	45
Mianserine	40
Clomipramine	13
Imipramine	13
Opipramol	8
Fluvoxamine	5
Doxepine	5
Dosulepine	4
Nomifensine	4
Trazodone	1
Nortriptyline	1
Trimipramine	1

and privately insured patients were studied; there the likelihood of missing some prescriptions seemed small.

The anti-depressant drugs listed in Table 2 were prescribed to ever-recipients of flunarizine. As imipramine is used in low dosage to treat enuresis, it was included only if prescribed at a dosage of 50 mg a day or higher. The anti-Parkinson drugs listed in Table 3 were found to be used in ever-recipients of flunarizine. For convenience, we refer hereafter to anti-depressant and anti-Parkinson drugs as "marker drugs".

The period of flunarizine or marker drug use was considered to begin with its first dispensing, and to continue as long as a refill occurred within 30 days after the legend duration of the previous prescription. The legend duration is the number of dosage forms dispensed divided by the prescribed number to be taken per day. The duration of drug effect, after the last prescription, was taken as the legend duration plus 30 days. Some patients had more than one period of use of a drug. The vast majority of flunarizine refills had legend durations of 60 days.

From the case reports, no clear picture emerges of the time relation of flunarizine use and subsequent development of problems: reactions within days and after several months of use were reported. We considered a reaction to

be possible during the whole time of exposure of flunarizine, and analyzed the data accordingly.

When a marker drug was already in use at the beginning of the observation period, there was no way of knowing whether it had been preceded by flunarizine use. To avoid this ambiguity, the first 90 days were excluded from the beginning of each analysis period. For the patients who had a marker drug prescribed in this 90-day interval, the period of analysis was taken to begin the 31st day after the end of the legend duration of the last marker drug prescription.

The incidence of first prescriptions of marker drugs during flunarizine use (I_u) was compared to the incidence in the period before and after flunarizine use (I_{nu}), i.e. the period of flunarizine non-use. The incidence is defined as the number of first prescriptions ("starts") per 1000 observation days in the corresponding period of flunarizine use or non-use, aggregated across patients. An incidence ratio (IR) was determined as I_u/I_{nu} . The null hypothesis is $I_u = I_{nu}$, or, $IR = 1$.

At least 2 weeks are required for most anti-depressant drugs to show therapeutic effect, and full therapeutic benefit is not usually evident before 4–8 weeks of treatment [9]. Shorter use of anti-depressant drugs is a somewhat ambiguous indicator of the existence of depression. Therefore, the analysis was also done separately for the histories in which the anti-depressant use exceeded 60 days.

To gauge the extent of co-medication besides flunarizine and the marker drugs, we determined the number of other drugs prescribed during 60 days prior to each dispensing of flunarizine in all 777 flunarizine recipients in the "flexible" database. We first made a per-patient average, and then averaged across patients.

Patients' ages were determined as of the end of the observation period.

RESULTS

Among 11 collaborating pharmacies serving approximately 105,000 people, 1284 patients were prescribed and dispensed flunarizine at some time in the 31-month observation period. Among the recipients of flunarizine, 180 (14%) also received prescriptions for one of the anti-depressant drugs listed in Table 2 sometime during the period of observation. In contrast, only 4% of the ever-recipients of any prescription drug from the collaborating pharmacies

Table 3. Anti-Parkinson drugs used by patients who also received flunarizine

Drug	Number of users
Levodopa/benserazide	4
Biperidene	3
Amantadine	3
Benzatropine	2
Levodopa	1
Levodopa/carbidopa	1
Dexetimide	1

Table 4. Distribution of anti-depressant (AD) starts in patients who also received flunarizine

		Days	AD starts	Incidence†
<i>(a) Total group (N = 155)</i>				
Before flunarizine	I	55036	87	1.58
During flunarizine	II	29746	61	2.05
After flunarizine	III	53613	79	1.47
IR = 1.342 (1.00–1.80)*				
<i>(b) Patients with multiple dispenses of flunarizine (N = 86)</i>				
	I	24629	37	1.50
	II	25963	49	1.88
	III	28038	43	1.53
IR = 1.242 (0.87–1.77)*				
<i>(c) Patients with a single dispense of flunarizine (N = 69)</i>				
	I	30407	50	1.64
	II	3783	12	3.17
	III	25575	36	1.41
IR = 2.065 (1.13–3.78)*				

*95% confidence interval.

†AD starts/1000 days.

Incidence ratio (IR) = incidence period II/incidence periods I + III.

were prescribed an anti-depressant during the same time period. For anti-depressant use to be considered attributable to flunarizine, however, it must occur in a temporal sequence consistent with causality.

Among the 180 ever-recipients of both flunarizine and an anti-depressant, 25 were excluded because their only prescriptions for an anti-depressant drug occurred during the first 90 days of pharmacy records. Among the 155 remaining patients, 227 anti-depressant "starts" were recorded; thus, some patients had more than one "start" during the observation period. The ever-recipients of both flunarizine and an anti-depressant had a mean age of 56 years; 77% were female.

The incidence of anti-depressant "starts" in the periods before vs after use of flunarizine, shown in Table 4, did not differ significantly, so these periods were merged into one period of

"flunarizine non-use". The incidence of anti-depressant "starts" during periods of flunarizine use is somewhat higher than in periods of flunarizine non-use, as shown in Table 4. In all 155 patients (Table 4(a)), the computed incidence ratio for the start of anti-depressant prescribing during flunarizine used was 1.34, and is marginally statistically significantly elevated; assuming a normal distribution for the logarithm of the incidence rate the 2-tailed *p* value was precisely 0.05.

In 86 of the 155 recipients of both flunarizine and an anti-depressant, flunarizine prescriptions were refilled at least once, suggesting that the patients took their flunarizine at least approximately as prescribed, and did so for an extended period of time. In this group of patients (Table 4(b)), the incidence ratio of anti-depressant "starts" was not statistically significantly elevated. In the remaining 69 patients, who

Table 5. Distribution of starts of anti-depressants (AD) used longer than 60 days in patients who also received flunarizine

		Days	AD starts	Incidence†
<i>(a) Patients with a single dispense of flunarizine (N = 53)</i>				
Before flunarizine	I	19451	36	1.85
During flunarizine	II	2562	10	3.90
After flunarizine	III	16688	28	1.68
IR = 2.204 (1.13–4.29)*				
<i>(b) Patients with multiple dispenses of flunarizine (N = 72)</i>				
	I	16732	30	1.79
	II	20954	42	2.00
	III	19764	34	1.72
IR = 1.143 (0.77–1.69)*				

*95% confidence interval.

†AD starts/1000 days.

Incidence ratio (IR) = incidence period II/incidence periods I + III.

Table 6. Distribution of anti-Parkinson (AP) medication starts in patients who also received flunarizine

	Days	AP starts	Incidence*
(A) During flunarizine	2587	4	1.55
(B) During non-use of flunarizine	4577	7	1.53
	IR = 1.01		

*AP starts/1000 days.

Incidence ratio (IR) = incidence period (A)/incidence period (B).

received only one prescription for flunarizine, and whose actual use of the drug is therefore ambiguous (Table 4(c)), the incidence ratio was 2.05 ($p < 0.05$). As shown by Table 5, the results are similar if relatively short periods of anti-depressant use are excluded.

In the group of 155 recipients of both flunarizine and an anti-depressant, 61 anti-depressant "starts" occurred during flunarizine use, while 45.4 is the calculated expected number, based on the incidence of anti-depressant "starts" in the periods of flunarizine non-use. The difference of 15.6 "starts" can be considered as the number of "starts" of anti-depressant drugs attributable to flunarizine. With 1284 patients having ever received flunarizine in the entire observation period, one may estimate that 1 flunarizine recipient in 82 (1284/15.6) received a drug-attributable cycle of anti-depressant treatment. During the same period of time, but unattributable to flunarizine use, 1 in 7 flunarizine recipients received a cycle of anti-depressant treatment.

Flunarizine recipients also receive a good deal of co-medication, besides just the marker drugs: 43% of the flunarizine recipients were dispensed 2 or more drugs, 30% were dispensed 1-2 drugs, and 27% averaged less than 1.

In the subset of data from the flexible databases, there were 777 flunarizine recipients, among whom 10 also received prescriptions for one or more of the anti-Parkinson drugs listed in Table 3. The mean age of these patients, 6 of whom were female, was 75.1 years. Two patients had to be excluded from further analysis because their only start of anti-Parkinson medication was in the first 90 days of the observation period. The incidence of starts of anti-Parkinson medication during periods of flunarizine use and non-use was almost equal (incidence ratio 1.01; Table 6). None of the 10 recipients of anti-Parkinson drugs received prescriptions for anti-depressants. This analysis was completed within 10 working days.

DISCUSSION

Sequence is crucial to the inference of causality. The high rate of anti-depressant prescribing before flunarizine was ever prescribed cannot have been caused by flunarizine. This high, pre-flunarizine rate of anti-depressant prescribing underscores the difficulty in selecting controls, had we chosen to assess the risk of flunarizine use with conventional case-referent or cohort study designs. A case-referent study would logically start with recipients of anti-depressant drugs, but our data indicate that there would be an unusually high representation of flunarizine recipients among patients prescribed anti-depressants. For a cohort study, the ideal control would be some other group of patients who never received flunarizine, but were alike in all other respects. Flunarizine is in a pharmacological class by itself, as the only drug with indications for vertigo as well as migraine; thus there is no obvious other drug as a control. Moreover, flunarizine recipients appear to be rather extensively medicalized patients, as shown by the high proportion receiving prescriptions for other drugs. Considering these factors, we chose as controls the flunarizine recipients themselves, during periods before and long after flunarizine use. The equal rates of initial prescribing of anti-depressants before and long after flunarizine use support this choice.

In the strictest sense, of course, the pre-flunarizine period is not a wholly satisfactory control for events occurring during and shortly after the period of flunarizine use. For example, some depressed patients may develop vertigo or migraine, which would lead to the prescribing of flunarizine or other anti-vertigo or anti-migraine agents. This potential confounding of indication with outcome may have occurred in a few cases, but it involves a process opposite to the one of concern in the present situation. It defies imagination to suppose that this type of confounding so perturbed the prescribing rates to have masked a significant risk of

flunarizine—particularly so in light of the multiple agents used in the treatment of depression and their long-time availability without evidence that they pose major risks of vertigo or migraine.

While anti-depressant drug use was initiated in 14% of the ever-recipients of flunarizine, only 4% of the recipients of any prescription drug were prescribed an anti-depressant drug during the same time period in the monitored population. In contrast, Avorn *et al.* found that 23% of ever-recipients of β -blockers were prescribed an anti-depressant drug during a time period of approximately similar length [10]. Avorn's work did not show the temporal sequences of prescribing, so whether this high rate of anti-depressant drug prescribing was coincidental or perhaps causally linked to β -blocker use is unclear. Whatever its base, the high frequency of anti-depressant drug usage in these groups deserves further study because of its medical and economic implications.

In our study, anti-depressant drug prescribing did cluster more conspicuously with single than with multiple prescriptions for flunarizine. The study design did not allow us to distinguish among several possible explanations. One is that patients with nonspecific complaints were initially prescribed flunarizine, but, when the complaints persisted, tended to be switched to an anti-depressant. Another explanation is that patients most sensitive to flunarizine rapidly developed signs and symptoms of depression, leading their physicians to discontinue the flunarizine and institute treatment with an anti-depressant. Whichever the case, we found overall only 15.6 starts of anti-depressant drugs, in excess of the background rate, during the periods of flunarizine use. These 15.6 attributable starts of an anti-depressant drug occurred in 1284 recipients of flunarizine. Thus, one flunarizine recipient in $1284/15.6 = 82$ might have obtained a prescription for an anti-depressant drug due to an unwanted reaction to flunarizine.

This attributable risk is to be contrasted with a background rate of anti-depressant drug prescribing that is 12 times higher: 1 flunarizine recipient in 7 contemporaneously began a course of anti-depressant drug treatment, but in a time sequence incompatible with a causal role of flunarizine. Perhaps this high background rate is attributable to some confounder, e.g. migraine, which is both an indication for flun-

arizine use and has a recognized association with depression [11–13].

Our estimate of the attributable risk of depression due to flunarizine is subject to several sources of error. We would have missed any cases where the physician responded to signs and symptoms of depression by simply discontinuing flunarizine, but not prescribing any anti-depressant drug. This conservative practice may have occurred in a minority of cases, but it is not consistent with the relatively liberal prescribing we found in the group as a whole. Another source of error is that anti-depressant drug prescribing is not a reliable indicator of true depression, because anti-depressant drugs are used in a variety of mood disturbances [9] of lesser severity than depression, that meet an accepted diagnostic standard [14]. For this reason, the figures on incidence and attributable risk relate to initiation of anti-depressant drug use, not of true depression.

These uncertainties necessarily limit the conclusions one can draw from prescription sequence data, but they would appear to be small in relation to the uncertainties inherent in other post-market surveillance methods. For example, Table 1 illustrates what case reports do and do not tell, and the spontaneous reporting systems, such as the British Yellow Cards, are complicated by gross under-reporting [15]. Dutch pharmacy data have a high degree of accuracy as to drug identity, quantity, and date dispensed, and the reimbursement arrangements insure virtual completeness of outpatients' records. This historical record constrains the interpretations that can justifiably be considered in any adverse reaction situation. In some medical circumstances, the sequence of prescriptions effectively outlines the nature and sequence of medical events, whereas in others it cannot. In the present situation, the residual uncertainties are ones of interpretation: why the drugs were prescribed, the occurrence of adverse events that are not signalled by outpatient prescriptions, and how often an adverse effect was masked because the first drug was discontinued instead of a second drug being added. Notwithstanding these limitations, the data allow us to say with confidence that many hundreds of patients received flunarizine over a period of many months with only a minor attributable risk of mental depression severe enough to warrant treatment with anti-depressant drugs. Had there been an epidemic of depression created by use of this drug, it surely

would have been clearly reflected in these drug histories.

Ten of the 777 users of flunarizine in the flexible database had an anti-Parkinson drug in their medication history. There was no indication for clustering of the starts of anti-Parkinson drug prescribing during flunarizine use. A much larger population of patients would have to be monitored in order to put this conclusion on a firm ground. The significance of this part of the study lies not so much in the relatively sparse amount of data, but more in the rapidity with which the database, once built, was analyzed for prescription sequences. The actual analysis time of 10 working days was dependent only in a minor way on the volume of prescribing. Thus, one can expect to be able to use dispensing data from community (and, where possible, hospital) pharmacies to provide prescription sequence data on an urgent basis when questions about the risk of adverse reactions suddenly arise. The method depends on the completeness of the records and the specificity of available pharmacotherapy for the adverse reaction in question. Obviously, many types of adverse reactions are not reflected by physicians' choices of prescriptions for out-patients, in which cases the method cannot be used.

Outside The Netherlands, complete dispensing records are likely to be present in certain health maintenance organizations and other insurance schemes. Perhaps the forthcoming Medicare system of prescription drug reimbursement in the U.S. will allow prescription sequence analysis on a broader base than could be possible in a small country like The Netherlands. Probably the main value of the method is to give rapid estimates of risk when case reports describe side effects but leave the risk of their occurrence to the imagination. While the randomized controlled trial remains the paradigm for definitive answers to such questions, the time and costs involved often preclude its use in situations where regulatory decisions

have to be taken on incomplete and imperfect data. In that situation, prescription sequence analysis can rapidly provide an estimate of likely risk.

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Markers of adverse drug reactions in medication histories

An analysis of inhaled steroid utilization

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Introduction

A therapeutic effect of a new drug is generally assessed by means of randomized clinical trials. Unwanted effects of drugs, however, are usually much more difficult to detect. Only a limited number of patients taking a drug experience an adverse reaction, and serious or fatal reactions are generally rare, though they may cluster in patients with special attributes. Until such attributes are understood, however, the incidence of the adverse reaction is expressed for the general population of patients. For the detection of rare adverse drug reactions, physician's reports on reactions in individual patients have been indispensable. Causality in individual cases, however, is difficult to assess, and adverse reactions that are conditions with a sizeable background incidence in non-users of drugs are, in general, overlooked. The publication of case reports presses for further investigation on a population level, and if a perceived problem gets general publicity, society seems to demand information about risk at short notice.

We have devised a method to study a subset of possible adverse drug reactions on a screening basis, within a few weeks. The approach is based on the observation that some unwanted drug effects lead to a condition that is treated with another drug. This concept of prescription sequence analysis can be depicted as:

drug A $\longrightarrow$ adverse reaction $\longrightarrow$ drug B

A is the drug that causes an adverse drug reaction and B is the drug, or group of drugs, given to treat the condition that followed the use of A. Patient drug histories should reveal in this situation a relatively high frequency of delivery of drug B after use of drug A [1 2].

Application of prescription sequence analysis

is limited to the group of adverse drug reactions where a specific drug therapy is available to treat the adverse reaction. Therapy should not be given to prevent an adverse reaction. Insight into the general use of the drugs should determine whether it is suited for prescription sequence analysis: a temporal relation of the use of two drugs may be determined by a third variable, i.e. when the drugs are given for different stages of the same disease. Sometimes additional information, such as the indication for the use of drugs A and B, will be needed. The analysis should take into account a certain lag-time for the adverse reaction to occur. Primarily, complete and reliable drug histories are needed as a basis for the analyses; to study rare reactions large numbers of drug histories are needed.

In the Netherlands, 70% of the population are insured in the health insurance funds, which require their members to designate one pharmacy to obtain all prescribed drugs. The majority of pharmacies have a computerized data base.

Application of prescription sequence analysis

As an application of prescription sequence analysis, we studied one class of drugs with a known side-effect, the inhalational steroids for asthma treatment are reported to cause oral candidiasis in 1-5% of the patients [3-6]. There is a specific therapy available for oral candidiasis: topical oral forms of drugs that counter the candida infection. Schematically presented:

inhaled steroid $\longrightarrow$ oral candidiasis $\longrightarrow$
antifungal drug

Oral candidiasis is not necessarily followed by antifungal therapy, but the more overt infections

Keywords

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Abstract

Prescription sequence analysis is based on the observation that a subset of adverse drug reactions are themselves indications for the prescription of another drug. We propose an approach to the analysis of clustering of prescriptions in medication histories that contain records of a presumed side-effect-causing drug A and a side-effect-alleviating drug B. This set of histories with records of both A and B is analysed in a logistic regression model that considers the start of B against exposure and non-exposure of A, stratified on the level of the individual histories. A correction is presented for the periods of B use, during which a new start of B cannot occur. Prescription sequence analysis is demonstrated with a set of histories of use of inhaled steroids (A) and topical oral anticandida drugs (B). A can cause oral candidiasis, B is therapy for this condition. An odds ratio of 1.43 was found for the association of A use and the initiation of therapy with B.

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Table 1

Association of the use of inhalational steroids and anticandida drugs in the study population

I reference population	64,712
II users of inhalational steroids (A)	700
III users of selected antifungal drugs (B)	815
IV users of both A and B	22
Crude odds ratio: $\frac{(I+IV-II-III) \cdot IV}{(II-IV) \cdot (III-IV)} = 2.58$	

are likely to be. Nystatin and miconazole, the two antifungal drugs available in the Netherlands for topical oral use, are specifically labelled for the treatment of candidiasis [7].

A data base of all patient drug histories from 5 Dutch community pharmacies was set up; 64,712 histories spanning a mean period of 31 months (range 21-40 months) were available. The data were anonymized before leaving the pharmacies, but could be recognized to belong to one patient. Due to Dutch administrative requirements the data base can be considered to contain virtually complete information on the non-hospital medication.

A selection was made of all medication histories that contained records of the dispensing of inhalational steroids as well as antifungal drugs (Table 1).

Out of 700 users of steroids 22 (3.1 %) had a topical antifungal drug at one time. This is in contrast with the 1.3% (815 out of 64,712) users of antifungal drugs in the reference population. However, as stated earlier, to assess causality we will have to consider the temporal association of use of A and B. The 3.1% can be seen as a maximum of drug-treated adverse reaction, since B that precedes A cannot be caused by drug A.

Data analysis

The usual cohort-type approach, where a drug which may cause a side-effect is compared with a control drug is questionable here, because of the difficulty of the choice of an appropriate control drug and because of the absence of data on morbidity and behavioural co-variables of the use of the different drugs. Therefore, we chose another comparison, within the patient medication history itself, using the fact that most patients who are prescribed a drug have records covering periods of time both prior to and after their use of the subject drug.

Patient medication histories were selected from the described data base. The selection criterion was: records of the use ever of A (inhalational steroids) and B (antifungal medication) should be in the history. In these histories the initiation of B medication is to be compared for the periods before, during, and after use of A. 'Initiation' is the first day of an inferred period of the use of B, i.e. the first of a series of dispensing of the drug. The periods of use of inhalational steroids were estimated from the amount of drug dispensed and the prescribed daily dose (PDD). A period of 30 days was added to the end of the cal-

culated period to adjust for irregular use and pharmacological half-life. For the antifungal drugs, which are typically used for short periods of 1-3 weeks and have a well-documented brief duration of action, no period at the end was added; however, a repeat prescription was considered to be continuous with the previous one if it was filled within 30 days after the calculated end of use.

Because drugs used in the first part of the observation period but prescribed before the start of the records, will not show up in the patient drug history, a window of 90 days was set at the beginning of the observation period. As the typical duration of the use of one steroid dispense is 90 days, drugs delivered in this period will appear at the redefined start of the medication histories (day 91), whereas before this point no certainty exists if a drug was used. Histories where the single dispense of B was used in the first three months of the observation period are excluded: in the redefined observation period after day 90 the condition of use of both drugs A and B is not met.

We want to apply a measure of temporal association of A and B, stratified on the level of the individual histories. The reason is that it seems not suitable to aggregate the data to obtain a one-level overall measure; the length of use of A and the number of B starts may vary considerably between histories of different patients. Confounding of the results to a positive association would occur if the number of B starts in the history is correlated to the fraction of time of A use, even if the B starts are distributed uniformly over the whole history. A measure of association of A use and the initiation of B should adjust for these differences in density of use of drugs between the individual histories.

A new period of dispensing of a drug can obviously only start after cessation of the previous period of use of the drug. This aspect is relevant for the periods of the use of B, the marker drug for a possible adverse reaction, for which the initiation of therapy is considered, i.e. the start of a period of treatment. In the analysis the period of use of B after its day of start will not be considered. The number of days with no start of B are composed from the periods before the start and after the end of the use of B (Fig. 1). The intervals of the use of B are deleted from the histories.

Patient-stratified analysis

Two variables, both of a binary nature, are to be considered: on any day medication B may be initiated or not; this initiation occurs during use or non-use of A. Each medication history can be considered to have a number of T_i observation days, with an outcome of two binary variables $x_i(t)$ and $y_i(t)$ on each day t :

$x_i(t)$: (1 use of A, 0 non-use of A)

$y_i(t)$: (1 initiation of B therapy,

0 no initiation of B)

Figure 1
Medication history of a patient with initiation of drug B therapy during use of drug A

Here i runs over the set of patient indices, t runs over the set of observation days for patient i .

Let $P_i(t)$ be the probability that $y_i(t) = 1$, that is, the probability that person i starts to take drug B at day t . The logit model in our data set is expressed as:

$$\log P_i(t) / [1 - P_i(t)] = \mu_i + \Theta \cdot x_i(t)$$

Our main concern is to assess the association of the use of drug A and the initiation of drug B; the null hypothesis can be defined as $H_0: \Theta = 0$.

The analysis is performed stratified to the level of the individual medication history, i.e. over the sets of T_i days of the i persons. The model is

Figure 2
Periods of use of steroid drugs (drug A) and antifungal drugs (drug B) of selected patients

fitted by the use of a logistic regression programme [8], which makes estimates of μ_i values of the individual histories and of the common value of Θ . The approach differs from the common application of a logistic regression analysis in the stratification, here each stratum is one of the individual patient data sets. The Θ parameter denotes the association of B starts to use of A, the μ_i values are presented in order to have knowledge about the interindividual variation of starts of B.

A binomial distribution is implicit for the use of a logistic regression model, but as in this case $P_i(t)$ is small, also the approximation of a Poisson distribution could be used. The design presented here could create the impression of a matched case-control study, which typically has 2-6 observations per stratum. By analysing a person's history in its component days a large number of observations is obtained, sufficient to apply the maximum-likelihood approach.

Susceptibility for an adverse reaction may increase with age, i.e. over the T_i observation days; as the time frame of the data base is small compared to a life span no adjustment will be presented here. Chronic therapy, i.e. use of A over most T_i observation days reduces the information content of the histories, as the logit model considers for each history days of A use against days of non-use of the drug.

Results

The crude odds ratio of the use ever of B of patients who had A is 2.58 (data from Table 1).

In the group of 22 users of A and B one history was excluded because the only dispense of B occurred in the first 90 days of the recorded history. A graphical presentation of the remaining 21 histories is given in Figure 2. The crude odds ratio of the one-stratum aggregated 21 histories is 1.66 (Table 2). For these histories the association of A use and the initiation of therapy with B was analysed stratified in a logit model, as described. With deletion of the periods of B use the odds ratio is 1.43 ($P = 0.22$, one-sided). The odds ratio has a value of 1.40 when the periods of B use are not deleted.

Discussion

In this paper we considered the measure of as-

sociation of the use of inhaled steroids and initiation of topical oral anticandida therapy in a logistic regression model. The logistic approach makes sense in that multiple maxima of the likelihood function are unlikely unless data are sparse or if gross discrepancies from the model exist [9 10]. The Mantel-Haenszel estimate is less appropriate for the data presented because of the occurrence of a zero value in one cell of each of the 21 2·2 tables [11].

In our set of data, which has a relatively modest size, combining all histories into one stratum (Table 2) results in a higher odds ratio than a stratified analysis. This higher odds ratio, however, gives a distorted view due to the confounding resulting from a correlation between the number of B starts in a history and the fraction of time of A use, regardless of the distribution of the B starts.

Also, the crude odds ratio of the use ever of both types of drugs (Table 1) is higher than the one calculated in the logistic regression. Here, the temporal relationships of drug use were not taken into account; further, the crude odds ratio may be confounded by a medicalization of patients with a chronically treated condition, like asthma, i.e. these patients tend to be treated also for other conditions.

Stratification to the level of the individual medication histories yields a moderately positive association here. The correction for periods of B use has no strong impact, as the anticandida drugs tended to be dispensed for a short period (Fig. 2). For more chronic types of therapy the situation may be very different, with a clear effect of the correction.

As was stated before, a larger fraction of users of inhalational steroids had at some time one of the selected antifungal drugs, compared to the reference population (3.1% versus 1.3%) (Table 1); the logistic regression still yields a positive association, but smaller than would be suggested by the raw comparison of the use ever of the drugs in Table 1. Thus, while the figure of 3.1% sets an upper limit for drug-treated risk, the inclusion of time relationships in the analysis lowers the degree of association.

This result suggests that a substantial part of oral candidiasis was not caused by inhaled steroids. Unrecognized background incidence of this condition is perhaps one explanation for the conflicting reports [3-6] on the frequency of oral candidiasis as a side-effect. These reports were based on patient series or cohort studies without a control group and were thus missing information on background incidence.

As only some of the people are treated medically for an adverse reaction, causality can be studied by looking at the time relationships of drug dispense, but not the actual absolute risk. Thus, the logit analysis performed here has solely the aim to be used in the assessment of causality, not in estimating the incidence of a reported problem.

Acknowledgement

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Table 2
*Initiation of drug B therapy during use or non-use of drug A, summated for the 21 medication histories**

$\Sigma a_i =$	16	$\Sigma b_i =$	15
$\Sigma c_i =$	8,011	$\Sigma d_i =$	12,451
Crude odds ratio = $\frac{16}{15} \cdot \frac{12,451}{8,011} = 1.66$			

* a_i : starts of B during A use; b_i : starts of B during A non-use; c_i : days of A use; d_i : days without A use.

where two of the authors (H.P. and T.K.) enjoyed hospitality in 1989. We are indebted to Prof. Dr. B. Efron and Prof. Dr. J. Urquhart for helpful discussions.

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APPENDIX TO CHAPTER 5.
(included for this thesis)

The study described in this chapter and the two articles reproduced in chapter 4 show applications of prescription sequence analysis. The three articles reflect the different ways by which we analyzed the data. In all three articles analyses were made to ascertain the temporal clustering of prescriptions in medication histories that contain records of a presumed side-effect causing drug A and a side-effect alleviating drug B. The initiation (or "start") of therapy with drug B is considered against the periods of inferred exposure and non-exposure to drug A in the drug histories.

The two articles in chapter 4 are both analyses of drug histories of recipients of the anti-vertigo/anti-migraine drug flunarizine. In the analysis of chapter 4a the observed number of starts of drug B over the periods of inferred use and non-use of drug A is tested with help of a distribution generated by a Monte-Carlo simulation. In this simulation, for each person's drug history, starts of drug B are generated at random over the periods of inferred use and non-use of drug A. In chapter 4b the incidence density of starts of drug B is determined for periods of inferred use of drug A and periods of non-use of drug A. An incidence density ratio is determined from the results of the two periods.

A need for another way to analyze the data was felt for three reasons:

- A) After start of drug B, B is used for a certain period, that varies within the drug histories and between the histories. The analysis should correct for these periods of use of B, during which no new start of B can occur.
 - B) Aggregating the data to obtain a one-level overall measure as was done in chapter 4b may confound the results and can yield a spurious association. In chapter 4b the incidence densities of starts of drug B were established for the periods of inferred use and non-use of A. For these both types of use the number of starts of B were aggregated across persons. The durations of use of A and the number of starts of B vary considerably between drug histories of different persons.
 - C) For future studies, analyses should be possible with more than one drug variable and with other exposure variables.
- A) In chapter 5 a correction was introduced for the inferred periods of B use, during which a new start of B cannot occur. The approach was to delete the periods of inferred B use from the drug histories before performing the logistic regression analysis. Thus, the problem reduces to describing the probability in a person of the occurrence of a condition (inducing the prescription of B) that lasts only one day, after which the person is again at risk to develop this condition. In the analysis presented in this chapter the periods of B use were rather short (figure 2), and the correction had no strong impact. For other studies, with longer periods of treatment with a drug B, this correction will have a more important effect.
- B) Prescription sequence analysis tests whether the initiation of therapy with drug B is dependent on exposure to drug A. In the selected patient drug histories initiation (or "start") of therapy with drug B occurs at least one time.

The problem is to estimate the risk of occurrence of the use of drug B dependent on the use of drug A and adjusted for individual determinants that could influence the relationship between the use of drug A and of drug B.

After deleting the periods of inferred B use, each day of the remaining drug history is an observation that is assumed to be independent of the use of B on other days. After one day of use of drug B the person is again at risk.

A logistic regression model is used to estimate the probability of the use of drug B dependent on the use of drug A and on the individual determinants.

The common application of logistic regression analysis considers for each person in a study group the value for the outcome variable and the values of each of the independent variables, that can be categorical or continuous.

In our data set for each person an outcome parameter (start or non-start of B) has to be considered for each day of the medication history. We used a model that considers each person's history as one stratum of observations, where the observations on each day are mutually independent outcomes. Thus, this outcome is only dependent on the use of drug A and on the individual who is observed.

If the variable Y has the value 1 at an initiation of drug B and a value 0 when drug B is not started then the probability that $Y=1$, $P(Y)$, is given by the logistic function:

$$P(Y) = \frac{1}{1 + e^{-z}} \quad (5A.1)$$

with z a linear function of the independent variables, i.e. the use of drug A and the individual determinants of the 21 persons whose drug history was observed. For this problem this function z is defined as

$$z = \alpha + \beta_A \cdot X_A + \sum_{i=1}^{21} \gamma_i \cdot C_i \quad (5A.2)$$

For every day of a drug history, the variable X_A has the value 1 if the drug A is used and 0 if A is not used.

The variable C_i with $i = 1, 2, \dots, 21$ has the value 1 if the data of person i are considered and the value 0 otherwise.

α , β_A and the γ_i 's are the parameters of the model that are estimated by maximizing the likelihood function that is based on the observed data.

For the person j all C_i 's are zero when the i 's do not equal j . Thus, for a day with no use of drug A the value of z equals $\alpha + \gamma_j$ and if drug A is used, z equals $\alpha + \beta_A + \gamma_j$.

The probability of the use of drug B dependent on the use of drug A and the individual whose drug history is observed, is estimated by

* In fact, this model is redundant and one of the terms $\gamma_i \cdot C_i$ is superfluous. In the model used in the article of chapter 5, γ_1 is set to zero. This means that the first person is the reference and the values of z of all other persons are compared with that of the first person.

$$P(Y) = \frac{1}{1 + e^{-(\alpha + \beta_A \cdot X_A + \sum_{i=1}^{21} \gamma_i \cdot C_i)}} \quad (5A.3)$$

The odds of event Y, Odds(Y), is defined as $P(y)/(1-P(Y))$ and the equation can be rewritten as

$$Odds(Y) = \frac{P(Y)}{1 - P(Y)} = e^{\alpha + \beta_A \cdot X_A + \sum_{i=1}^{21} \gamma_i \cdot C_i} \quad (5A.4)$$

For a person j and a day that drug A is not used, the estimated Odds(Y) equals $\exp(\alpha + \gamma_j)$ and on a day that drug A is used, Odds(Y) equals $\exp(\alpha + \beta_A + \gamma_j)$. The estimated ratio of Odds(Y) of days of use and non-use of drug A equals $\exp(\beta_A)$, a common parameter for all persons.

Thus, this Odds Ratio $\exp(\beta_A)$ can be seen as a measure of the association between the use of drug B and drug A, adjusted for the characteristics of the individual whose drug history is observed.

C) For the assessment of the impact of more than one drug variables or other exposure variables and based on the drug histories of N persons, the model can be adapted to a more general form

$$Odds(Y) = e^{\alpha + \beta_A \cdot X_A + \sum_{i=1}^N \gamma_i \cdot C_i + \sum_{j=1}^M \Phi_j \cdot Z_j} \quad (5A.5)$$

The additional exposure variables are represented by the M variables Z_j and Φ_j represents their related coefficients.

* In the article of Chapter 5 another notation was used. The Odds(Y) was only defined for one person i. In formula (5A.4) α is identical with μ and β is identical with Φ .

CHANNELING BIAS IN THE INTERPRETATION OF DRUG EFFECTS

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SUMMARY

Channeling is a form of allocation bias, where drugs with similar therapeutic indications are prescribed to groups of patients with prognostic differences. Claimed advantages of a new drug may channel it to patients with special pre-existing morbidity, with the consequence that disease states can be incorrectly attributed to use of the drug. For the study of adverse drug reactions, large databases supply information on co-medication and morbidity of patients. For diseases with a stepped-care approach, the drug history of patients, as available from some databases, can show channeling of drugs to patients with markers of relatively severe disease.

INTRODUCTION

When a new treatment is introduced it competes with pre-existing methods of treatment for the same conditions. Claimed advantages of the new treatment may be general superiority over pre-existing methods, but often narrowly defined advantages are all that can be claimed. Practitioners may adopt the new treatment method by displacing or supplementing pre-existing treatments or by prescribing selectively to new patients. If the promotion of the new product has succeeded in creating in physicians' minds a particular patient profile for the new product, then comparisons between observational data gathered on recipients of the new product versus recipients of the older products will be confounded by different morbidities in the two patient groups. Channeling is the term we have coined for this application of drugs in groups of patients who have a susceptibility to problems or who have special pre-existing morbidity.^{1,2}

Channeling can be considered as a special form of allocation bias, where interventions, self-selected or clinically assigned, are given to people with major prognostic differences.³ Drugs with similar actions that enter the market at different times, and thus in different competitive situations, may be channeled to different groups of patients. For example, a late-entry drug is more likely to be given to patients who have not responded satisfactorily to therapy with an established, early-entry drug. If competitive claims are made for a later-entry drug that differentiate it from earlier-entry products, the associated promotion may influence physicians to select different prognostic types of patients to receive the various products in a pharmacologic class.

Another factor that may be pertinent is patient and physician age. Since patients and physicians tend to grow old together, elderly patients may be more likely to use early-entry medicines, because they tend to be treated by longer-practising physicians, who tend to adopt later-entry medicines more slowly.

These varied reasons for such channeling by medical or prognostic status also tend to confound patient-related factors with drug-related factors. An often-used claim is less severe or fewer side-

effects for the new drug. This claim can lead to selective prescription of the drug to patients who experienced side-effect problems during treatment with an earlier-entry drug. Also, a claimed higher efficacy for the drug may channel it to patients where a prior treatment had failed. Thus, the later-entry product is also likely to end up in use by patients with different attributes.

An example of channeling appears to have occurred after the introduction of 'Osmosin', a controlled-release form of indomethacin, for which claims of fewer gastro-intestinal side-effects were vigorously promoted. When Inman studied this product using the prescription event monitoring method, he found a much higher prevalence of gastro-intestinal complaints among patients long after the end of use of the drug.⁴ This suggests that the product had been channeled to patients most likely to suffer from these disturbances. The product was withdrawn on the basis of reports suggesting an unexpectedly high occurrence of gastro-intestinal ulcerations, bleeding, or perforation. Inman pointed out, however, that because the drug was claimed to have fewer side-effects, it likely had been prescribed for patients who were most likely to develop these side-effects.

POPULATION-BASED STUDIES

Adverse drug reactions are often recognized only after market introduction of the new substance. The rarer reactions cannot be assessed in premarket clinical trials which include a limited number of patients. Also, more common but less obvious side-effects often are recognized only after a period of use in a larger and medically more diverse general population group than was studied in premarket trials.⁵

Thus, the study of adverse drug reactions necessarily involves larger groups of patients than can be economically or logistically managed in randomized, controlled trials. However, studies are observational, rather than controlled, and thus are subject to various biases, including channeling bias. The occurrence of side-effects of drugs in one therapeutic class can be compared. A central issue in this situation is whether the groups of users are comparable in relevant characteristics: the treated disease, co-morbidity, age, sex, and other factors.

CHOICE OF CONTROLS

The effects of drugs – beneficial or unwanted – are often best studied in comparison to other drugs with similar therapeutic indications. For a new drug which is the first treatment for a condition, comparison to a placebo reference group is appropriate. In contrast, when other therapies exist, the comparison of the new drug should be to the existing therapies. A similar statement can be made for side-effects, especially as a new drug's main benefit is often claimed to be fewer side-effects than old therapies.

In observational studies channeling will often make this type of comparison invalid. Generally, the analysis for such comparisons tries to correct for relevant patient baseline characteristics. Many can be collected in the data, but obviously some cannot, because the factors are not known or because the data cannot be gathered. This problem is ubiquitous in databases collected for one purpose and later used for other purposes.

Studies with existing databases are comparable in this respect to classical case-control or historical cohort studies where inevitably some relevant patient variables from the past will not be known. Even if a database was conceived for research purposes, later studies will be likely to suffer from a lack of relevant data, be it directly on medical aspects such as comorbidity or medication, or more indirectly on behavioural factors like smoking or occupational activities.⁶ These points are independent of whether the database is computerized or not.

MEDICATION-USE DATABASE

The situation is quite different for coding medicine use than for coding other types of therapy or diagnoses. Owing to reimbursement requirements, pharmacy dispensing records are unequivocal about names of drugs, drug regimens, and amounts dispensed. Data are less specific for procedures like surgical operations which often have many variants. Diagnostic data tend to be the most difficult to classify, for diagnosis is a process with many uncertainties and many, often arbitrary, criteria.

While the nomenclature of medicines has few problems, other aspects of database use should not be ignored. The data on drugs may not be complete, or may not be identifiable on the individual patient level. Data on outpatient drug use can be collected from pharmacies or from health insurers. Pharmacies in most countries have no complete data on drug use at the individual patient level. An exception occurs in The Netherlands, where the national insurance scheme requires participating patients to designate one pharmacy from which they obtain all reimbursed drugs.⁵ In the U.S. a comparable situation prevails in some Medicaid data⁷ and in some managed care situations. Confidentiality regulations sometimes preclude the use of medication data for research purposes, as, for example, in the rather extreme Swedish case where privacy concerns preclude storing medication data in pharmacies⁸ for more than a day or two.

Having complete records on individual patients is essential, and the longer the duration spanned by the records, the better. A peculiarity of many administrative databases is they do not define a distinct start for the patient's record. Thus, even if the data are complete over a certain period it may be that only the first records of delivered care indicate coverage, leaving the preceding time ambiguous about actual coverage.

AN EXAMPLE: CHANNELING OF MEDICATION FOR ASTHMA

If a disease is treated in a stepped-care approach, the drugs given can be used as markers for disease severity. We studied the use of asthma medication for channeling of aerosol beta agonists,² as recorded in a large pharmacy database. These aerosol beta agonists tend to be used as a first-line therapy for asthma, while inhalational steroids and other drugs are supplemented for the more severe disease. The three aerosol beta agonists available in The Netherlands differed considerably in concomitant use of inhalational steroids: 23.0 per cent of albuterol (salbutamol) recipients, 35.4 per cent of terbutaline recipients and 42.4 per cent of fenoterol recipients used inhalational steroids. These data support the notion that physicians channel fenoterol to patients with more severe asthma. This channeling of fenoterol may lead to a non-causal linkage of the drug to consequences of severe asthma.

NON-ETIOLOGICAL STUDIES

Databases are useful for other analyses than just drug intervention effects, for example, drug and facilities utilization studies. A rational use of health care facilities is promoted by knowledge of such aspects as the indication for prescription of drugs, multiple use of drugs, and markers of the health status of patients. Differences of delivered care in separate insurance schemes may reveal types of procedures or therapies that depend heavily on reimbursement. Between-physician and between-hospital differences in delivered care suggest inefficiencies or underuse or overuse of certain types of care. A strong variation in therapy use across physicians or regions can help identify the less useful therapies, though a final appraisal of efficacy can only come from a properly controlled trial.

H. PETRI AND J. URQUHART

CHANNELING IN SURGERY

Channeling is especially prominent in surgical therapy, not only because of surgeons' reluctance to operate on high-risk patients, but also when different procedures are perceived to entail different risks. An apparent example of this issue is recent controversy^{9, 10} over a study of the effectiveness and long-term mortality of transurethral versus open prostatectomies for prostatic hyperplasia.

AN APPROACH TO AVOID CHANNELING BIAS

The choice of an appropriate control group is essential for any form of observational study. In studies of treatment effects, baseline characteristics pertaining to the outcome should be identified in advance. Stratification of the subjects into subgroups for these characteristics can correct for imbalances, though often not all relevant factors are known.

For some questions the selection of control patients can be obviated by comparing different periods of a person's medical history. This is analogous to the crossover design in experimental studies. An example is a recent study, in which we considered whether a widely-used anti-vertigo/anti-migraine drug, flunarizine, was responsible for causing mental depression. We studied drug dispensing records in a group of 155 patients who had, at some time during the period of data collection, received both flunarizine and an anti-depressant drug.¹¹ We looked for a temporal clustering of prescriptions for anti-depressant drugs following the start of flunarizine.

Control data were taken not from other groups of patients, but from the patients themselves, in the periods before and long after their use of flunarizine. The within-patient comparisons revealed evidence of only a small risk of flunarizine-related depression because we avoided the confounding effect of what was a very sizeable channeling of flunarizine into use by depression-prone patients. The eventual recipients of flunarizine had a 3.5-fold higher background rate of anti-depressant drug prescribing than a reference group of recipients of any drug.

The actual within-patient comparison was done by comparing the incidence of initiation of anti-depressant therapy during the periods of flunarizine use (I_u) with the incidence during the rest of the time covered by the database, that is, the periods before and after use of flunarizine (I_{nu}). The incidence is defined as the number of first prescriptions per 1000 observation days. An incidence ratio was determined as I_u/I_{nu} .

CONCLUSION

Channeling can be considered as a type of misclassification when not recognized in the analysis of observational studies. A consequence of the misclassification is that disease states can be incorrectly attributed to use of a drug. Alternatively, when there is knowledge about the differential use of a drug in different stages of a disease, or if a disease has a stepped-care treatment with medicines, the information about a patient's medication can be used to stratify for severity of condition. Within-patient control data can also help avoid channeling bias.

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POSMAR 00004

Characteristics of Patients Prescribed Three Different Inhalational Beta-2 Agonists: An Example of the Channeling Phenomenon

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Summary

In order to detect channeling of medication for asthma to patients differing in disease severity, prescription drug histories of users of three inhalational beta agonists were compared. We looked at markers of asthma severity and of concomitant cardiovascular disease and diabetes.

We found 2—2.5 times more concomitant systemic steroid therapy prescribed to fenoterol recipients than to salbutamol recipients. Terbutaline recipients were intermediate. We found the highest proportions of other anti-asthma medications among fenoterol recipients, intermediate proportions among terbutaline recipients, lowest proportions among salbutamol recipients. Thus, Dutch physicians seem to channel terbutaline and especially fenoterol to patients with more severe forms of asthma.

There were no differences with respect to prescriptions for cardiovascular or diabetic drugs.

If not recognized, channeling may result in allocation bias in observational studies on drug effects.

Key Words — Pharmacoepidemiology; asthma; fenoterol; terbutaline; salbutamol; aerosol therapy; adverse drug reactions

Introduction

Increase of asthma mortality has been reported in the last two decades from several countries.¹⁻³ An earlier apparent epidemic occurred in the mid-sixties in Britain, Australia and New Zealand.⁴⁻⁶ More recently, increase of asthma mortality is reported in more countries, especially in New Zealand, where a marked increase was observed in the late seventies.⁷ Several reasons for the observed increased asthma mortality have been forwarded: increased prevalence of asthma, increased severity, changes in diagnostic classification, better ascertainment, changes in therapy including the use of multiple drugs.^{6,8,9}

Since their introduction in the 1960s, inhalational beta agonist drugs have been a cornerstone in asthma therapy. However, concern about increased risk of sudden death of asthmatics in relation to use of the drugs has frequently been raised.^{6,10-12} The existence of a causal link between death from asthma and the use of pressurized aerosols has been controversial. A problem is that there are many pitfalls in observational studies on a disease such as asthma which is difficult to stage with respect to severity and tends to be treated with multiple drugs.^{6,9}

A recent study¹³ suggested a difference in risk of fenoterol and salbutamol. In this case-control study, mortality was found to be associated to patients who were prescribed fenoterol in metered-dose inhaler form.

The study of infrequent adverse drug reactions relies on methods that, unlike randomized controlled trials, are inherently susceptible to biases.^{14,15} In case-control studies on drug effects, the choice of an appropriate control group is a special problem, and the debate on fenoterol-associated mortality¹³ was focussed especially on the selection of the control patients.¹⁵⁻¹⁷ Additional issues are whether the drug was actually used during the attack and whether the drug has a direct adverse effect or its use leads to delay in seeking help.

Initial experiences with a new drug tend to establish a pattern of subsequent use, leading to "channeling", the term we use for selective prescribing of a drug to patients with special prognostic characteristics or degrees of disease severity.^{18,19}

In observational studies, channeling will act as a form of allocation bias if differences of baseline characteristics go unrecognized or not adjusted-for. The subject of our study relates to the comparability of patients using the various inhalational beta-2 agonist drugs. In The Netherlands, salbutamol was introduced in 1968, terbutaline in 1970 and fenoterol in 1971. Later-introduced drugs are more likely to find their principal first uses in patients who have not responded satisfactorily to previously available drugs.²⁰

Asthmatics are often treated with a stepped-care approach, with a spectrum of drugs of presumed increasing potency but decreasing therapeutic benefit/risk ratio.

Established practice in The Netherlands and other countries is that inhalational beta-2 agonists are used initially, and if this mode of treatment proves insufficient, inhalational steroids are added, and then, if that proves still insufficient, systemic treatment with theophylline is added, followed (or replaced), if necessary, by systemic steroid treatment.^{21,22} European practice differs from North American in reserving systemic theophylline treatment for patients who have not responded satisfactorily to inhalational drugs.

We used outpatient prescription drug histories as markers of severity of asthma, based on the assumption that prescribing was substantially driven by physicians' adherence to the foregoing stepped-care system of treatment. We also used these histories to identify patients with concomitant cardiovascular disease or diabetes, both being conditions with characteristic and specific drug therapy. Cardiovascular disease and diabetes are also two major recognized causes of sudden death.

We used a large database of outpatient drug dispensing histories. In The Netherlands, the majority of the patients are insured in a general health insurance system called *Ziekenfonds*, which requires patients to designate one pharmacy from which they obtain all reimbursed drugs. Also, pharmacies have computerized record-keeping as the basis for reimbursement. These two factors insured that almost complete medication histories were available for our study.

Methods

The five inhaled beta agonists available in The Netherlands are salbutamol, terbutaline, fenoterol, isoprenaline, and rimiterol.

The data source was a 12-pharmacy database covering all medications prescribed and dispensed in the year 1988 (referred to hereafter as the "one-year database"). This reference population encompasses 121,000 patients, two-thirds of them insured by the *Ziekenfonds*.

Patients' drug histories and data relating to the prescribing physicians were anonymized before leaving the pharmacy. In our database all prescriptions dispensed

to each patient had a unique code number to maintain separate but anonymous identity of each patient's prescription drug history.

We studied beta-2 agonists that were dispensed to at least 10 patients in the metered-dose aerosol or inhaled dry powder formulation.

We determined the following:

- recipients of prescriptions for each inhalational beta-2 agonist, their sex distribution and median age, in the one-year database (Table I);
- the recipients of inhalational beta-2 agonists who:
 - were prescribed and dispensed systemic steroids within a six-month time window (Table II);
 - were prescribed 1, 2, 3 or more different categories of anti-asthma medications within a six-month time window (Tables III and IV);
 - were prescribed cardiovascular or antidiabetic medication, within a six-month time window (Tables V and VI).

The six-month time window for assessing co-medication was set to indicate concomitant use of the various types of drugs, recognizing that most prescriptions are dispensed in quantities sufficient to last for 2–3 months. A 6-month time window is a compromise choice — long enough to see at least one dispense in chronic medication, but not so long as to make it likely that agents were used in different periods, rather than concomitantly, within the time window.

Following the age grouping defined by Crane *et al.*,¹³ we divided patients into those aged 5–45 years and those aged over 45 years, at December 31, 1988.

To judge co-medication with inhalational beta-agonist drugs, we selected categories of drugs according to the ATC drug classification,²³ as follows:

respiratory drugs (Tables II, III and IV)

- inhaled glucocorticoids (R03BA)
- theophylline and derivatives (R03DA)
- cromoglycate (R03BC01)
- systemic beta-agonists (R03CC)
- ipratropium (R03BB01)

— systemic glucocorticoids (H02AB)

antidiabetic drugs (Tables V and VI)

- insulines (A10AA)
- biguanides (A10BA)
- sulphonamides, urea derivatives (A10BB)

systemic cardiovascular medication (Tables V and VI)

- cardiac glycosides (C01A)
- beta-blockers (C07A)
- calcium re-entry blockers (C02DE)
- coronary vasodilators (C01DA)
- diuretics (C03)

- antithrombotic agents (B01A)
- anti-arrhythmic drugs (C01B)
- lipid lowering drugs (B04)
- ACE-inhibitors (C02EA)

Results and Discussion

The results are shown in Tables I–VI. Table I shows that salbutamol is the most prescribed inhalational adrenergic drug in The Netherlands. Fenoterol and terbutaline have far less users. Not included are the inhaled powder form of terbutaline and all inhaled forms of rimiterol and isoprenaline; these products did not reach the criterion of 10 users to be included in the analyses. For salbutamol it is also evident that the dry powder form is used much more than the pressurized aerosol (Table I). Because some patients had received both aerosol and dry powder capsules of a drug, results in the tables cannot be added.

The 5–45 year age group is chosen in order to compare the data with the results of the New Zealand Asthma Mortality study,¹³ in which this same age grouping was used. The data presented here are for patients with all degrees of asthma severity, with drug dispensing taken as selection criterion. Obviously, the New Zealand study covers a very different patient group: cases and controls were selected, respectively, for death due to asthma or for hospitalization for asthma. The effects of these selection criteria are reflected in the degree of drug use of the patients: 44% of the control patients in the New Zealand study were using three or more asthma drugs at the time of hospital admission, while in our study the patients tended to receive less drugs (Table III). For example, 49 of 250 salbutamol aerosol users (19.6%) were concomitantly treated with two or more other anti-asthma drugs.

Our assessment of co-medication, which encompassed a 6-month period, will lead to a somewhat higher count than an assessment encompassing one reference day, as was done in the New Zealand study. Even so, patients in different subgroups of the 5–45 year age group had a lower number of asthma drugs than found in the New Zealand study (Table III). Both differences point to a greater severity of disease in the patients in the New Zealand study than in ours.

The fraction of younger recipients of three or more other types of asthma drugs was highest in the fenoterol aerosol group and lowest in the salbutamol groups (Table III); recipients of terbutaline aerosol had an intermediate position. We found a similar pattern of differential use of multiple anti-asthma drugs in the older group, against a background of more co-medication in all subgroups of older patients, compared to younger patients (Table IV).

TABLE I

Numbers and median ages of male (M) and female (F) users of inhaled beta-2 agonist drugs of all ages, during a one-year observation period

	No. of Users		Median Age (years)	
	M	F	M	F
Fenoterol aerosol 0.2 mg	43	46	37	46.5
Fenoterol powder 0.2 mg	26	29	29	39
Salbutamol aerosol 0.1 mg	368	264	36	45.5
Salbutamol powder 0.2 mg	513	395	17	22
Salbutamol powder 0.4 mg	1011	1299	41	56
Terbutaline aerosol 0.25 mg	65	64	24	25.5

TABLE II

Numbers of beta-2 agonist users, by age, with systemic steroid co-medication during a 6-month observation period

	5-45 Years		> 45 Years	
	N	With steroids	N	With steroids
Fenoterol aerosol 0.2 mg	36	8 (22%)	27	15 (55%)
Fenoterol powder 0.2 mg	30	6 (20%)	14	8 (57%)
Salbutamol aerosol 0.1 mg	250	23 (9%)	175	54 (31%)
Salbutamol powder 0.2 mg	437	18 (4%)	152	32 (21%)
Salbutamol powder 0.4 mg	764	64 (8%)	1012	229 (23%)
Terbutaline aerosol 0.25 mg	46	6 (13%)	29	13 (45%)

TABLE III

Co-medication with other drugs for respiratory conditions during a 6-month period, of patients aged 5-45 years using inhalational beta-2 drugs

	No. of respiratory drugs used as co-medication			
	N	None	1-2	3 or more
Fenoterol aerosol 0.2 mg	36	13 (36%)	13 (36%)	10 (28%)
Fenoterol powder 0.2 mg	30	19 (63%)	6 (20%)	5 (17%)
Salbutamol aerosol 0.1 mg	250	159 (64%)	65 (26%)	26 (10%)
Salbutamol powder 0.2 mg	437	287 (66%)	112 (26%)	38 (9%)
Salbutamol powder 0.4 mg	764	476 (62%)	200 (26%)	88 (12%)
Terbutaline aerosol 0.25 mg	46	19 (41%)	16 (35%)	11 (24%)

TABLE IV

Co-medication with other drugs for respiratory conditions during a 6-month period, of patients aged >45 years using inhalational beta-2 drugs

	No. of respiratory drugs used as co-medication			
	N	None	1-2	3 or more
Fenoterol aerosol 0.2 mg	27	5 (19%)	5 (19%)	17 (63%)
Fenoterol powder 0.2 mg	14	2 (14%)	6 (43%)	6 (43%)
Salbutamol aerosol 0.1 mg	175	71 (41%)	56 (32%)	48 (27%)
Salbutamol powder 0.2 mg	152	75 (49%)	43 (28%)	34 (22%)
Salbutamol powder 0.4 mg	1012	380 (38%)	377 (37%)	255 (25%)
Terbutaline aerosol 0.25 mg	29	9 (31%)	8 (28%)	12 (41%)

TABLE V

Co-medication with cardiovascular or antidiabetic drugs during a 6-month period, of patients aged 5–45 years using inhalational beta-2 drugs

	N	Users of Cardiovascular Drugs	Users of Antidiabetic Drugs
Fenoterol aerosol 0.2 mg	36	0 (0%)	1
Fenoterol powder 0.2 mg	30	1 (3%)	0
Salbutamol aerosol 0.1 mg	250	7 (3%)	0
Salbutamol powder 0.2 mg	437	3 (1%)	0
Salbutamol powder 0.4 mg	764	19 (2%)	4
Terbutaline aerosol 0.25 mg	46	0 (0%)	0

TABLE VI

Co-medication with cardiovascular or antidiabetic drugs during a 6-month period, of patients aged > 45 years using inhalational beta-2 drugs

	N	Users of Cardiovascular Drugs	Users of Antidiabetic Drugs
Fenoterol aerosol 0.2 mg	27	8 (30%)	0
Fenoterol powder 0.2 mg	14	7 (50%)	2
Salbutamol aerosol 0.1 mg	175	65 (37%)	5
Salbutamol powder 0.2 mg	152	63 (41%)	9
Salbutamol powder 0.4 mg	1012	398 (39%)	40
Terbutaline aerosol 0.25 mg	29	11 (38%)	1

The degree of co-medication with systemic corticosteroids is shown in Table II. This group of drugs is analysed also separately because it can be considered to be used by patients with more severe forms of asthma. In the younger age group, the use of systemic corticosteroids was highest in the group of fenoterol aerosol

recipients: 22%, and nearly as high (20%) for the fenoterol dry powder users (Table II). In contrast, less than 10% of the younger recipients of different forms of salbutamol had also received systemic steroids. Terbutaline was intermediate. Similar differences were found in the older age group (Table II).

Cardiovascular and diabetes co-medication was not markedly different between the asthma drug groups (Tables V and VI). It is low in the younger group but considerable in the older group.

In conclusion, the data show that inhalational fenoterol and terbutaline are channeled into use in more patients with severe asthma than inhaled salbutamol. In contrast, the users of inhalational fenoterol, terbutaline and salbutamol do not have different patterns of co-medication with cardiovascular or diabetes drugs.

Compared to inhalational salbutamol, in The Netherlands inhalational terbutaline and especially fenoterol are dispensed to patients with more severe forms of asthma. Unless recognized, this channeling can be expected to result in allocation bias in observational studies. In turn, this can lead to unjustified conclusions about the individual drugs' differential therapeutic effects or propensities to cause adverse reactions.

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Channeling of antidepressant drugs to patients with cardiovascular disease

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Summary

Antidepressant drugs differ in their propensity to cause cardiac side-effects. Claimed advantages of a drug may channel it to patients with special pre-existing morbidity, with the consequence that patient characteristics may be confounded with drug effects. We measured the relative usage of the various antidepressant drugs in patients with and without cardiovascular disease, particularly to learn whether antidepressant drugs without cardiac side-effects were more likely to be prescribed for patients with concomitant cardiovascular conditions. Our primary data were the drug-dispensing records from Dutch community pharmacies, covering 1173 anonymized recipients of antidepressant drugs in a 6-month period. We interpreted as marker of cardiovascular disease the concomitant prescribing of major cardiovascular drugs, such as cardiac glycosides, beta blockers, calcium antagonists and the like. The differences in the percentage of recipients of antidepressant drugs concomitantly prescribed major cardiac agents were considerable. At the high end were mianserin (36%) and doxepin (35%); at the low end were fluoxetine (13%) and clomipramine (18%). When the data were stratified for age and sex, however, no significant residual differences remained with respect to cardiovascular co-medication. Thus, channeling occurs in some drugs, but apparently partly via the indirect way of age/sex differences of the recipients of the drugs.

Key words: Pharmacoepidemiology; Antidepressant drugs; Mental depression; Cardiac disease; Adverse drug reactions

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Introduction

Tricyclic antidepressant (TCA) drugs have significant cardiovascular effects. The effects can be classified as conductivity disturbances, arrhythmias and orthostatic hypotension^{1,2}. In therapeutic dosages these effects are considered to be a problem only with persons with actual cardiac disease^{2,3}, but overdosage with TCA drugs can induce life-threatening arrhythmias^{2,4-6}. The newer, non-TCAs form a heterogeneous group of drugs; some are considered to be more safe with respect to the cardiovascular system^{1,2,4,7}.

Cardiovascular disease is quite common in the age group of users of antidepressants and thus a problem of therapeutic choice will arise frequently. The antidepressants available differ in their labelling as concerns use in patients with cardiovascular disease. Thus, selective prescribing of certain antidepressants to groups of patients treated for cardiovascular disease can be expected, but it is not known to what extent this happens.

Channeling occurs when drugs with similar therapeutic indications are prescribed to groups of patients with different health status^{8,9} (Fig. 1). Channeling can occur due to differences in labelled characteristics of drugs, but also as a consequence of less obvious factors, such as time of introduction or different promotion of new products. Knowledge about channeling is important in the interpretation of adverse reactions, to avoid confusion between problems attributable to patients' concomitant diseases or disease-severity and problems attributable to a particular drug.

The use of cardiovascular drugs is a marker for conditions that may make patients vulnerable to cardiotoxic effects of antidepressant drugs. Also, cardiac events will occur with a relatively high incidence in users of cardiac drugs, independently of concurrent antidepressant medication. Channeling of certain antidepressants to these patients may lead to an artificial association of cardiac events to antidepressant use.

The *Farmacotherapeutisch Kompas* published by the public insurers is the reference book on prescription drugs most consulted by Dutch physicians. In the 1990 edition for most antidepressant drugs, a recent myocardial infarction is listed as an absolute contraindication and physicians are advised to refrain from using antidepressant drugs in a variety of conditions, including cardiovascular disease in general¹⁰. For four drugs, mianserine, fluvoxamine, fluoxetine and trazodone, no restrictions in the cardiovascular field are given. It is not known whether these drugs are more likely to be the prescribed antidepressant in patients with serious cardiovascular problems, so this is what we sought to learn by comparing the use

Fig. 1. Channeling of a drug to a subgroup atypical of the general patient population.

of cardiovascular drugs in people who are treated with one of the antidepressant agents available in The Netherlands.

Methods

To be compared are age, sex, and use of cardiovascular drugs in the groups which had received one of the antidepressant drugs available in The Netherlands. The data source is a 12-pharmacy database covering all medications dispensed in the year 1989 and the first 6 months of 1990. This reference population encompasses a population of approximately 130 000 patients. The source pharmacies are spread over the country.

Patients' drug histories and data relating to the prescribing physicians were anonymized before leaving the pharmacy. In our database all prescriptions dispensed to each patient have a unique code number to maintain separate but anonymous identity of each patient's prescription drug history.

As antidepressants are selected the drugs in category N06AA-AE (all non-MAO inhibitor antidepressants) of the ATC Index of the World Health Organization¹¹. All drugs in this class available in The Netherlands as products with a single active substance are included.

For each antidepressant drug the following is determined:

- The number of recipients of the drug, their sex distribution and median age
- The number of recipients who were prescribed and dispensed cardiovascular medication

In Table 1, an overview is given of the number of recipients of each antidepressant; the numbers cannot be added because some persons received more than one antidepressant. To simplify, and in order to compare individual drugs, in the other tables the data are for persons who received only one of the listed antidepressants; results are given for drugs that were dispensed to at least 20 persons, i.e. for the 10 largest groups.

For each of these 10 groups of recipients of antidepressants, the presence of cardiovascular co-medication is compared with the other nine groups of recipients of antidepressants. Ten odds ratios ad/bc are calculated, with

(a) recipients of the specific antidepressant who had cardiovascular co-medication

TABLE 1
Use of antidepressant drugs, sex distribution and age

	Users (number)	Female (fraction)	Age (yrs) median
(1) Amitriptyline	348	0.66	53
(2) Clomipramine	213	0.67	43
(3) Maprotiline	191	0.71	54
(4) Fluvoxamine	112	0.76	44.5
(5) Mianserine	100	0.69	60
(6) Imipramine	98	0.53	44
(7) Doxepin	63	0.71	55
(8) Fluoxetine	52	0.58	49
(9) Dosulepine	30	0.60	46.5
(10) Opipramol	29	0.83	54
(11) Trazodone	13	0.85	69
(12) Nortriptyline	6	1.00	58
(13) Melitracene	6	0.5	71.5
(14) Trimipramine	5	0.8	60
(15) Desipramine	2	0.5	60.5
(16) Dibenazepine	0	—	—

TABLE 2
Age distribution of users of antidepressant drugs

Age (yrs)	Number of users
0-14	27
15-29	94
30-44	324
45-59	331
60-74	237
75->	160

- (b) recipients of the specific antidepressant who had no cardiovascular co-medication
- (c) recipients of other antidepressants who had cardiovascular medication
- (d) recipients of other antidepressants who had no cardiovascular medication

Age and sex can be expected to be related with the use of both antidepressants and cardiovascular medication. Therefore, the odds ratios will also be determined stratified for age and sex with the Mantel-Haenszel procedure¹². The age categories selected are the five highest groups of Table 2. The youngest group is taken out and considered separately, as children are likely to have received the drugs for another indication than depression, i.e. enuresis.

The selected groups of cardiovascular drugs, with their ATC-code, are:

- C01A cardiac glycosides
- C01B anti-arrhythmics, classes I and III
- C07 beta blocking agents
- C02DE calcium antagonists
- C02EA converting enzyme blockers
- C01DA anti-anginal vasodilators
- C03 diuretic drugs
- B01AA oral anticoagulants (dicoumarol group)
- B04A cholesterol- and triglyceride reducers

All calculations were done for a 6-month time period (1.1 to 1.7 1990). This window was set to indicate concomitant use of the various types of drugs. A 6-month time window is long enough to see at least one dispensing in chronic medication, but not

so long as to make it likely that agents were used in different periods, rather than concomitantly.

Results

The number of recipients of antidepressant drugs in the 6-month observation window is 1173, i.e. about 1% of the covered population. A majority is female, 790 users, i.e. 67%. A minority of 86 persons (7.3%) had received more than one type of antidepressant drug. The number of recipients of the individual drugs are listed in Table 1, together with the median age of the recipients. Amitriptyline is the drug most dispensed, followed by clomipramine and maprotiline. There were marked differences in age among the users of the different drugs. For the most used 10 drugs, the median age varied between 43 years (clomipramine) to 60 years (mianserine).

Table 2 gives the age distribution of the whole group of antidepressant drugs. Most of the drugs were dispensed to middle-aged or older persons. We considered separately the 27 users in the age group of 0–14 years (Table 2), as use of the drugs in this age is more likely to be for enuresis than depression. Of these 27 persons, 24 had received imipramine, which is the only one of the selected drugs labelled also for enuresis. The other analyses were done with exclusion of this special younger group. This restriction to persons aged over 14 years hardly changes the value for the median age of the recipients of antidepressants, with the exception of imipramine (51.5 years in the restricted group, 44 years in the complete group as in Table 1).

Table 3 shows the degree of cardiovascular co-medication for recipients of the 10 most dispensed antidepressants. The data are for recipients of a single antidepressant aged over 14 years. The highest degree of cardiovascular co-medication is in the groups of users of mianserine (36%) and doxepine (35%), the lowest in the clomipramine (18%) and fluoxetine (13%) groups. The distribution of the presence of cardiovascular co-medication over the 10 groups is significantly uneven ($p=0.022$; Chi-square 19.37 df 9). While about two times more women had received antidepressants than men, the proportion within the sex groups that had cardiovascular co-medication was not much different; in the group of drugs listed in Table 3, 28% of women and 22% of men had cardiovascular co-medication.

For each of the antidepressants the degree of co-medication with cardiovascular drugs was also calculated as an uncorrected odds ratio, and stratified for age and

TABLE 3

Cardiovascular co-medication with 10 most dispensed antidepressant drugs (users of a single antidepressant; 15 years and older)

	No. of users	(Cardiovascular co-medication)	
		any	none
(1) Amitriptyline	308	84 (27%)	224
(2) Clomipramine	182	32 (18%)	150
(3) Maprotiline	161	49 (30%)	112
(4) Fluvoxamine	94	21 (22%)	73
(5) Mianserine	83	30 (36%)	53
(6) Imipramine	68	17 (25%)	51
(7) Doxepin	55	19 (35%)	36
(8) Fluoxetine	38	5 (13%)	33
(9) Dosulepine	23	5 (22%)	18
(10) Opipramol	24	6 (25%)	18

Chi square= 19.37; df 9; two-tailed $p=0.022$

sex, as described in the Methods section. Unadjusted odds ratios significantly different from unity were found for mianserin (OR 1.70) and clomipramine (OR 0.56) ($p < 0.05$). After correction for age and sex differences, however, none of the odds ratios were significantly differing from unity.

Discussion

The results show that usage of antidepressant drugs varies with age and cardiovascular co-medication. A simple comparison of the degree of cardiovascular co-medication across the 10 largest groups of antidepressant recipients shows large differences. Two of the drugs showed significant channeling, when tested individually. After adjustment for age and sex differences however, no significant independent association remains between use of the different antidepressant drugs and cardiovascular medication. It can be concluded that there are marked differences between the antidepressants with respect to cardiovascular medication, but that no independent effect on the presence of cardiovascular medication can be shown.

However, channeling occurs, in that the antidepressants are prescribed to groups of patients differing in age and sex distribution, and hence with a different degree of cardiovascular medication. Mianserine was the drug most channeled to patients with this type of medication; this group was also relatively old. This is in accordance with mianserine's relative freedom of cardiovascular side-effects and the lack of warnings with respect to this in medical literature¹³⁻¹⁵. At the same time, this channeling can be expected to lead to more cardiac events in the group of users of mianserine. In observational studies on drug effects the existing baseline differences between groups of users of specific antidepressants should be assessed. If these differences are not recognized, the studies may lead to wrong conclusions about the association of use of specific drugs and events in the groups of users of these drugs.

For fluvoxamine and fluoxetine, the other drugs without restrictions in the cardiovascular field, the degree of cardiovascular co-medication was much lower (Table 3). However, users of fluvoxamine and fluoxetine tend to be younger than recipients of mianserine. The two drugs were introduced on the Dutch market in 1985 and 1989, respectively; mianserine was introduced earlier, in 1982. Marketing for mianserine explicitly put emphasis on the tolerance of patients with cardiac disease for the drug¹⁶: "...no deleterious effect on the heart". For fluvoxamine and fluoxetine, cardiac safety has not been taken up as an explicit marketing item. Further, the recipients of these drugs were younger; the background for the age differences between the users of various antidepressants is not clear, but younger users can be expected to have less co-medication in the cardiovascular field. These results show that while several drugs may be suitable for use in patients with a pre-existing condition, not all of them are actually prescribed to a substantial degree for patients with this condition.

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Do prescribed drugs always follow the patients to hospital?

Paulien A.W. Van Hessen, Hans Petri and John Urquhart

Introduction

When patients are admitted to hospital, there should be a rational continuity of the prescribed medications they have been taking as out-patients prior to admission. 'Rational continuity' does not mean that all out-patient medication should necessarily be continued in hospital, but that the out-patient medications should be carefully evaluated at the time of admission and rational choices made for in-hospital medication. To achieve this goal of rational continuity, it is of great importance to have a complete list of the medications the patient has been taking, so that these medications are not stopped inadvertently, but only after proper medical consideration. Not only is it unsatisfactory that patients be inadvertently deprived of needed drug actions, but there are some drugs for which a sudden stop has been proved to be potentially dangerous, because of rebound effects [1].

For these reasons, the history taken at the time of hospital admission includes questions about the medications the patient has been taking. However, research has shown that patients are often unable to tell exactly which medications they have been taking [2-4]. Even when they are requested to bring all their medication, there is no guarantee of completeness [5]. Moreover, neither physicians nor medical records are always able to give a proper and complete list of the drugs actually prescribed and taken by the patient [2 5-11]. Most of the errors in physician recall and medical records are errors of omission, in which the record fails to show a drug that has been prescribed in the past and is still being taken by the patient [2 3 5 7]. This being the case, it is not surprising that Duthie *et al.* recently found that 29% of the patients taking major cardiovascular medications had these medications inadvertently stopped when they were admitted to hospital for surgery [12].

The aim of the research was to measure the reliability with which out-patient medications are identified when patients are admitted to hospital in the Dutch situation. We recognize that there is a general feeling that the so-called medication bag brought to hospital by the patient is fully reliable, but we doubted that view. An underutilized source of information on patient's out-patient medication use is the community pharmacy regularly visited by the patient. This data is considered to be reasonably valid [8], although it may also show omission and commission errors [6]. In the Netherlands, in the case of health insurance funds patients, the administrative requirement to designate a single community pharmacy for all reimbursed prescription drugs ensures a highly reliable and complete record of drug use. In this study, we used the records of a Dutch community pharmacy as the source of reliable information on the out-patient medications of patients admitted to hospital.

A series of steps were required to determine whether important errors did occur in therapeutic management as patients made the transition from out-patient to in-patient care. First, we compared community-pharmacy records and hospital-pharmacy records of each patient. The discrepancies were classified by a panel of experts as to their potential seriousness. When we found what appeared to be serious discrepancies, we consulted the patient's medical record to ascertain, from the subsequent course of events, whether the stopping of medication had been inadvertent or on purpose.

Methods

Population

Our starting population consisted of all 546 admissions to hospital H between 1 February 1988 and 1 August 1988 of inhabitants of the municipi-

Keywords

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Abstract

The reliability was measured with which out-patient medications were identified at the time of a patient's admission to a Dutch hospital. The hospital-pharmacy records and the community-pharmacy records of 205 patients have been reviewed with the help of an expert panel. We established that 15 inadvertent drug discontinuations of a serious nature occurred among 12 patients. While the results are not necessarily representative of the overall Dutch situation, they indicate errors that can be reduced. Improvement is suggested by transmission of computerized data from the community pharmacy to the hospital whenever a patient is admitted and agrees with this transmission.

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pality M. M has only one community pharmacy, visited by the vast majority of about 12,000 inhabitants. At the same time, most hospital admissions of the inhabitants of M are in H, the nearest hospital. H can be best described as a small regional hospital. One patient could account for more than one admission.

At our disposal was data on 365 of these admissions, being those of patients who received one or more medications from the hospital pharmacy during their stay in hospital. Of these, 325 were identified in the records of the community pharmacy as being either a health care insurance patient or a privately insured patient and as having received at least one prescription drug from the community pharmacy in the 30 days prior to hospital admission. Privately insured patients were not otherwise included in the analysis; this tight criterion was used to diminish the likelihood of inclusion of privately insured patients who changed pharmacy just before hospital admission. Thus identified, the patients were numbered and treated anonymously.

Among the 546 admissions to H, 181 patients did not receive medications while in hospital. Many of these patients were admitted for childbirth and as newborns. Many of the others had brief stays for relatively minor surgical procedures, e.g. tonsillectomy.

Of the 325 patients who received prescription drugs both as out-patients and in-patients, 10 were not further investigated, because they were admitted directly to the intensive-care unit, where medications are managed apart from the hospital pharmacy.

Use of out-patient medication

The 315 remaining patients were judged on their use of out-patient medication at the moment of admission to H according to the data from the community pharmacy. The judgment of present use of out-patient medication was based on the most recent time of dispensing of the drug and the legend duration of the prescription. In the case of single-dispensed drugs, the legend duration was defined as the number of dosage forms dispensed, divided by the prescribed number of dosage forms to be taken per day. In the case of serially refilled drugs, present use was determined with 14 days added to the legend duration as defined.

We excluded certain prescription drugs and other items because of their self-evidently minor role in the patient's care. Excluded medications, based on categories in the formulary of the Dutch health insurance funds ('Farmacotherapeutisch Kompas') were:

- vehicles and indifferent dermatologies;
- local anti-infective agents;
- cutaneous antipruritics;
- rubefacients *etc.*;
- other dermatologic agents;
- diet and food agents.

We also excluded items under the category of 'bandages and various devices.'

As a result, 110 patients were considered to be receiving no out-patient medication of conse-

quence at the time of admission, leaving 205 patients who were receiving 709 drugs as out-patient medication, i.e. a mean of 3.46 each. These 709 drugs were evaluated in respect of their continuation in the hospital.

Continuation of out-patient medication

The 709 out-patient medications of 205 patients were compared, by a rather extensive set of criteria, with the medications that were prescribed during the first two days of the patients' stay in hospital. The criteria of comparison are described in the following paragraph.

Each drug was identified by its anatomical therapeutical chemical (ATC) code [13]. If the first three levels of the ATC code of the hospital medication corresponded to those of the out-patient medication, the out-patient medication was judged to have been continued, even though a different drug of the same class may have been substituted. In addition, a 4-person group of pharmacologically knowledgeable people reviewed other apparent substitutions, and judged the out-patient medication to have been continued if the substitution was deemed therapeutically rational, even when there were differences in the first three levels of ATC code. Examples of such judgments were drugs of the therapeutic sub-groups 'Synthetic agents and papaverine' (A03A) and 'Belladonna and derivatives' (A03B) of the chief therapeutic group 'Spasmolytics and anti-cholinergic drugs of the gastro-intestinal tract' (A03), which were considered equivalent for the purposes of this study.

From this process, cases were selected that were considered as having one or more home drugs stopped at the time of hospital admission. These were next evaluated with regard to their potential seriousness.

Interpretation of the potential seriousness of stopped medication

Of each of the admissions where a medication appeared to have been stopped, an overview was made of the patient's age, gender, admitting speciality, all out-patient medications, and all hospital medications during the first two days of the hospital stay. These overviews were put before a panel of 2 internists and 2 pharmacists from other medical institutions in other parts of the country, and thus with no links to the hospital or to the community pharmacy. The panel members, meeting together, were asked to give their opinion on each discontinuation.

The 'stops' were classified in 3 categories:

- 1 cessation of this out-patient medication will not cause problems with this patient;
- 2 cessation of this out-patient medication will probably cause no problems, but problems cannot be totally excluded;
- 3 cessation of this out-patient medication should not have occurred, unless purposefully done on the advice of the attending physician.

From this point onward, we focused attention on 'category 3 stops,' in order to learn if they were accidental or intended. A special category was created for stops of oral contraceptives, which were never dispensed in hospital.

Further assessment

For our final judgment, the medical records of the patients with 'category 3 stops' were examined. One of the records could not be retrieved. A sample of 6 patients with oral contraceptive 'stops' was analysed. The medical record was searched for:

- admitting diagnosis;
- use in the hospital of drugs brought in by the patients themselves;
- start of the out-patient medication after two days of hospital stay;
- deliberate cessation of out-patient medications by a physician;
- indications of cessation of the out-patient medication prior to admission;
- type of insurance, as a check for the data in the pharmacy.

For all drugs that still seemed to have been inadvertently stopped after this examination of the medical record, the data of the community pharmacy was reviewed to see whether the drugs were restarted after the patient's discharge from the hospital.

Results

Based on our criteria for continuation of out-patient medication, 143 of the 205 users of any out-patient medication had a total of 263 out-patient medications that were provisionally regarded as 'stopped.'

The panel judged 68 'stops,' involving 41 cases, as belonging to category 3. Thus, 26% of the original 263 'stops' were appraised as potentially hazardous if done accidentally. Oral contraceptives were 'stopped' 17 times. The panel thought it most probable that their use was continued by the patients themselves during their hospital stay. They noted, however, that this practice had the potential problem of leading to faulty compliance and unwanted conception.

Examination of the medical records and post-discharge community pharmacy data produced the following results on 67 'stops,' one record was unavailable for review. 16 'Stops' involved medication that had already been stopped prior to hospital admission. 5 'Stops' turned out to be wrongly judged, as the drugs were brought in by the patients themselves and continued in the hospital. 3 'Stops' involved drugs that, while not administered during the first two days, were resumed later. 26 Drugs were deliberately stopped by an attending physician. 2 'Stops' could not be further judged because of ambiguous data.

The remaining 15 stopped drugs, involving 12 patients, seemed inadvertent, *i.e.* no information was found that could explain the sudden stop of their use. Use of 9 of these was resumed after hospital discharge. Table 1 lists all 15 stopped drugs, together with some salient characteristics of the patients.

In the case of 6 patients whose records were examined regarding the in-hospital use of oral contraceptives, this use was mentioned in the medical records of 3 patients, whereas no information on oral contraceptive use was found for the other 3. All 6 patients continued oral contraceptive use after discharge.

Discussion

Methodological considerations

By relying on written data, we have three main uncertainties to consider:

- we cannot exclude that the patient simply did not take drugs dispensed by the community pharmacy;
- we cannot be entirely certain that the attending physician had deliberately stopped the drugs concerned without making any written notation of it;
- it is also possible that the patients continued taking drugs brought from home whilst in hospital.

These three points are considered in turn in the following paragraphs.

For the first point, 10 of the 15 serious omissions involved drugs refilled in the community pharmacy before the time of hospital admission, and 9 were refilled again after the patient returned home. Timely refills are a generally dependable indication of drug compliance [11].

The second point is a possible but unlikely basis for error. Certainly, a hospital admission can be the occasion to review the patient's medical status and to make changes in prescribed drugs, but such changes would normally be documented when they involve discontinuation of important ('category 3') drugs.

For the third point, the in-hospital use of important medications brought from home is also possible, but constitutes a procedural error of another kind, and is therefore deemed unlikely.

It should be noted that our analysis did not include patients who, though taking out-patient medications, received no medications at all while in hospital. Because we used hospital pharmacy records as the starting point to identify admitted patients, we would have missed any such patients, who are probably relatively few. Future studies of this problem might usefully begin with admitted patients rather than with in-hospital recipients of prescription drugs. Future studies might also focus on the characteristics of the patients with important drug omissions.

Conclusions

In general, the situation is less than optimal. Although at first sight, 263 of all 709 out-patient medications appeared to have been discontinued, only 68 of these were deemed of potential concern, and only 15 omissions of potential concern appeared to have been inadvertently made on hospital admission. Of the 205 evaluable patients at risk of having any medication inadvertently stopped, 15 inadvertent omissions of a serious ('category 3') nature occurred among 12 patients.

As we did not feel justified in requiring the four experts to categorize the drugs of all 205 evaluable patients, we cannot say for certain how many of the 205 patients were taking 'category 3' drugs, but certainly not all were. Thus, we cannot exactly say what the likelihood is that a patient taking a 'category 3' drug as out-patient medication had that drug inadvertently omitted at hospitalization. It occurred in at least 6% of

Table 1
Information on the 12 patients who had 15 out-patient medications inadvertently stopped

Gender (f/m)/age	Inadvertently omitted drug	Other drugs continued	Refills before admission	Continued after discharge	Admitting diagnosis
F/69	Metoprolol (Seloken®)	yes	yes	yes	angina pectoris
	Digoxin (Lanoxin®)	yes	yes	yes	
F/48	Furosemide (Fusid®)	yes	yes	no	depression
F/40	Famotidine (Pepcidin®)	no	no	yes	lumpectomy
M/61	Trimethoprim-sulfamethoxazole (co-trimoxazol)	no	no	no	abdominal pain
F/67	Maprotiline (Ludiomil®)	yes	no	no	depression
	Perazine (Taxilan®)	yes	yes	yes	
F/69	Mianserin (Tolvon®)	yes	yes	yes	nausea/vomiting
	Oxazepam (Seresta®)	yes	yes	yes	
F/82	Furosemide (Fusid®)	yes	yes	yes	'pseudo-dementia'
M/31	Doxycycline (Unidox®)	yes	no	no	herpes zoster
M/47	Doxycycline (Unidox®)	no	no	no	appendical infiltration
F/81	Triamterene/hydrochlorothiazide	no	yes	yes	sick sinus syndrome
F/45	Furosemide (Fusid®)	yes	yes	yes	battered female
F/60	Disopyramide (Ritmoforine®)	yes	yes	no	depression

patients, and doubtless in a somewhat higher percentage. This finding does not support the opinion that drug histories obtained at the time of hospital admission are always accurate.

The 'category 3' drug omission rate we found was appreciably lower than the rate found by Duthie *et al.* among patients admitted for surgery in Glasgow [12]. By limiting their focus to surgical patients, Duthie *et al.* had a much higher proportion of admissions for emergency surgery. For many reasons there is less likelihood of ascertaining a correct medication history at emergency surgery. In contrast, we included in our studies various kinds of admissions, the vast majority of which was elective rather than emergency. Also, our study did not include patients admitted directly to the intensive-care unit.

Neither is it considered advisable to allow patients to manage their own oral contraceptive dosing, without involvement of the hospital pharmacy, as probably has happened. It opens the possibility of missed doses and unrecognized drug interactions. Oral contraceptives are known to be susceptible to several interactions with other drugs [14].

It was beyond the scope of this study to attempt to assess the risks to patients created by these inadvertent omissions. We can say that none of the 15 inadvertent omissions of 'category 3' drugs led to problems attributable to the omissions. Assessment of the risk of sudden cessation of prescription drug therapy is, in general, specific to drug, disease, severity of the disease, and patient characteristics.

Opportunities for improvement

While our results are not necessarily representative of the overall Dutch situation, they indicate errors that can be reduced, if not altogether avoided, through provision of better quality information to hospital staff about patients' out-patient medications. One approach would be the general use of some type of 'medical passport' [15], in written form or as an electronic 'smart card' [16 17]. However, such approaches would require a nation-wide revision of current practice. This seems hard to achieve as the failure of the medical passport in the past suggests [18].

A far simpler way to improve the quality of information on patients' out-patient medication history is to make use of the information already

available in community pharmacies. Pilot studies might usefully be undertaken in making available to hospitals at the time of admission the salient parts of patients' out-patient medication histories. With the widespread adoption of computerized records in community pharmacies, and the increasing use of facsimile transmission, such communication could be organized to be done with little delay. It could even be available on an urgent basis for emergency admissions.

There is a certain issue about obtaining consent for communicating this information to the hospital physician, but that can reasonably be handled in the same manner as information exchanges between the various physicians involved in the patients care. If the errors we found prove to be representative, it would seem only logical to take medical advantage of information in community pharmacies that presently has already administrative and research value [19].

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Comparison of questionnaire information and pharmacy data on drug use

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Introduction

In large-scale prospective epidemiologic studies increased use is made of self-administered questionnaires to estimate exposure to various environmental factors, including prescription drugs. Self-administered questionnaires (as well as personal interviews) are, however, subject to response errors.

Studies on the validity of questionnaire-derived drug history information have been reviewed recently [1]. Most studies focused on reproduction-related drug use, like oral contraceptives [2], estrogen use [3] and pregnancy-related drug use [4]. Very few studies have evaluated non-hormonal or non-pregnancy-related medication [5, 6].

We studied the validity of questionnaire information on general drug use. This questionnaire was used in an ongoing large-scale prospective cohort study on diet, other lifestyle factors (such as long-term drug use) and the incidence of cancer in the Netherlands. The validity of the information on drug use was investigated by comparing the questionnaire data with pharmacy records of dispensed drugs. We also analysed personal characteristics as potential determinants of the quality of questionnaire information, as has been done with regard to reporting of medical conditions [7]. Dutch pharmacy records are uniquely complete on the level of an individual patient, due to insurance requirements. In 1986, 67% of the Dutch population was enrolled in the health insurance fund scheme which require them to designate a single pharmacy from which they receive all reimbursed prescription drugs [8].

Methods

Cohort study

The prospective cohort study started in 1986 with the baseline exposure measurement. The cohort ($n = 120,852$) of 55-69 year old men and women originates from 204 municipal population registries. Follow-up for cancer consists of record linkage to cancer and pathology registries [9]. The baseline exposure measurement involved completing a self-administered questionnaire on diet, medical history, history of long-term drug use, smoking, occupation and various other factors. The question on drug history was open-ended, asking for drugs that had been taken for a period of at least 6 months at any time in the past. The generic or trade name of the drug was asked for, and for each drug the therapeutic indication and the calendar period of usage in years. The space on the questionnaire allowed for 4 drugs to be mentioned.

Validation study

In the municipality where the validation study was conducted, 239 subjects participated in the baseline measurement. The town (with 14,000 inhabitants) is served by 1 pharmacy, which keeps records on all dispensed drugs, patient by patient. There are no other pharmacies within a radius of 5 km. Because the patients in the health insurance fund scheme are required to designate a single pharmacy for all reimbursed drugs, they are known to their designated pharmacy, whether they use drugs or not. Whereas the cohort questionnaire was completed in September-October 1986, the computerized rec-

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Questionnaires
Validity

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Abstract

Information on chronic drug use at any time in the past was collected with a self-administered questionnaire as part of a prospective cohort study on diet, other life-style factors and cancer among subjects aged 55-69 years. The validity of the questionnaire information on drug use was evaluated among 207 subjects by comparing it to pharmacy records of dispensed drugs. The comparison could be made for the 2.5-year period preceding the questionnaire administration. Since the study subjects did not mention prescription drugs that were not dispensed by their pharmacy, indicating no errors of commission, the analyses were focused on the estimation of sensitivity of drug recall and its correlates. Questionnaire recall of drug use amounted overall to 61.2% of drugs prescribed to the subjects for at least 6 months. Drug recall decreased with increasing age and with increasing number of prescribed chronic use of drugs per subject. No difference in recall was observed between men and women. Recall tended to improve with increasing duration of use and varied with type of drug. When only long-term drug use at the time of questionnaire administration was considered, overall recall of drug use was 68.8%.

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Table 1
Levels of the ATC classification scheme

Level	Name	Example
1	anatomic level	central nervous system
2	therapeutic main group	psycholeptics
3	therapeutic subgroup	tranquillizers
4	chemical main group	benzodiazepines
5	chemical entity	diazepam

ords of the pharmacy were only available from April 1984 onwards. This study is therefore limited to drug recall from the period April 1984 until September 1986.

Of the 239 cohort members in the study town 207 subjects (93 men, 114 women) were also registered in the pharmacy. The remaining 32 subjects were either living in a nearby village, which is served by another pharmacy, or were privately insured and had not used drugs from the study pharmacy. The pharmacy records representing drugs dispensed to the 207 subjects were selected from the computerized data base. There were 138 (67%) health insurance fund patients and 69 (33%) privately insured patients among the 207 subjects, as observed in September 1986. The 69 privately insured patients could remain in the study population since the analysis could be concentrated on sensitivity of recall (see *Statistical analysis*). The validation study was focused on drugs for systemic use; local applications for skin, ear, eye and mouth were therefore excluded from consideration. Also, homoeopathic drugs and vitamins and mineral supplements were excluded as these items may not be perceived as drugs by the subjects.

Next, the prescribed dosages and dispensing dates of the remaining pharmacy records of the 207 subjects were used to construct drug histories for each subject. The duration of use was determined by dividing the number of dispensed doses by the number of prescribed doses per day. When a prescription for the same drug was dispensed within 30 days of the calculated end of the previous prescription, drug use was considered to be continuous. Long-term drug use was defined as continuous use of a drug over a

period of at least 180 days. The cohort questionnaire also asked the subjects to list drugs that had been taken for at least 6 months. These questionnaire responses were compared to the pharmacy records of the 207 subjects.

The questionnaire information on drug types, as well as the pharmacy data were classified according to the Anatomic Therapeutic Chemical (ATC) classification scheme [10]. With this hierarchical scheme, drugs are classified on five levels defined by anatomic, therapeutic and chemical characteristics of the drug and the indication for which it is used. The five levels are: anatomic main group, therapeutic main and subgroup, chemical main and subgroup. The first, most general, level represents classification of drugs into anatomic groups, *i.e.* the site at which treatment is directed. The fifth and most specific level is defined by the chemical entity or structure of the drug. An example of this hierarchy is given in Table 1.

Statistical analysis

The accuracy of drug recall obtained by questionnaire was measured by assessing the degree to which drugs, which had been chronically used according to the pharmacy data, were correctly recalled by the respondents. No prescription drug was listed for the period 1984-1986 by respondents that was not dispensed (*i.e.* no errors of commission occurred). Therefore, the analysis further concentrated on errors of omission and the sensitivity of the drug recollection. In estimating these sensitivity rates, agreement on the individual drug level (*i.e.* the fifth and most detailed level of the ATC classification code) was required.

The analyses were stratified according to various factors, to determine what influence these might have on the sensitivity rates. These factors include: gender, age, number of prescribed drugs per subject, duration of use and type of drug. Separate analyses were carried out for drugs that were in use at the time the questionnaire was administered in the cohort.

While in the analyses mentioned above agreement on individual drug level was required, we also estimated the sensitivity rates on a level of more general classes of medication as defined by the ATC classification code.

Results

Of the 207 respondents who were included in the analysis, the pharmacy records showed that 186 were recipients of one or more prescribed drugs in the period April 1984 to September 1986. A total of 87 subjects (36 men, 51 women) were defined as long-term drug users (*i.e.* at least 180 days of continuous prescription), based on the pharmacy records. Thus, 42% of the respondents were long-term drug users. As can be seen from Table 2, the proportion of long-term drug users is greater among women than men (44.7 and 38.7%, respectively) and increases with age. The 87 subjects had been prescribed 242 drugs for at least 6 months in the period 1984-1986. Table 3 shows long-term drug use, stratified by type of drug. Most drugs used are for cardio-

Table 2
Description of study population used for validation study of drug recall

Characteristic	Number of subjects	Long-term drug users (%)
Gender		
- men	93	36 (38.7)
- women	114	51 (44.7)
Age (years)		
- 55-59	85	31 (36.5)
- 60-64	71	32 (45.1)
- 65-69	51	24 (47.1)

Table 3

Long-term drug use according to the pharmacy in the period 1984-1986, stratified by type of drug and ordered by number of users

Type of drug*	Number of pharmacy records (%)	Number of users (% of all long-term drug users)
Cardiovascular system	138 (57.0)	62 (71.3)
Central nervous system	43 (17.8)	30 (34.5)
Alimentary tract and metabolism	25 (10.3)	16 (18.4)
Blood and blood-forming organs	11 (4.6)	11 (12.6)
Respiratory system	8 (3.3)	5 (5.8)
Systemic hormonal preparations, excluding sex hormones	4 (1.7)	3 (3.5)
Musculo-skeletal system, genito-urinary system and sex hormones	5 (2.1)	3 (3.5)
Menopausal hormones, urology drugs	2 (0.8)	2 (2.3)
General anti-infectives, systemic	1 (0.4)	1 (1.2)
Antineoplastic and immuno-suppressive drugs	2 (0.8)	1 (1.2)
Other	3 (1.2)	3 (3.5)

*Drugs categorized according to first level of ATC classification scheme [10]; see also Table 1.

vascular conditions, followed by drugs indicated for central nervous system disorders, alimentary tract conditions, and haematologic conditions. Together, these categories comprise almost 90% of drugs taken chronically by the subjects.

Of the 242 chronically used drugs, 148 were reported in the questionnaire, when agreement on the fifth (most detailed) level of the ATC code was required. The overall sensitivity, *i.e.* percentage of pharmacy-recorded drugs reported in the questionnaire, was therefore 61.2%. Table 4 pre-

sents the sensitivity of drug recall stratified by various factors. Table 4 shows that gender was not related to drug recall: the sensitivity rates were 61.5% and 60.9% for men and women, respectively. With increasing age, recall decreased slightly from 65.3% among 55-59-year old people to 60.2% among 60-64-year old people and 58.4% for 65-69-year old subjects. Drug recall was somewhat increased when the duration of use was longer: recall was 59.0%, 61.8% and 63.6% for drugs used 6-11.9, 12-23.9 and 24 months or longer, respectively.

When a stratification was made on the number of chronically used drugs per subject, recall per drug decreased from 70.8% for subjects using one drug to 64.0% when using two drugs and 58.9% when using three drugs or more. With respect to the type of drug, it was found that cardiovascular drugs showed a better recall (65.9%) than alimentary tract drugs (48.0%) or drugs used for central nervous system disorders (53.5%). Other drugs were not separately considered because they were too few in number.

As the decreased recall with increasing age might be due to the fact that the subjects use more drugs or vice versa, we also conducted analyses stratified by age and the number of prescribed drugs. When the percentage recall is considered for each of the cells (Table 5), there is no longer a clear trend with either of the two factors, probably due to small numbers. Subjects from the youngest age group seem to recall drugs somewhat better, independent of the number of drugs being used. Also, in two age groups subjects using at least three drugs show a lower recall than subjects using one drug. Thus, the effects of both stratification factors seem independent of each other.

Table 6 shows the percentage recall per type of drug, stratified by gender, age, duration of use and number of prescribed drugs. For this calculation the two categories of drugs used for the alimentary tract and central nervous system disorders were combined in order to avoid very

Table 4
Questionnaire recall of long-term drug use compared to pharmacy records, stratified by selected characteristics

Characteristic	Number of pharmacy records	Number of questionnaire responses (% recall)
All	242	148 (61.2)
Gender		
- men	104	64 (61.5)
- women	138	84 (60.9)
Age (years)		
- 55-59	72	47 (65.3)
- 60-64	93	56 (60.2)
- 65-69	77	45 (58.4)
Duration of use (months)		
- 6-11.9	100	59 (59.0)
- 12-23.9	76	47 (61.8)
- ≥24	66	42 (63.6)
Number of prescribed drugs		
- 1	24	17 (70.8)
- 2	50	32 (64.0)
- ≥3	168	99 (58.9)
Type of drug		
- alimentary tract	25	12 (48.0)
- cardiovascular system	138	91 (65.9)
- central nervous system	43	23 (53.5)
- other	36	22 (61.1)

Table 5
Questionnaire recall of long-term drug use, stratified by age and number of prescribed drugs

Age (years)	Number of prescribed drugs	Number of pharmacy records	Number of questionnaire responses (% recall)
55-59	1	10	9 (90.0)
	2	26	13 (50.0)
	≥3	36	25 (69.4)
60-64	1	8	4 (50.0)
	2	16	15 (93.8)
	≥3	69	37 (53.6)
65-69	1	6	4 (66.7)
	2	8	4 (50.0)
	≥3	63	37 (58.7)

small numbers per cell and thus unstable estimates of recall. Also, the overall recall percentages for these two groups were relatively close to each other, as was shown in Table 4. As can be seen from Table 6, the percentage recall for cardiovascular drugs is consistently higher than for other types of drugs. For cardiovascular drugs, the trends in recall according to the various levels of the stratification factors, are similar to what was observed for overall long-term drug use (Table 4). For alimentary tract or central nervous system drugs and other drugs the trends are less clear, which may also be due to the small number of observations per cell.

The recall might be lower when drugs are not actually used at the time of the baseline questionnaire. To evaluate this possibility, we also analyzed the quality of reporting of current long-term drug use (Table 7). Current use in this situation means long-term drug use at the time of the questionnaire baseline measurement in the cohort study (September 1986). Among the total group of 87 long-term drug users, 69 were chronically using drugs at the time of the baseline measurement. On average, these participants used 1.9 drugs chronically per subject. Table 7 shows that reporting of current long-term drug use is somewhat better than reporting of all long-term drug use in the period 1984-1986. Overall, 68.8% of current long-term drug use was correctly reported (analysis on the chemical entity level), compared to 61.2% among all long-term drug users.

The downward trend in recall with increasing number of drugs and with increasing age among current users is comparable to the trend among all long-term drug users. Gender has no substantial effect on drug reporting in this group. There was no consistent trend in drug reporting with duration of use in this group. Again, cardiovascular-oriented drugs were the type of drugs that showed the highest degree of reporting (76.6%), followed by alimentary tract drugs (64.7%). Reporting of alimentary tract drugs is substantially improved when current use instead of all long-term drug use in the period 1984-1986 is considered.

Finally, sensitivity rates were determined when agreement on a less detailed level of the

Table 6
Questionnaire recall of long term drug use per type of drug, stratified by selected characteristics

Characteristic	Type of drug					
	alimentary tract/ central nervous system		cardiovascular system		other	
	number of pharmacy records	recall (%)	number of pharmacy records	recall (%)	number of pharmacy records	recall (%)
All	68	51.5	138	65.9	36	61.1
Gender						
- men	31	54.8	57	68.4	16	50.0
- women	37	48.6	81	64.2	20	70.0
Age (years)						
- 55-59	25	56.0	38	71.1	9	66.7
- 60-64	22	45.5	59	64.4	12	66.7
- 65-69	21	52.4	41	63.4	15	53.3
Duration of use (months)						
- 6-11.9	26	46.2	53	62.3	21	66.7
- 12-23.9	14	57.1	53	66.0	9	44.4
- ≥24	28	53.6	32	71.9	6	66.7
Number of prescribed drugs						
- 1	9	77.8	11	72.7	4	50.0
- 2	14	57.1	25	60.0	11	81.8
- ≥3	45	44.4	102	66.7	21	52.4

Table 7
Questionnaire reporting of current long-term drug use compared to pharmacy records, stratified by selected characteristics

Characteristic	Number of pharmacy records	Number of questionnaire responses (% recall)
All	128	88 (68.8)
Gender		
- men	60	40 (66.7)
- women	68	48 (70.6)
Age (years)		
- 55-59	33	26 (78.8)
- 60-64	49	33 (67.3)
- 65-69	46	29 (63.0)
Duration of use (months)		
- 6-11.9	35	24 (68.6)
- 12-23.9	34	26 (76.5)
- ≥24	59	38 (64.4)
Number of currently prescribed drugs		
- 1	35	27 (77.1)
- 2	32	23 (71.9)
- ≥3	61	38 (62.3)
Type of drug		
- alimentary tract	17	11 (64.7)
- cardiovascular system	64	49 (76.6)
- central nervous system	31	18 (58.1)
- other	16	10 (62.5)

ATC code was required. The results are presented in Table 8. When agreement was examined on the second level of the ATC code, *i.e.* the therapeutic main group, sensitivity rates were increased. Whereas the overall sensitivity rate was increased to 72.7% when all long-term drug use in 1984-1986 was considered, it rose to 74.2% when only current long-term drug use was considered. When agreement was required on the third level of the ATC code, *i.e.* the therapeutic subgroup, the overall sensitivity was 65.3%, and 71.1%, respectively.

Discussion

In this study on the validity of drug recall, pharmacy records can be considered an objective standard for the use of prescribed drugs for the 30 months preceding the cohort baseline measurement. This is due to the administrative

requirement that health insurance fund patients designate a single pharmacy for all reimbursed drugs, plus the geographic isolation of the study town with its single pharmacy. Given the age of our study population and the 30-month coverage period of the pharmacy, it was not possible to study recall of oral contraceptive use or menopausal estrogens. These two types of medication have been most extensively studied in this respect [1].

We observed that recall of drug use decreased somewhat with increasing age of the respondent. An age trend in recall has not been reported by other investigators of drug recall. With regard to medical conditions, no specific response pattern associated with age was found recently [7]. These same investigators reported a better recall of conditions by males than by females. In our study, drug reporting was essentially the same in both genders.

Another potential determinant of correct recall is duration of use. In our study with pharmacy records covering 30 months, this determinant could only be investigated to a limited extent. Nevertheless, there is a trend indicating better recall when the duration of use is longer. A similar finding was reported with regard to the duration of work assignments in an occupational study [11]. The study by Bond *et al.* [11] also indicated that recall was worse when the number of work assignments increased. We too found reduced reporting accuracy with increasing number of prescribed drugs. In this respect, it should be mentioned that a reduced recall might have resulted to some extent from the limited space on the questionnaire (*i.e.*, up to four drugs could be listed). Also, the number of prescribed drugs tends to rise with age, but stratification on age and number of drugs did not yield additional insight into this, probably due to small numbers.

Recall varied with the type of drug, with cardiovascular drugs showing the highest degree of correct reporting (65.9%). In a study among elderly women, Paganini-Hill and Ross [5] evaluated agreement between personal interview and medical chart data for thyroid medication, reserpine, other antihypertensives, steroids, barbiturates and ataractics. They found that antihypertensive drugs and thyroid medication showed the highest percentage of agreement. The percentage recall of thyroid drugs was 100% in our study, but was based on only three pharmacy records. The recall of antihypertensives was also relatively good in our study (68.4%), based on 19 records.

We observed a relatively poor recall of drugs used for disorders of the central nervous system (53.5%). This may partly be explained by the fact that people may be reluctant to report about these drugs (*e.g.* tranquillizers) or that in general the psychological indication for which they are prescribed leads to poor recall. Paganini-Hill and Ross [5] also observed a low agreement between interview and medical chart for the barbiturate and ataractic subgroup of the central nervous system drugs. We could not evaluate the recall of barbiturates since these are now rarely used. This aspect of rare use also applies to another

Table 8
Questionnaire recall of long-term drug use, by level of agreement in ATC code

Agreement on level of ATC code	Percentage recall	
	all long-term drug use	current long-term drug use
Therapeutic main group	72.7	74.2
Therapeutic subgroup	65.3	71.1
Chemical entity	61.2	68.8

subgroup of drugs for the central nervous system, phenothiazines, for which Adam *et al.* [6] reported low agreement between questionnaire reporting and general practitioner records.

It is unclear why recall of alimentary tract drugs was relatively poor in our study population (48.0%). One reason might be the poor reporting of prescriptions for weight loss: none of the three prescriptions were reported by respondents. Excluding this subgroup, the percentage recall would be 54.5% for alimentary tract drugs. Unfortunately, no other investigators have looked at this group of drugs. A considerable improvement in drug reporting of this group was observed when only current long-term use was evaluated (resulting in a sensitivity of 64.7%).

The questionnaire contained an open-ended question on drug use. While a closed question on drug use would lead to a considerable number of false-positives (in terms of exposure) as found by Paganini-Hill and Ross [5], an open-ended question would generally have very high specificity, which also seems to apply to occupational exposures [11]. Thus, it seems that open-ended questions may lead to less false-positives but they also reduce the true-positive rate or sensitivity [12]. The seriousness of the consequences of either an elevated false-positive rate or an elevated false-negative rate depends on the purpose of the study.

Whereas overall 61.2% of all long-term drug use was correctly reported by the respondents, reporting was better when drugs were used at the time of baseline measurement in the cohort. The length of elapsed time since drugs were taken therefore may be an important determinant of recall. In occupational settings, a decreased recall of earlier exposures such as work assignments has also been noted [11].

Conclusion

The sensitivity of drug recall as measured by a self-administered questionnaire in this general population cohort, compared to pharmacy records varied to some extent with characteristics as age, duration of use and number of prescribed drugs. Recall was also found to vary with type of drug, with cardiovascular drugs showing the highest sensitivity. When recall was analysed with regard to therapeutic main groups, rather than on chemical entity level, recall was improved. The study was based on relatively small numbers and was also limited by the 30-month period of coverage by the pharmacy; a study comprising a longer observation period is warranted to further evaluate the influence of duration of use as a determinant of recall. The determinants of drug recall quality were quite comparable to determinants of work assignment recall [11], whereas less similarity was noted with studies on recall of medical conditions [7]. Whether this is due to the difference in question style (open-ended versus closed questions), interview setting (questionnaire, telephone or personal interview) and whether determinants of recall are different for other exposure types requires further investigation.

This study indicates that 60-70%, depending on

the required level of detail, of the dispensed drugs are also reported by subjects. It is interesting to note that this sensitivity level is comparable to the levels of compliance that are observed in many clinical trials on drugs. While measurement of compliance by questionnaire or interview is influenced both by the subjects' memory and his true compliance, compliance measurements using an electronic monitoring device (MEMS[®]) also indicate levels of 70% [13].

Thus, while there is undoubtedly underreporting of true drug use in our questionnaire, the dispensing of drugs may not necessarily imply that they are always used, although regular refills of drugs for long-term use suggest a certain degree of compliance. This underreporting and its possible relationship to compliance behaviour, as well as quantification of both components warrant further investigation.

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studies on effects of industrial exposure, observational studies on effects of drugs are more likely to raise interpretation problems, especially if large, but incomplete databases are used, because the former involves mainly healthy workers and the latter involves mainly the sick and/or the elderly.

We think that for studies on channeling and prescribing practices in general, the prescription drug history will remain to be valuable as a separate source of information. In future, however, many studies will probably use computerized drug records, while additional information is collected from other records and from questionnaires or interviews. In this case, computerized records on drugs dispensed may be used as a source from which recipients of specific drugs are identified, e.g. for cohort tracing. Additional information on health status and relevant determinants are to be collected from records in general practice or in hospitals and by interviews.⁶

As concerns the availability of basic data, the health care insurers seems to be the most promising source. Data from comprehensive regional insurance schemes (e.g. Saskatchewan⁷) or, in the U.S., regional ones that cover subgroups in the population have been successfully used for studies on drug effects.^{8,9}

In the Netherlands, the main insurers (*ziekenfonds*) have recorded information on many procedures in individual persons; these data were audited to control the degree of use of certain procedures. Data on reimbursement of drugs were, however, not filed on the level of the insured individual. This is changing now together with the introduction of a new auditing scheme in which data on the drugs that were dispensed are sent from the pharmacy to the *ziekenfonds*. Advantage should be taken of the availability of data on drugs dispensed and procedures, indications for procedures, and other disease-related information in one organization.

One of the conclusions of chapter 9 was that, in order to prevent mistakes with medication, it seems worthwhile to transmit a drug history from the community pharmacy to the hospital whenever a patient is admitted. One of the prerequisites for such a procedure is that the drug history is reasonably complete, and this can only be achieved if the patient relies on one pharmacy. The *ziekenfonds* require that their clients choose a general practitioner and a dentist for their medical and dental care, and that they patronize one pharmacy from which reimbursed drugs are to be obtained. This linkage of patients to caregivers facilitates health care tailored to the individual, with insight into his or her history. Periodically, the designated pharmacy system has been challenged on economical or political grounds. Its value as a source of integrated drug information should not be overlooked in this discussion.

A combination of health insurance regulations and practice of pharmacy in the Netherlands made possible the studies presented in this thesis. General practice in the Netherlands also has gained much from the fact that individual persons register with one family physician. The patient file in general practice is of potential value for epidemiological studies because of this patient-doctor linkage, which helps to get a good medical history; use of computers will stimulate the use of this potential. We hope that, both for patient care itself and for its value for research, the linkage of individual patients to individual professionals in health care will remain. This linkage and the use of computers in various areas of health care will also enable a more instructive flow of information to and from among the insurer, the pharmacist, and the practicing physician.

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SUMMARY

New drugs are registered for use in the general population after an elaborate process of development, toxicological studies, and randomized controlled trials. New knowledge about wanted and unwanted effects is also gained after the introduction of a drug for use in the general population. Pharmacoepidemiology is the study of characteristics of groups of recipients of specific drugs and of the effects of drugs in large populations.

Chapter 1 describes the structure of this thesis. Studies were done on different subjects, common for these studies is the analysis of drug histories of relatively large numbers of persons.

Chapter 2 provides an overview of the types of studies in pharmacoepidemiology. A description is given of the various approaches in relation to the type and frequency of the problems to be studied. The many interpretation problems in observational studies on drug effects are reviewed. Whereas the availability of large databases with health-related information is now changing the field of pharmacoepidemiology, it is concluded that many of the interpretational problems will remain or may even worsen.

One of the issues is the quality of the data on drug exposure in pharmacoepidemiological studies. Our work centers on methods for ascertaining drug use and on methods to interpret drug histories of large groups of patients.

Chapter 3 describes the exposition data of our studies, Dutch pharmacy data, in relation to other types of information on drug dispense and drug use (questionnaires, pill counts, external monitoring, biological monitoring). The use of these pharmacy data for research purposes is described.

On account of insurance regulations, the majority of Dutch population have to choose one pharmacy from which all reimbursed drugs are to be obtained. Moreover, pharmacies in the Netherlands tend to be large and the majority keep patient drug histories on computer file. These circumstances make it possible to gather large numbers of complete or nearly-complete outpatient prescription drug histories from the general population. Patient anonymity is maintained as the histories leave the pharmacy with information on age and gender, but without name or address.

In *chapter 4* the approach of prescription sequence analysis is presented. This method is applied for drugs with a possible side-effect that could lead to a condition for which specific drug therapy is available. If such side-effects indeed occur with any appreciable incidence, they would be revealed by a characteristic sequence of prescriptions in patients' drug histories. The technique is to be used to assess the risk of certain drugs in situations where an urgent need arises to obtain information about the plausibility of reports of an adverse drug reaction.

An analysis was made of computerized drug histories of users of the anti-migraine/anti-vertigo drug flunarizine, after the publication of case-reports suggesting that the drug might cause mental depression and parkinsonism. We selected the drug histories from patients who had received both flunarizine and an anti-depressant drug at some time in the available history. The initiation (i.e. "start") of antidepressant therapy was considered as to be a marker of the occurrence of mental depression. The occurrence of these starts were compared in the periods before, during and long after the dispensing of flunarizine. In the largest of our two studies (*chapter 4b*) the incidence of antidepressant starts was slightly higher during flunarizine use than before or long after. Consequently, the possibility that flunarizine induces drug-treated mental depression cannot be excluded, although the association found could be explained by alternative mechanisms.

An additional finding was that a remarkably large proportion of the recipients of flunarizine had received an antidepressant drug at some time during the available drug history. Therefore, it appears that flunarizine is prescribed to a group of patients for whom antidepressant drugs are frequently prescribed, presumably indicative of an

unusual prevalence of depression or depression-like symptoms in these patients. This kind of knowledge on the background of drug-treated persons should be relevant for other types of studies which try to distinguish a drug effect from a condition already present in the persons studied.

Chapter 5 describes an analysis of patients' drug histories that include inhaled steroids and topical oral anticandida medication. The use of inhaled steroids (A) can induce oral candidiasis, and we considered the dispensing of topical oral anticandida medication (B) to be a marker of oral candidiasis. Thus, A can cause oral candidiasis, while B is a therapy for this condition. The approach of prescription sequence analysis of chapter 4 was used here, with modifications. In this analysis a positive association, though not a strong one, was found between exposure to inhaled steroids and start of anticandida drugs.

In *chapter 6* the concept of channeling is presented. This phenomenon occurs when drugs with similar therapeutic indications are prescribed to groups of patients with a different health status or prognostic characteristics. Time of introduction or specific marketing claims may result in channeling of a new drug to a group of patients different from the users of pharmacologically related drugs. A late-entry drug is more likely to be given to patients who have not responded satisfactorily to therapy with an established, early-entry drug. The claim that a drug causes few side-effects may lead to selective prescribing to patients with pre-existing morbidity. Consequently, more problems may be observed in a group of patients that is treated with a drug that should cause few problems. If channeling is not recognized, confounding by indication may be introduced in observational studies on drug effects.

Chapter 7 describes how three asthma drugs in one pharmacologic class, the beta-2 agonist class, are channeled to patients with a different severity of asthma, as expressed by concomitant medication. The drug histories of recipients of the inhalational beta-2 agonists salbutamol, fenoterol and terbutaline were compared for markers of severe or difficult-to-treat asthma, diabetes and cardiovascular conditions. We considered the use of systemic corticosteroids by asthmatics to be such a marker of severe or difficult-to-treat asthma. In a database covering the medication of 121,000 persons the drug histories of recipients of one of the three inhalational beta-2 agonists were retrieved and analyzed. We found 2-2.5 times more co-medication with systemic steroid drugs in the group of recipients of fenoterol than in the recipients of salbutamol. Terbutaline recipients were intermediate. Also, the proportion with one or more other asthma drugs was highest among fenoterol recipients and lowest among salbutamol recipients; terbutaline was again intermediate in this respect. Therefore, it appears that Dutch physicians prescribe terbutaline and fenoterol to patients with more severe forms of asthma than salbutamol.

In *Chapter 8* a study on the channeling of antidepressant drugs is presented. The labelling of most of these drugs set various restrictions with respect to prescribing to patients with cardiovascular co-morbidity; for some of the antidepressants no such restrictions are given. Our question was whether these differences in labelling were reflected in selective prescription of certain antidepressants to persons with cardiovascular conditions.

The primary data were extracted from a drug database covering a population of approximately 130,000 persons, of whom 1173 had received an antidepressant within a six month time frame. As a marker of cardiovascular disease we considered medication with one or more cardiovascular drugs. The recipients of the various antidepressant drugs differed considerably with respect to the dispensed medication for cardiovascular conditions. Relatively high in this respect were recipients of mianserin (36%) and

doxepin (35%); at the low end were fluoxetine (13%) and clomipramine (18%). However, the groups of recipients of the antidepressants varied considerably as to age and sex and after stratification for these two variables no significant residual differences remained with respect to cardiovascular co-medication. Apparently, channeling occurs with some drugs, but partly via the indirect way of age/sex differences of the recipients of antidepressants.

The results of the analysis show that the antidepressants that are specifically suited for persons with pre-existing cardiovascular conditions are not all used to the same extent by these patients. It is discussed how time of introduction and marketing activities may have had a role in these differences.

The work presented in *chapter 9* was inspired by literature reports on a problem of unintended cessation of medication in patients who are admitted to hospital. In view of this, we studied the continuity of medication of a group of patients admitted to a Dutch hospital. Outpatient drug histories from the only pharmacy in one of the towns in the hospital's catchment area were matched to records of drugs dispensed to patients during their stay in the near-by hospital. The hospital and community pharmacy records of 205 patients were reviewed with the help of an expert panel. The discrepancies were classified by this panel as to their potential seriousness. When we found what appeared to be serious discrepancies, we consulted the patient's medical record to ascertain, from the subsequent course of events, whether the stopping of medication had been inadvertent or purposeful. The panel judged 68 'stops', involving 41 patients, as potentially hazardous if done accidentally. Examination of the medical records led to the conclusion that 15 inadvertent drug discontinuations of a more serious nature occurred, involving 12 patients.

The results are not necessarily representative of the overall Dutch situation, but they indicate that there are errors that can be reduced. Improvement is suggested by transmission of computerized data from the community pharmacy to the hospital whenever a patient is admitted.

Chapter 10 describes a study on the validity of information from a patient questionnaire on chronic use of drugs. This questionnaire was used in a large-scale prospective cohort study on diet, other lifestyle factors (such as long-term drug use) and the incidence of cancer. The validity of the information on drug use was investigated by comparing the questionnaire data with pharmacy records on dispensed drugs. The validation study was conducted in a municipality served by one pharmacy for the persons who had returned the questionnaire.

All drugs mentioned in the questionnaire to be used at the moment of the baseline measurement were traceable in the pharmacy record. Since there were no errors of commission, i.e. drugs mentioned but not dispensed in the pharmacy, the analyses were focussed on errors of omission, drugs dispensed but not mentioned in the questionnaire. Of the 207 cohort members 69 chronically received drugs at the time of the baseline measurement. On average, these participants received 1.9 drugs for at least 6 months. Overall, 68.8% of current long-term use was correctly reported. Drugs chronically dispensed but whose use ceased before the baseline measurement were reported less adequately.

In conclusion, the open-ended question on drug use had a high specificity but a rather low sensitivity, i.e. the absence of false positive answers is accompanied by defaults in the reporting of drugs that were dispensed to the cohort members. Relevant for other studies in pharmacoepidemiology is the high reliability of pharmacy data when a history of the drugs received by individuals is required.

The *epilogue* gives an overview of the work presented in this thesis and some of its implications. The opportunities for future studies are discussed, especially for the field of record linkage. It is concluded that the prescription drug history has a value in research both as a separate source of information and in combination with other health-related data. The value of longer drug histories, as could be built up in pharmacies or by insurers, is emphasized for surveys of changes of pharmacotherapeutic practices and for studies on long-term effects of drugs.

Reliable prescription drug histories are a cornerstone of pharmacoepidemiology. Practices in Dutch health care and regulations of insurers have stimulated the adherence of patients to one pharmacy, analogous to the adoption by patients of a general practitioner and a dentist. This linkage of individual patients to individual professionals in health care has advantages both for patient care and for research purposes; for these reasons its continued existence is advocated.

SAMENVATTING

De toelating van nieuwe geneesmiddelen gebeurt na een uitgebreid proces van ontwikkeling, toxicologische studies en een zg. klinische trial. Nieuwe kennis over gewenste en ongewenste werkingen wordt vaak ook nog verkregen na introductie van een middel voor gebruik in de algemene bevolking. Farmaco-epidemiologie is de studie van kenmerken van gebruikers van geneesmiddelen en van de effecten van deze middelen in de bevolking.

Hoofdstuk 1 beschrijft de opzet van het proefschrift. Studies over verschillende onderwerpen worden gepresenteerd in dit proefschrift, gemeenschappelijk is de analyse van medicatiegeschiedenissen van een relatief groot aantal mensen.

Hoofdstuk 2 is een algemene inleiding over onderzoek op het terrein van de farmaco-epidemiologie. Verschillende benaderingen worden beschreven, in relatie met het type en de frequentie van het te onderzoeken probleem. De vele interpretatieproblemen bij observationeel onderzoek naar effecten van geneesmiddelen komen aan de orde. De toenemende beschikbaarheid van grote geautomatiseerde databestanden heeft de mogelijkheden voor populatiegericht onderzoek naar effecten van geneesmiddelen vergroot; wel is het zo dat veel interpretatieproblemen zullen blijven of zelfs kunnen toenemen.

Het is belangrijk in farmaco-epidemiologisch onderzoek dat gegevens met betrekking tot het gebruik van geneesmiddelen volledig zijn. Centraal in ons werk staat de methodiek van het verzamelen en interpreteren van medicatiegeschiedenissen van grote groepen patiënten.

Hoofdstuk 3 beschrijft het voor ons onderzoek gebruikte materiaal, gegevens zoals bewaard in apotheken met een geautomatiseerd databeheer, in vergelijking met andere types informatie over gebruik van geneesmiddelen: patiënt-vragenlijsten, tellingen van niet gebruikte medicatie, externe monitoring en biologische monitoring. De toepassing van de apotheekgegevens voor onderzoek wordt beschreven.

Als gevolg van regels van de ziekenfondsen moet een meerderheid van de bevolking in Nederland een vaste apotheek uitkiezen. Verder is het zo dat de apotheken in Nederland relatief groot zijn en meestal de medicatiegeschiedenis van patiënten in een computerbestand bewaren. Door deze omstandigheden is het mogelijk grote aantallen bijna volledige of volledige medicatiegeschiedenissen te verzamelen. De anonimiteit van patiënten wordt beschermd doordat de medicatiegeschiedenissen de apotheek verlaten met informatie over leeftijd en sekse, maar zonder naam of adres van de patiënt.

Hoofdstuk 4 geeft een beschrijving van de benadering van prescriptie-sequentie analyse. Deze methode is toe te passen voor bijwerkingen van geneesmiddelen die leiden tot een toestand waarvoor specifieke medicamenteuze therapie beschikbaar is. Als een dergelijke bijwerking optreedt moet dit zijn weerslag hebben in de medicatiegeschiedenis van patiënten. De benadering is bedoeld om, als casuïstische meldingen daartoe aanleiding geven, op korte termijn het mogelijke risico van een middel te onderzoeken. Naar aanleiding van meldingen over depressie en parkinsonisme na gebruik van flunarizine, een middel voorgeschreven bij migraine en duizeligheid, analyseerden we medicatiegeschiedenissen van ontvangers van dit middel. Uit geautomatiseerde apotheekbestanden selecteerden we de medicatiegeschiedenissen van personen die zowel flunarizine als een antidepressivum hadden ontvangen. De eerste aflevering (d.i. de "start") van een periode van therapie met een antidepressivum is beschouwd als indicatie van het optreden van medicamenteus behandelde depressie. Het optreden van deze starts is vergeleken in de periodes voor, tijdens, en lang na het afleveren van flunarizine. In de analyse die de meeste gegevens omvatte (hoofdstuk 4b) was de incidentie van starts van therapie met antidepressiva tijdens gebruik van flunarizine enigszins hoger dan in de periodes voor of lang na gebruik van flunarizine.

Op grond van dit resultaat kan niet worden uitgesloten dat gebruik van flunarizine medicamenteus behandelde depressie induceert, al is de associatie met andere mechanismen te verklaren.

Een ander resultaat van dit onderzoek was dat een opmerkelijk groot deel van de ontvangers van flunarizine in de periode die bestreken werd door de medicatie-geschiedenissen ook ooit een antidepressivum had ontvangen. Kennelijk wordt flunarizine voorgeschreven aan een groep patiënten met een grote consumptie van antidepressiva, wat suggereert dat depressie of depressie-achtige verschijnselen in deze groep patiënten op ruime schaal voorkomt. Dit soort kennis over de achtergrond van personen lijkt relevant voor vele soorten onderzoek waarbij een effect van een geneesmiddel onderscheiden moet worden van een al bestaande toestand bij patiënten.

Hoofdstuk 5 beschrijft een analyse van patiënt-medicatiegeschiedenissen die afleveringen omvatten van inhalatiesteroiden en medicatie tegen candida-infecties in de mond. Het gebruik van inhalatiesteroiden (A) kan orale candida-infecties (B) induceren. We beschouwden een aflevering van lokale orale candidamedicatie als indicatie van het optreden van een candida-infectie in de mond. Met andere woorden, A kan de lokale candida-infectie veroorzaken, B is de therapie ertegen.

De in hoofdstuk 4 voorgestelde methode van prescriptie-sequentie analyse is met enkele modificaties hier toegepast. In deze analyse is een positief, hoewel niet sterk, verband gevonden tussen het gebruik van inhalatiesteroiden en de start van medicatie met een anti-candidamiddel.

In *hoofdstuk 6* wordt het concept "channeling" (leiden, sturen) geïntroduceerd. Dit verschijnsel treedt op als geneesmiddelen met eenzelfde therapeutische indicatie worden voorgeschreven aan groepen patiënten die verschillen wat betreft gezondheid of prognostische eigenschappen. Het tijdstip van introductie of specifieke promotionele activiteiten van de fabrikant kunnen resulteren in channeling van een nieuw middel naar een groep patiënten die verschilt van de gebruikers van farmacologisch verwante middelen. Een later geïntroduceerd middel zal met name ook worden voorgeschreven aan mensen waarbij therapie met een ouder, gevestigd middel geen succes was. Een bewering dat een middel weinig bijwerkingen heeft kan leiden tot het selectief voorschrijven ervan aan patiënten met veel morbiditeit in de voorgeschiedenis. Als gevolg hiervan kunnen meer problemen worden gezien in de groep patiënten die wordt behandeld met een middel dat juist weinig problemen zou moeten veroorzaken. Als channeling niet wordt onderkend kan vertekening van de resultaten optreden in observationeel onderzoek naar effecten van geneesmiddelen.

Hoofdstuk 7 laat zien dat drie farmacologisch verwante astmamiddelen worden voorgeschreven aan groepen patiënten met een verschillende graad van ernst van astma, zoals deze tot uiting komt in medicatie. De medicatiegeschiedenissen van ontvangers van te inhaleren vormen van salbutamol, fenoterol en terbutaline zijn vergeleken wat betreft indicaties voor de aanwezigheid van ernstige of moeilijk te behandelen astma, diabetes en cardiovasculaire aandoeningen. We beschouwden het gebruik van systemische glucocorticosteroiden als zo'n indicatie voor de aanwezigheid van ernstige of moeilijk te behandelen astma. In een databestand dat de medicatie van 121.000 personen omvatte, zijn de medicatiegeschiedenissen van de ontvangers van salbutamol, fenoterol en terbutaline geselecteerd en geanalyseerd. Bij de groep ontvangers van fenoterol vonden we, in vergelijking met de ontvangers van salbutamol, 2-2,5 maal vaker comedatie met systemische steroïden. Ontvangers van terbutaline hadden wat dit betreft een tussenpositie. Ook het aantal patiënten met één of meer andere astmamiddelen was het hoogst voor fenoterol en het laagst voor salbutamol. Terbutaline had hier weer een tussenpositie. Concluderend lijkt het erop dat artsen in

Nederland fenoterol en terbutaline, in vergelijking met salbutamol, aan patiënten met meer ernstige vormen van astma voorschrijven.

In *hoofdstuk 8* wordt een onderzoek naar channeling van antidepressiva gepresenteerd. De bijsluiter van de meeste middelen in deze groep stelt beperkingen ten aanzien van de toepassing bij patiënten met een cardiovasculaire aandoening; bij enkele antidepressiva was er geen sprake van een contra-indicatie op dit terrein. Onze vraag was of deze verschillen in de bijsluiter samenhangen met de mate waarin de verschillende antidepressiva worden voorgeschreven aan patiënten met een cardiovasculaire aandoening.

De gegevens waren afkomstig uit een medicatie-databestand dat een bevolking van 130.000 mensen bestrijkt; 1173 personen hadden in een tijdspanne van zes maanden een antidepressivum ontvangen. Afgifte van één of meer cardiovasculaire middelen is beschouwd als indicatie voor de aanwezigheid van een cardiovasculaire aandoening. De groepen ontvangers van diverse antidepressiva verschilden sterk wat betreft de mate van comedatie in verband met cardiovasculaire aandoeningen. Deze medicatie was afgeleverd aan een relatief groot deel van de groep ontvangers van mianserine (36%) en doxepine (35%); relatief klein was dit aandeel bij de ontvangers van fluoxetine (13%) en clomipramine (18%). Er moet worden opgemerkt dat de groepen ontvangers van de diverse antidepressiva sterk verschilden wat betreft de verdeling van leeftijd en sekse, en na stratificering voor deze variabelen waren er geen residuele significante verschillen wat betreft cardiovasculaire comedatie. Er was bij enkele middelen sprake van channeling, maar kennelijk gedeeltelijk indirect, via verschillen in leeftijd en sekse van de ontvangers van de antidepressiva.

De analyse laat zien dat antidepressiva die geschikt zijn voor patiënten met een aanwezige cardiovasculaire aandoening toch niet relatief vaak worden voorgeschreven aan deze groep patiënten. Besproken wordt hoe het tijdstip van introductie en promotionele activiteiten van de fabrikant een rol kunnen hebben bij het ontstaan van de gevonden verschillen.

Hoofdstuk 9 beschrijft een onderzoek dat gedaan is naar aanleiding van publicaties over onbedoeld stoppen van het gebruik van geneesmiddelen bij opname in het ziekenhuis. In dit kader onderzochten we de continuïteit van medicatie bij een groep in het ziekenhuis opgenomen patiënten. Medicatiegeschiedenissen afkomstig van de enige apotheek in een dorp in het verzorgingsgebied van het ziekenhuis werden vergeleken met gegevens over tijdens het ziekenhuisverblijf afgeleverde medicatie. De gegevens van de openbare en de ziekenhuisapotheek werden voor 205 patiënten vergeleken door een panel van deskundigen op het terrein van farmacotherapie. Discrepanties werden door het panel ingedeeld op grond van de potentiële mate van ernst. Als de discrepanties ernstig leken gingen we in medisch dossier na of de medicatie bij de opname bewust was afgebroken. Het panel beoordeelde 68 "stops", die 41 patiënten betroffen, als potentieel riskant als deze stops het gevolg zouden zijn van een vergissing. Bestudering van de medische dossiers leidde tot de conclusie dat 15 afbrekingen niet bedoeld waren; hierbij waren 12 patiënten betrokken.

Deze bevindingen zijn niet noodzakelijkerwijs representatief voor de gang van zaken bij opname in het ziekenhuis in het algemeen, wel is er de suggestie dat er vermijdbare fouten worden gemaakt. Overdracht van gegevens van de openbare apotheek naar het ziekenhuis langs elektronische weg wordt gesuggereerd om de anamnese bij opname van patiënten te ondersteunen.

Hoofdstuk 10 beschrijft een onderzoek naar de kwaliteit van informatie verkregen met een schriftelijke vraag over chronisch gebruik van geneesmiddelen. De vraag was onderdeel van een vragenlijst die gebruikt is in het kader van een groot prospectief

onderzoek naar de invloed van voedingsgewoonten en andere met leefstijl samenhangende factoren (zoals chronisch gebruik van geneesmiddelen) op het optreden van kanker. De betrouwbaarheid van de informatie over geneesmiddelgebruik uit de vragenlijst werd onderzocht door de gegevens van de vragenlijst te vergelijken met in de apotheek bewaarde informatie over afgeleverde medicatie. De vergelijking werd uitgevoerd in een gemeente met één apotheek voor personen die de vragenlijst ingevuld hadden teruggestuurd.

Alle geneesmiddelen waarvan in de vragenlijst was opgevoerd dat ze werden gebruikt op het moment van de enquête waren ook geregistreerd in het historisch bestand van de apotheek. Omdat er in de vragenlijsten geen middelen waren opgevoerd die niet waren afgeleverd in de apotheek, hebben we het apotheekbestand als referentie beschouwd en geanalyseerd hoe volledig er was geantwoord op de vraag naar chronisch gebruikte geneesmiddelen. Van de 207 leden van het cohort ontvingen er 69 chronisch medicatie toen de enquête werd uitgevoerd. Gemiddeld ontvingen deze 69 personen 1,9 middelen op chronische basis, d.i. gedurende een periode van minstens zes maanden. Van deze afgeleverde middelen is 68,8 % (88 van 128) in de antwoorden van de vragenlijst terug te vinden. De middelen die wel op chronische basis waren afgeleverd, maar waarbij dit was opgehouden ruim voor de enquête, werden relatief minder frequent opgevoerd in de vragenlijst.

De conclusie was dat de open vraag over gebruik van geneesmiddelen een hoge specificiteit maar een lage sensitiviteit had, d.w.z. de afwezigheid van fout-positieve antwoorden ging samen met lacunes in het opgeven van de middelen die waren afgeleverd aan de leden van het cohort. Belangrijk in verband met onderzoek op het terrein van de farmaco-epidemiologie is hier de hoge betrouwbaarheid van de individuele medicatiegeschiedenis zoals deze in de apotheek wordt bewaard.

In de *epiloog* komen de methoden en enkele implicaties van de resultaten van het werk voor dit proefschrift aan de orde. Benaderingen voor nieuw onderzoek worden besproken, met name het koppelen van verschillende informatiebestanden in de gezondheidszorg, de zg. record linkage. De conclusie is dat patiënt-medicatiegeschiedenissen informatieve waarde hebben in geïsoleerde vorm en in combinatie met andere gezondheidsgebonden gegevens. In apotheken en bij verzekeraars zijn in principe langere medicatiegeschiedenissen op te bouwen, deze hebben waarde in het kader van de bestudering van veranderend therapiebeleid en voor onderzoek naar lange-termijn effecten van geneesmiddelen.

Betrouwbare medicatiegeschiedenissen zijn een hoeksteen van de farmaco-epidemiologie. De ziekenfondsen, en de gezondheidszorg in het algemeen in Nederland, hebben bevorderd dat patiënten één apotheek bezoeken, analoog aan de inschrijving bij een huisarts en een tandarts. Deze verbinding tussen individuele patiënten en individuele hulpverleners in de gezondheidszorg heeft voordelen in het kader van de zorg en ook voor onderzoek; het blijven bestaan van deze verbinding wordt bepleit.

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Jack Naus was al vanaf het begin van het onderzoek de middelaar bij het verzamelen van gegevens uit apotheken en daarmee een steunpilaar van het onderzoek.

Met prof. Albert Bakker, Bert Leufkens, Ron Herings en Rob Heerdink van Utrechtse faculteit farmacie heb ik in een aantal projekten prettig samengewerkt.

Binnen de vakgroep heeft een goede samenwerking met Paulien van Hessen en Piet van den Brandt geleid tot twee artikelen die in dit proefschrift te lezen zijn. In de begintijd van het projekt heeft Riekje de Vet ook een bijdrage aan het werk geleverd.

Reinhilde Silkens en Ed Gronenschild hebben ervoor gezorgd dat de gegevens door de computer verwerkt konden worden.

Thum Aarts was regelmatig een ad hoc leraar tekstverwerking; ook is de uiteindelijke vormgeving van dit boekje vooral door hem verzorgd.

Verder dank ik al degenen die op de één of andere manier aan de totstandkoming van dit proefschrift hebben bijgedragen.

CURRICULUM VITAE

Hans Petri is geboren op 5 september 1954 te Leiden. De eerste schooljaren waren te Dakar (Senegal). Het VWO-diploma werd te Zutphen behaald in 1974. In hetzelfde jaar ving hij aan met de studie psychologie aan de Universiteit van Amsterdam (propaedeuse 1975). Aan de Rijksuniversiteit Limburg (RL) studeerde hij vanaf 1976 geneeskunde. Het artsexamen is afgelegd in 1982. Hij doorliep in 1983-1984 de huisartsopleiding en in 1985-1986 de door de RL ingestelde huisartsonderzoekeropleiding; in dat kader deed hij bij prof. K.H. Rahn onderzoek op het terrein van de klinische farmacologie. Tussendoor was er een periode van waarneming in de huisartspraktijk en bij een bedrijfsgeneeskundige dienst. Vanaf 1986 is hij als toegevoegd onderzoeker werkzaam bij de vakgroep Epidemiologie van de RL; bij prof. J. Urquhart en prof. F. Sturmans is het onderzoek gedaan dat geleid heeft tot dit proefschrift. Tevens is hij als consulent verbonden aan het Instituut voor Farmaco-epidemiologie van België (Brussel).