

**On drug use, multiple medication  
and polypharmacy in a national population**



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**ON DRUG USE, MULTIPLE  
MEDICATION AND POLY-  
PHARMACY IN A NATIONAL  
POPULATION**

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ON DRUG USE, MULTIPLE MEDICATION AND POLYPHARMACY  
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## Abstract

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The application of multiple medications has successively increased during a number of years and has thereby increased the potential risks of adverse drug reactions, interactions and non-adherence to drug therapy. This may result in unnecessary health expenditure, directly due to redundant drug sales, and indirectly due to the increased hospitalization caused by drug-related problems. The overall aim of this thesis was to investigate the occurrence and development of drug use, multiple medication, and polypharmacy in an entire national population by using individual-based data on dispensed drugs. The studies (I-V) in the thesis are based on data of dispensed prescription drugs for up to 6.2 million individuals obtained from the Swedish Prescribed Drug Register. The data in the studies cover different periods of time between July 2005–Sept 2008, and the data have been analyzed on the basis of epidemiological measures and statistical methods. The major conclusions of the studies are: the prevalence of dispensed drugs and multiple medications were extensive in all age groups and were higher for females than for males. Multiple medications should be regarded as a risk in terms of potential drug-drug interactions and adverse drug reactions in all age groups (I). Regional differences in the prevalence of polypharmacy was observed and partly explained by the regional age distribution in Sweden. The use of a novel weighted polypharmacy index indicated regional differences in drug therapy for individuals with polypharmacy (II). The number of drugs used by an individual not only increased the potential risks associated with multiple drug use, but also the potential burden of an increased therapeutic intensity, especially for elderly (III). Individuals with ten or more drugs accounted for almost fifty percent of the total acquisition costs of dispensed drugs. Therefore, interventions with a focus on the reduction of the number of prescription drugs for the group of patients with a large number of different drugs may also result in a substantial reduction in the total drug costs (IV). In spite of national and regional efforts to reduce polypharmacy, the prevalence of polypharmacy and excessive polypharmacy and the mean number of drugs per individual continued to increase year-by-year in Sweden 2005-2008 (V). The observed increase in polypharmacy underlines the importance of monitoring the development of drug use in all ages. Individual-based register studies of dispensed drugs provide high quality data and could serve as the basis for further research and also in terms of training health care personnel. It can also be used as a base for interventions and the evaluation of drug use. To enable better comparisons on drug use and its consequences, there is a need for standards concerning measurements, classification and criteria which encompass all types of medications. For clinicians, there is a need for information concerning the patient's actual use of all different types of medications.



To my family



## List of papers

The thesis is based on the following original papers, which are referred to in the text by their Roman numerals.

- I      Dispensed drugs and multiple medications in the Swedish population: an individual-based register study.**  
  
Hovstadius B, Åstrand B, Petersson G.  
BMC Clin Pharmacol. 2009, 9:11
- II     Assessment of regional variation in polypharmacy.**  
  
Hovstadius B, Åstrand B, Petersson G.  
Pharmacoepidemiology and Drug Safety 2010; 19: 375-383.
- III    Prevalence and therapeutic intensity of dispensed drug groups for individuals with multiple medications: a register based study of 2.2 million individuals.**  
  
Hovstadius B, Tågerud S, Petersson G, Åstrand B.  
Submitted
- IV    Acquisition cost of dispensed drugs for individuals with multiple medications – a register-based study.**  
  
Hovstadius B, Persson U, Åstrand B, Petersson G.  
Submitted
- V     Increasing polypharmacy – an individual-based study of the Swedish population 2005-2008.**  
  
Hovstadius B, Hovstadius K, Åstrand B, Petersson G.  
Submitted

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## Populärvetenskaplig sammanfattning

Förekomsten av multimedicinering har successivt ökat under många år och därmed har även de potentiella riskerna för läkemedelsrelaterade problem ökat. Multimedicinering kan även orsaka onödiga sjukvårdskostnader, direkt genom överflödigt läkemedelsförsäljning och indirekt genom en ökad andel inläggningar på sjukhus orsakad av läkemedelsrelaterade problem. Syftet med avhandlingen var att studera förekomst och utveckling av läkemedelsanvändning, multimedicinering och polyfarmaci (samtidig användning) inom en hel nationell befolkning genom att använda individbaserade data om uthämtade läkemedel. Avhandlingens delarbeten (I-V) är baserade på uppgifter från Svenska Läkemedelsregistret med upp till 6,2 miljoner individers uthämtade läkemedel. Uppgifterna täcker olika tidsperioder mellan juli 2005 och september 2008, och har analyserats med epidemiologiska och statistiska metoder. De viktigaste slutsatserna är: andelen individer med läkemedelsanvändning och multimedicinering var hög inom alla åldersgrupper och var högre för kvinnor än för män. Multimedicinering bör beaktas som en riskfaktor för potentiella läkemedelsrelaterade problem inom alla åldersgrupper (I). Regionala skillnader i andelen individer med polyfarmaci observerades och förklarades delvis av den regionala åldersfördelningen i Sverige. Användningen av ett nytt vägt polyfarmaci-index indikerade regionala skillnader i läkemedelsterapi för individer med polyfarmaci (II). Antalet läkemedel per individ ökade inte enbart de potentiella riskerna som är förenade med multimedicinering, utan även den potentiella bördan av ett ökat antal doser per läkemedel, speciellt för äldre (III). Individer med tio eller fler läkemedel stod för nära hälften av de totala läkemedelskostnaderna för uthämtade läkemedel. Insatser med fokus att reducera antalet läkemedel för denna grupp av patienter med många läkemedel kan därför även medföra en väsentlig minskning av de totala läkemedelskostnaderna (IV). Trots olika nationella och regionala insatser att reducera polyfarmacin, så ökade årligen antalet uthämtade läkemedel per individ, andelen individer med polyfarmaci och extrem polyfarmaci i Sverige mellan 2005 och 2008 (V). Den observerade ökningen av polyfarmaci understryker betydelsen av att övervaka utveckling av läkemedelsanvändningen i alla åldrar. Individbaserade registerstudier över uthämtade läkemedel ger högkvalitativa data och kan användas som grund för vidare forskning och för utbildning av hälso- och sjukvårdspersonal. Registerstudier kan även användas som underlag för förändring och utvärdering av läkemedelsanvändning. För att kunna göra bättre jämförelser av läkemedelsanvändning och dess konsekvenser behövs enhetligare mätmetoder, klassificeringar och kriterier som inkluderar alla olika typer av läkemedel. För läkare finns behov av information om patientens verkliga användning av alla olika typer av läkemedel.



# Contents

Contents .....	1
Abbreviations .....	2
Introduction .....	3
Background .....	3
Pharmacoinformatics, pharmacoconomics and pharmacoepidemiology .....	7
Drug use, multiple medication and polypharmacy .....	9
Definitions .....	9
Measurements .....	12
Occurrence .....	20
Consequences .....	24
Aims of the thesis .....	29
Materials and methods .....	30
Materials .....	30
The Swedish Prescribed Drug Register .....	31
Study design (I-V) .....	32
Methods (I-V) .....	35
Ethical considerations .....	38
Results (I-V) .....	39
Discussion .....	44
Conclusions and implications .....	48
Acknowledgements .....	51
List of references .....	53
Papers I-V .....	66

## Abbreviations

ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical classification
BTC	Behind The Counter
CAM	Complementary and Alternative Medicine
DDD	Defined Daily Doses
DP	Dispensed Prescription drugs
GP	General Practitioner
IDIS	Iowa Drug Information System
ICT	Information and Communication Technologies
MAI	Medical Appropriateness Index
OTC	Over The Counter
RR	Relative Risk
TM	Traditional Medicine
WHO	World Health Organization

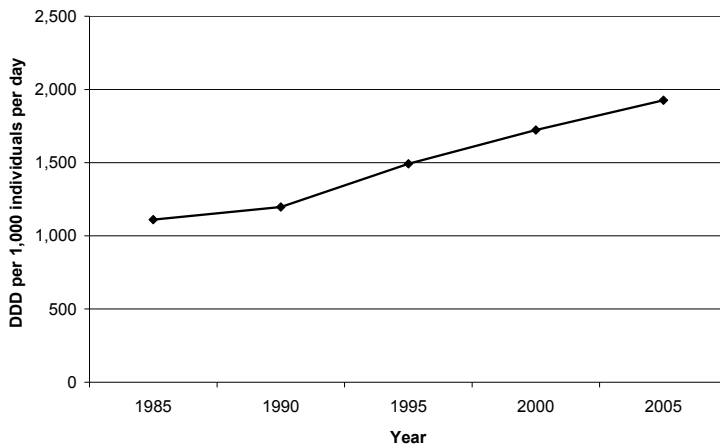
# Introduction

## Background

### The use of medications

The use of medications is for many individuals a part of their everyday life. Medications are used in all age groups and this use increases with morbidity and age. Differences in drug use are normally found to exist between genders, and also between different socioeconomic groups. The vast majority of all medications are prescription drugs, but in-hospital medications, over-the-counter (OTC) drugs, dietary supplements, and complementary and alternative medicine (CAM), all contribute to the total drug consumption [1-3].

Prescribing a drug is the most frequent and most cost-effective medical intervention performed by a doctor [4, 5]. The proportion of the total national health budget spent on drugs in developed countries is between 10 to 20% [5], e.g. in Sweden the cost for prescription drugs, OTC drugs, and in-hospital medications account for 13% of the total national health care costs in 2005 [3]. In developing countries, the medication share of the health budget is between 20 and 40% [5].



*Figure 1. Sales volume of DDD per 1,000 individuals per day in Sweden 1985 to 2005 [6].*

## Development of drug use

The global sales of medicines has increased successively during the last two decades [6, 7], e.g. between 1985 and 2005, sales increased from US \$ 82 billion to 605 billion (+638%) [8, 9]. In Sweden, the drug cost per individual increased from SEK 751 to 3,477 (+367%) and the sales volume, measured in defined daily doses (DDD) per individual, increased by 73% between 1985 and 2005 (Figure 1) [6].

The increase in overall drug sales has several explanations, e.g. introduction of new drugs, new medical recommendations to treat morbidity in higher ages, and an increase in drug use to prevent health-related disorders among healthy individuals [10-15]. All together, the increase in drug use is assumed to be a major contributing factor to the well being of large groups of individuals with different diseases. In contrast to the large increase in the use of medicines, there is a concomitant frequent underuse of effective medicines [5].

The development of drug use shows a similar trend all over the world [8] but differences in drug use exist between countries. An illustration of differences in drug use is that even between the relatively similar Nordic countries (Denmark, Finland, Norway and Sweden), there are substantial differences in the volume of drug consumption, e.g. Swedes consume approximate 30% more DDD per individual than Danes or Norwegians and 20% more than the Finns in 2007 (Figure 2) [16, 17]. On the other hand, there are also similarities in drug use between these countries, e.g. in all Nordic countries, cardiovascular medicines and drugs for diseases of the nervous system are the most common drugs for chronic use. Drugs for diseases of the alimentary tract and metabolism are in third place, followed by drugs for respiratory diseases [18].

The actual differences in the volume of drug consumption between countries may have several causes; morbidity may differ, and there may be variation in proportion of men and women or there may exist age groups with high relative consumption of specific drugs. Also, there may be different therapeutic traditions and variations in prescribing habits at local geographic levels within each country that may influence the total drug consumption, as well as governmental regulations and financing schemes. Furthermore, medical care and availability of drugs may differ between countries [18]. In addition, the observed differences in the volume of drug consumption between countries may also be explained by differences in measurement methods.

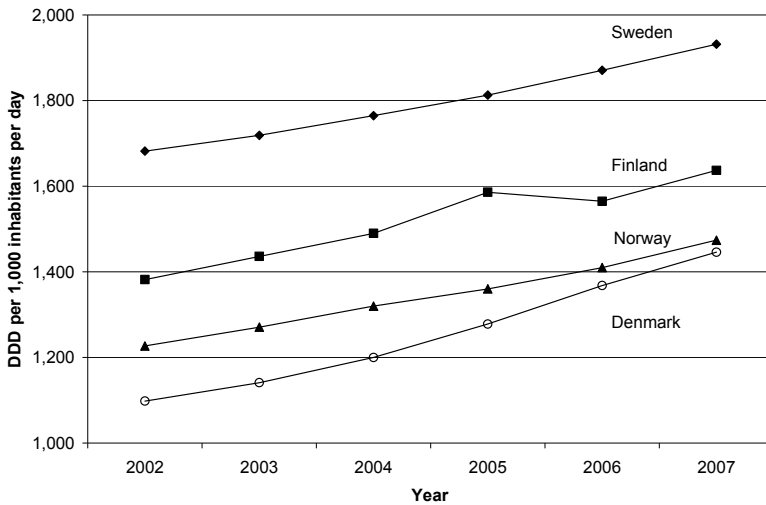


Figure 2. DDD per 1,000 inhabitants per day in Sweden, Finland, Norway, and Denmark 2002–2007 [16, 17].

### Problems with drug use

The use of medications is associated with some well known problems. The efficacy of drug use may be reduced due to prescribing errors, dispensing errors, administration errors, patient non-adherence and medication ineffectiveness. Prescribing errors include both irrational, inappropriate and ineffective prescribing, underprescribing and overprescribing [19]. In the UK, a recent review of the quality of medication use in primary care suggests that only between 4 and 21% of patients achieve the optimum benefit from their medication [20]. Furthermore, less than 20% of patients with myocardial infarction and stroke in middle-income countries received optimal medication therapy, indicating that effective medicines are frequently underused [21]. On the other hand, there is evidence for an overuse of a large number of drugs [5]. Studies in Indonesia, India and Pakistan show that over 70% of patients were prescribed antibiotics and up to 90% of injections were estimated to be unnecessary [9]. According to WHO, only 50% of patients with chronic disease in developed countries adhere to the prescribed drug therapy [22].

### Multiple drug use and polypharmacy

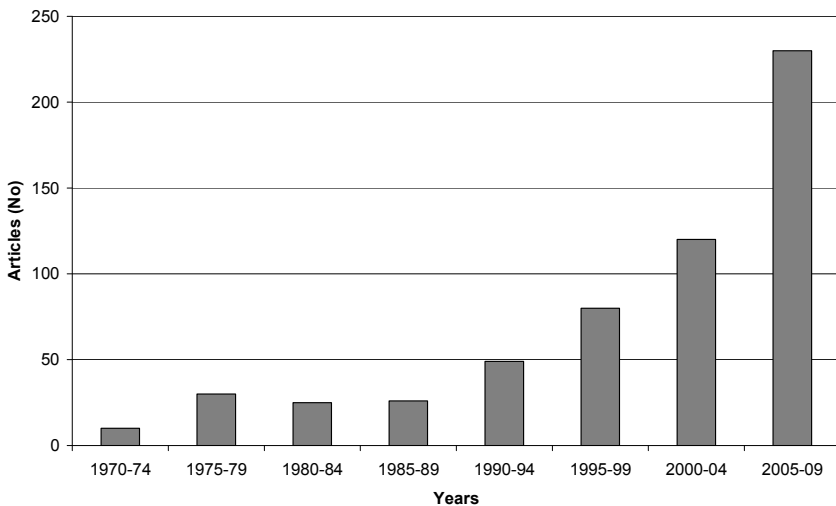
The proportion of individuals using several different drugs has increased during the last decades [23–26]. The use of a number of drugs is for many individuals a rational and a necessary therapy with undisputable benefits. However, multiple medications are also commonly associated with an irrational, excessive use

of drugs, and if concomitantly taken constitute a well known risk factor in terms of patient's health due to the increased risk of adverse drug reactions [23, 27-31], interactions [23, 28-31], medication errors [27, 31], hospitalization [27, 28, 30], and diminishing adherence to drug therapy [23, 27-32]. Furthermore, the proportion of inappropriate medications is assumed to increase with the number of drugs [28, 33].

Multiple medications may also result in unnecessary health expenditure [27-29], directly due to redundant drug sales and indirectly due to the increased hospitalization caused by drug-related problems [27, 34].

In recent years, the interest in multiple drug use and polypharmacy has increased [10]. Studies have dealt with questions such as: How many of the elderly are using five or more, or ten or more different drugs? What type of drugs do individuals with polypharmacy take? Is there a relationship between the increasing number of drugs and inappropriate drug therapy? What are the total drug costs for individuals with five or more drugs?

Since 1985, the number of scientific articles on polypharmacy or multiple medications has increased substantially, and the last five years the number of articles has doubled compared to the previous five-year period (Figure 3). The settings, measurements and methods for these studies vary widely. Many studies have been carried out in small samples of elderly patients [27, 35].



*Figure 3. Number of Pubmed indexed articles with "Polypharmacy" or "Multiple medication" in the title per 5-year periods, 1970-2009.*

## Pharmacoinformatics, pharmacoeconomics and pharmacoepidemiology

Informatics in health care goes by a variety of labels: Medical informatics, Health informatics, or Health care informatics. In the following, *Health informatics* is used as the intersection of information science, computer science, and health care. Health informatics deals with the resources, devices, and methods required for the optimization of the acquisition, storage, retrieval, and use of information in health and biomedicine. Health informatics tools include computers, clinical guidelines, formal medical terminologies, and information and communication systems. Health informatics is applied to the areas of nursing, clinical care, dentistry, pharmacy, public health and medical research [36].

*Pharmacoinformatics* can be regarded as a part of health informatics and can be defined as the discipline in which information and communication technologies (ICT) intersect with any aspect of drug delivery, from the basic sciences to the clinical use of medications in individual populations. Pharmacoinformatics includes all health care systems related to medications and clinical decision support, and analysis and research related to data generated by the use of these systems. It also includes the development of new technologies that improve the quality and safety of therapeutic care related to medication use [37].

*Health economics* is an area of economics that analyzes health, health care and the supply and demand of health care resources, and the effect of health services on a population [38].

*Pharmacoeconomics* is a sub-discipline of health economics that particularly considers drug therapy. Pharmacoeconomics evaluates the clinical, economic and humanistic aspects of drug therapy, pharmaceutical products, services, and programs. Pharmacoeconomics also evaluates and compares the cost (expressed in monetary terms) and effects (expressed in terms of monetary value, efficacy or enhanced quality of life) of pharmaceutical products with a collection of descriptive and analytic techniques [38, 39].

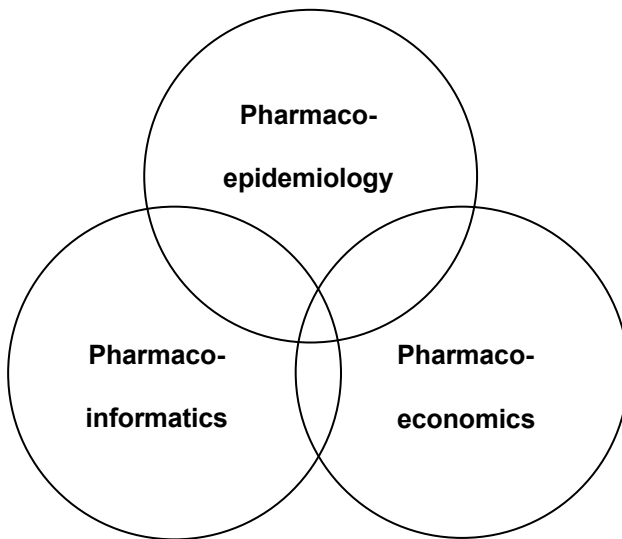
*Pharmacoepidemiology* is defined as the study of the use and the effects of drugs in a large number of people. Pharmacoepidemiology combines the disciplines of epidemiology and clinical pharmacology [40].

The development of pharmacoepidemiology has followed the history of major adverse drug reaction “disasters” and has recently expanded its focus to other issues e.g. [40]:

- A) Information which supplements the information available from premarket studies – better quantification of the incidence of known adverse and beneficial effects
- B) New types of information not available from premarket studies
  1. Discovery of previous undetected adverse and beneficial effects
  2. Patterns of drug utilization
  3. The effects of drug overdoses
  4. The economic implications of drug use

Depending on the research question, pharmacoepidemiology studies of drug use have been conducted by gathering information from drug sales statistics at a national level, from the registers of individual-based drug data for large population groups or from interviews with samples of drug users, which are interpolated to general conditions by statistical methods [41].

In this thesis, the studies use large databases with information of dispensed drugs in large numbers of people for analyzing patterns of drug utilization and drug costs, and can be seen as a cross disciplinary combination of the applied disciplines of pharmacoinformatics, pharmacoeconomics and pharmacoepidemiology (Figure 4).



*Figure 4. The principal intersections between pharmacoinformatics, pharmacoeconomics and pharmacoepidemiology.*

# Drug use, multiple medication and polypharmacy

## Definitions

### Drug

A drug can be defined as an article “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease”, or an article (other than food) “intended to affect the structure or any function of the body” [42, 43]. Usually, drugs are regulated by specific laws specifying drugs into prescription drugs, which only may be dispensed with a prescription from a licensed professional with a statutory regulated privilege to prescribe (e.g. a physician, a dentist or a nurse) and nonprescription drugs, which can be purchased without a prescription. In many countries, the nonprescription drugs are divided into several subgroups after the restrictions under which nonprescription drugs are sold; Behind the counter (BTC) drugs: only available in pharmacies and a contact with pharmacist is required. Pharmacy: only available in pharmacies, contact with a pharmacist is not required. Drugstore: only available in pharmacies or drugstores, a contact with pharmacist is not required. OTC/pharmacist: available for self-selection in pharmacies and other retail outlets, but a pharmacist must be present. OTC: available for self-selection in pharmacies and other retail outlets, including those without pharmacists or druggists [44]. In the vast majority of studies concerning drug utilization, nonprescription drugs are labeled OTC drugs and in the following *OTC drugs* are used for all nonprescription drugs (Table 1).

In addition to prescription drugs and OTC drugs, there are also other substances that are used for health benefits and which are sometimes included in the drug context; dietary supplements, which include medicinal herbs and nutraceuticals, and complementary and alternative medicine (CAM), which includes a variety of therapies, which are not included in standard Western medicine (Table 1). CAM is also called traditional medicine (TM) [45].

**Table 1.** Product/substance intended for medication use.

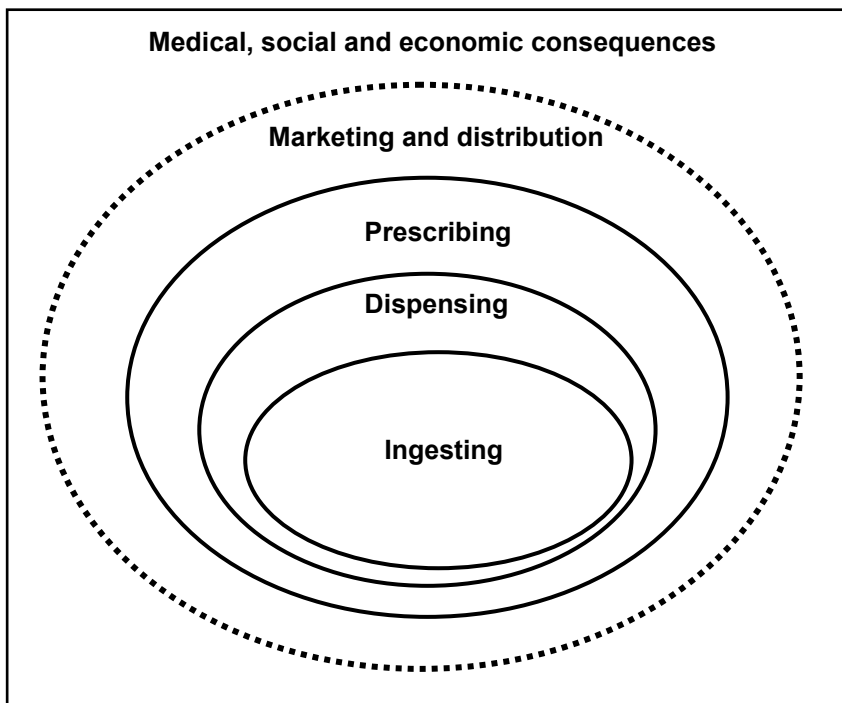
Law regulated substance (drug)	None regulated substance
Prescription drugs	Dietary supplements (vitamins, minerals)
Non-prescription drugs:	Complementary and alternative medicine (CAM)
- BTC	
- Pharmacy	
- Drugstore	
- OTC/pharmacist	
- OTC	

Usually, prescription drugs cover the entire spectrum of drug therapies for various diseases. In this respect, OTC drugs, dietary supplements, and CAM can be seen as a complement to the prescription drugs in certain therapeutic areas. The drugs that are regulated on a statutory basis and those drugs that are classified as prescription drugs differ between countries, e.g. in Sweden all anti-infectives for systemic use are prescription drugs, but two-thirds of global antibiotic sales are estimated to be sold as OTC, due to under-regulated private sectors [9].

### Drug utilization

Drug use can simply be defined as the ingesting of a drug during a certain period of time. Depending on the purpose of the research, the ingesting can be during one day, one week, one month, and one year or just once in a lifetime (Figure 5).

Drug utilization also has a broader “process” definition as “the prescribing, dispensing and ingesting of drugs” [41] (Figure 5).



*Figure 5. Descriptions of drug use.*

The WHO definition of drug utilization is even broader, including various outcomes of drug use; “the marketing, distribution, prescribing and use of a drug in a society, with special emphasis on the resulting medical, social and economic consequences” [46]. Both of the broad definitions of drug utilization focus, implicitly, on prescription drugs even if other drugs are not excluded (Figure 5).

### **Multiple medication**

Multiple medication is defined as the intake of more than one drug during a certain period of time. The time interval can be from one day to one year, and can include continuous use, as needed use and short periods of drug use without taking into account the concurrency of the drug use.

### **Polypharmacy**

Polypharmacy has two definitions. The first definition is the concurrent use of many different drugs. The second definition is the excessive use of drugs, e.g. the use of more drugs than are clinically indicated or the use of an excessive number of inappropriate drugs [47].

Similar to multiple medication, polypharmacy includes the use of chronic medication, as needed medication and short periods of drug use, but polypharmacy is intended to yield a total of the individual’s concomitantly used drugs.

Whether any given number of drugs are relevant as a measure of polypharmacy from a clinical perspective is under debate [35, 48], and studies have argued that selecting appropriate limits for the number of medications may be counterproductive in populations with multiple co-morbidities [49].

## Measurements

### **The Anatomical Therapeutic Chemical (ATC) classification**

One cornerstone in pharmacoepidemiology studies is the classification of all different drugs into uniform drug groups. Today, the WHO's Anatomical Therapeutic Chemical (ATC) classification is a well-accepted standard, even if there are other classifications of drugs, e.g. the Iowa Drug Information System (IDIS) [27, 41, 50].

### **Defined daily doses (DDD)**

Another cornerstone in pharmacoepidemiology studies is to use uniform measurements for the volume of drugs in relation to their purposes. DDD is established by an international expert panel under WHO to represent the typical maintenance dose for a drug, when it is used by an adult for its main indications. The DDD is a technical unit of measurement making it possible to compare data on drug use with different potency levels [50].

To enable comparisons of drug use between countries, regions, and different health care settings, and to facilitate the examination of trends of drug use over time and in different settings, the application of the ATC/DDD system allows for the standardization of drug groupings and a stable drug utilization metric [51].

### **Source of data**

Depending on the research question, the use of drugs can be measured by sale statistics, by data from medical or pharmacy records, and by interviews.

#### *Sale statistics*

Drug sale statistics can be seen as a crude indicator of drug use in an entire population. When using sales statistics, drug sales during a month or a year are often related to the total number of individuals in the population. A common measurement in comparative studies based on sale statistics is the number of DDD for a certain drug per inhabitant during a given year, or DDD per inhabitant per day. A major advantage with sales statistics is that they often cover all regulated drugs. Since sale statistics cannot be linked to individuals, they are not suitable for establishing estimations of individuals' exposure to drugs or for studies of multiple medications or polypharmacy (Table 2).

### *Registers*

Data regarding drug use in a population may also be available from pharmacies or from the prescribers' medical records. The use of registers with information on individuals' drug use in large populations has introduced new opportunities for research. In certain countries, there are national registers covering information on all dispensed drugs regarding the entire population [52]. The time periods for analysis of register data are days, months, or years. A main advantage in research is the low cost for allocating data and the fact the data is free from sampling, recall or interviewer bias. A disadvantage is that registers usually do not cover OTC drugs, CAM, and dietary supplements [53] (Table 2).

### *Interviews*

Data on drug use, multiple medication and polypharmacy in a population can also be collected by interviews of samples of individuals. The results can then be extrapolated to general assumptions regarding drug use in a larger population. The major advantages with interviews are that they can cover all types of drugs and that the respondents' answers are intended to cover the actual use of drugs and also their various effects. The main disadvantages with interview studies are that they are associated with sampling, recall, and interview bias. The results can also be biased by unintended and intended memory failures and are also dependent on whether the questions in the interview are general or specific [54] (Table 2).

In interview studies, the focus is on the drugs taken on the same day, the previous week or the previous two weeks. Usually, it is irrelevant to ask individuals about the drugs they ingested the previous month or the previous year.

## **Epidemiological measures**

Depending on the research question, drug use can be studied pharmacoepidemiologically by several scientific measures regarding the occurrence, distribution and determination of drug use.

### *Incidence*

Incidence is a measure of the risk of developing a new condition within a specified period of time. Incidence rate is the number of new cases of a disease that occur during a specified period of time in a population at risk for developing the disease [55].

In pharmacoepidemiology, the incidence can be defined as the proportion of new individuals in a population that are prescribed, or have dispensed or ingested a certain medication at a given time.

**Table 2.** Certain characteristics of drug utilizations studies with different data collection sources.

Study focus	Data collection source		
	Sale statistics	Register data	Interviews
<i>Drug type:</i> - Prescribed - OTC - Dietary suppl. - CAM	Yes Yes No No	Yes No No No	Yes Yes Yes Yes
Time period	Month - Year	Day - Month - Year	Day - Week
- Drug use - Multiple Medications - Polypharmacy	No No No	Yes Yes Yes	Yes Yes Yes
Study cost	Low	Low	High
<i>Measurements:</i> - Volume - Therapeutic intensity - Prevalence - Cost	DDD/inhabitant DDD/inhabitant No Per inhabitant	DDD/user DDD/user Yes Per user	DDD/user DDD/user Yes (estimated) (Per user)
<i>Potential risk:</i> - ADR - Drug-drug interactions - Diminishing adherence - Inappropriate drugs	No No No No	No Yes No (Yes)	Yes Yes Yes Yes
Main advantage:	Published regularly each year.	High quality data. Often full census. Data already collected.	Possible to estimate actual consumption of a drug. Possible to see consequences of drug use.
Main disadvantage:	No link to individuals drug users or user in proportion of population.	Only prescribed or dispensed drugs. Not known which drugs individuals actually use. Cannot study drug effects.	Sampling bias, recall bias, interview bias, and memory bias.

### *Prevalence*

In scientific English, prevalence means "proportion" and is typically expressed as a percentage. In medicine, prevalence is defined as the total number of cases of a disease in a population at any given time, or the total number of cases in the population, divided by the number of individuals in the population. Prevalence is thereby expressed as a ratio in which the number of events is the numerator and the population at risk is the denominator. Prevalence may also be expressed in terms of subgroups of the population based on different denominators.

In pharmacoepidemiology, the prevalence is defined as the proportion of individuals that are prescribed, or have dispensed or ingested a certain medication in a population at a given time.

Prevalence can be measured as point prevalence; the proportion of individuals that are prescribed, or have dispensed or ingested a certain medication in a population at a specific time. Prevalence can also be measured as period prevalence; the proportion of individuals that are prescribed, or have dispensed or ingested a certain medication in a population during a specified period, e.g. annual or lifetime [55].

### *Relative risk*

In epidemiology, relative risk (RR) is the risk of an event relative to exposure. Relative risk is a ratio of the probability of the event occurring in the exposed group vs. a non-exposed group [55]. Relative risk can also express the ratio of the event occurring in one exposed group vs. the event occurring in another exposed group, e.g. the prevalence of a disease in one group divided by the prevalence of the disease in another group.

### *Therapeutic intensity*

In pharmacoepidemiology studies, therapeutic intensity is measured as the number of Defined Daily Doses/1,000 inhabitants per day (DDD/TID) [53]. Therapeutic intensity can also be measured as the number of DDD/per individual of subgroups of the population, e.g. individuals with five or more dispensed drugs [41].

## **Measurements of prescription drugs, OTC drugs, dietary supplements and CAM**

Prescription drugs are seen as the core base in studies of drug utilization. This is perhaps primarily due to the implicit definition of drug use, the ease-of-access of accurate data from medical or pharmacy records, but is also due to the fact that physicians, researchers and patients often consider prescription drugs

as being more potent and important than other types of drugs, e.g. 40% of the population believe that OTC drugs are too weak to cause any real harm [56]. Furthermore, in studies of drug utilization the focus is often on chronically applied drugs and, for example, GP's have been reported to exclude as needed and topical medications when counting their patients medications [57].

In studies of individuals' drug use, OTC drugs are not always included. Normally, there are valid sales data for OTC drugs but as sales data often can not be linked to the individual drug user; the total amount of OTC drugs is related only to the total population. Therefore, our knowledge of the use of OTC drugs in different genders, age or health strata is often based on interview studies whose results are extrapolated to general assumptions of the use of OTC drugs in entire populations.

Even though the use of dietary supplements and CAM is extensive [58], and the substances may interact with the individual's conventional drugs, these are most often excluded in studies of drug use. A common reason for the exclusion is the poor sale statistics of non-regulated substances, but also the researcher's traditional focus on prescription medications.

## Measurements of drug use, multiple medication and polypharmacy

### *Drug use*

Drug use can be measured as e.g. the number of individuals that have ingested or have been prescribed or dispensed a drug during a specific period of time, or the number of individuals with drug use per 1,000 inhabitants. Drug use can also be measured as the average number of DDDs per individual of a specific drug that is prescribed or dispensed in a given population during a certain time period.

According to WHO, drug consumption figures should preferably be presented as number of DDDs/1,000 inhabitants/day. Sales or prescription data presented in DDDs/1,000 inhabitants/day may provide a rough estimate of the proportion of the population treated daily with certain drugs. For example, the figure 10 DDDs/1,000 inhabitants/day indicates that 1% of the population on average receives a certain treatment on a daily basis [51].

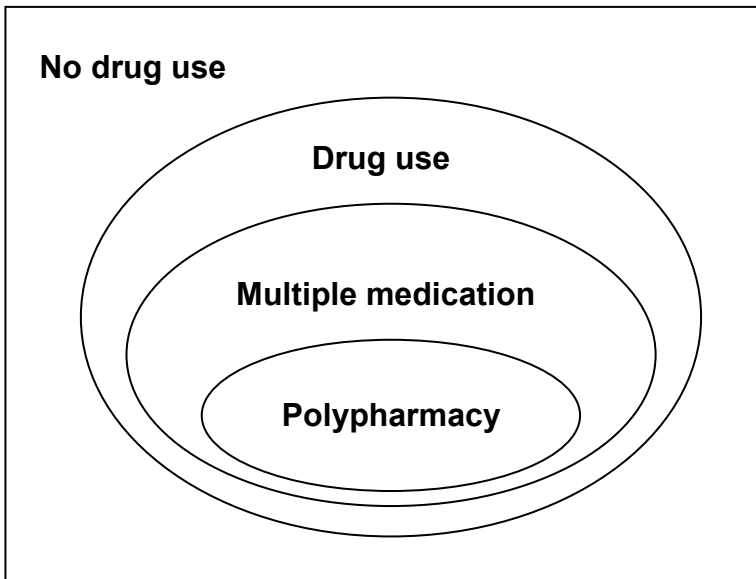
For anti-infectives (or other drugs normally used for short periods) it is often considered most appropriate to present the figures as the numbers of DDDs per inhabitant per year, which provides an estimate of the number of days for which each inhabitant is, on average, treated annually. For example, five DDDs/inhabitant/year indicates that the consumption is equivalent to the treatment of each inhabitant on the basis of a five days course during a given 12-month period [51].

### *Multiple medication*

Multiple medication is measured in terms of the number of individuals that have ingested, or have been prescribed or dispensed more than one drug during a certain period of time. Multiple medication always includes polypharmacy (Figure 6). However, as polypharmacy can be defined as the concurrent use of more than one drug, and since dispensed drugs during a 3-month period often is applied as an indicator of polypharmacy (see below), multiple medication has become a concept referring to the use of more than one drug during a time period longer than 3 months.

### *Polypharmacy*

Polypharmacy is defined as the concurrent use of different drugs and is, therefore, measured as the number of individuals ingesting a certain number of drugs on a particular day. However, polypharmacy may also be measured as a period prevalence, e.g. the number of prescribed or dispensed drugs during three months is used as an indicator of polypharmacy [59].



*Figure 6. Description of the relation between drug use, multiple medication and polypharmacy in a population.*

Based on estimation methods, polypharmacy can be divided into three sub-types: *cumulative polypharmacy* which counts the number of different drugs an individual has received during a particular period, usually 30 or 90 days with

the intent to use the shortest time interval capturing ongoing medication, but even 6 months has been seen to comprise the shortest interval that can identify the existence of ongoing medications [29]. Also the number of drugs purchased in a 3-month period was found to be valid in identifying individuals with polypharmacy [27]. A second method, *continuous polypharmacy*, only focuses on and counts which drugs an individual uses in two different time periods, e.g. two six months observation periods which are six months apart. A third method, *simultaneous polypharmacy*, estimates the number of drugs a patient is receiving at any given point in time [29]. The different estimate methods have varying strengths and weaknesses and address varying aspects of the drug use. Cumulative and continuous polypharmacy represent a period prevalence, while simultaneous polypharmacy represents point prevalence. Both period and point prevalence are occasionally estimated by using DDD, although there is no consensus as to whether it is preferable to purchase data [60].

As a threshold for polypharmacy, two or more [25, 61], three or more [62], four or more [63], five or more [24, 27, 35, 64-66] six or more [26, 61], seven or more [67], nine or more [68, 69] and ten or more [59, 64, 67, 70] drugs have been used. The majority of studies have used five or more (prescribed) drugs as the threshold for polypharmacy [30, 35, 64]. Over time, when the number of concomitantly used drugs increased, the focus on the number changed. Early studies of polypharmacy focused on the concurrent use of two, three, or four drugs. In an article from 1997, concomitant use of 2-4 drugs was defined as “minor” polypharmacy and the use of five or more drugs as “major” polypharmacy [27]. A commonly cited article from year 2000 classified 2-3 drugs as “minor”, 4-5 drugs as “moderate”, and six or more as major polypharmacy [61].

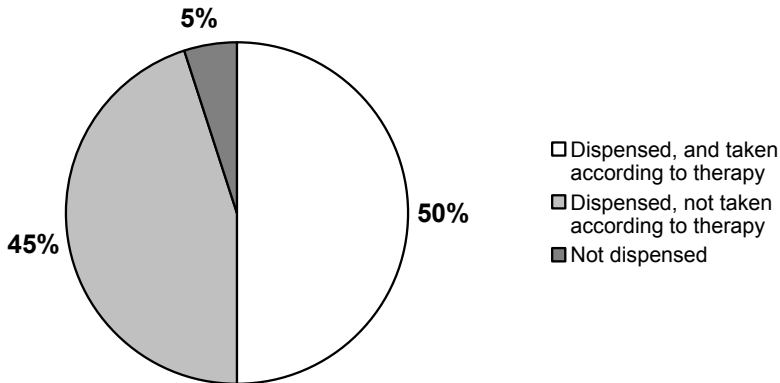
Today, the use of five or more drugs has become a form of standard “cut off” for clinically relevant polypharmacy, but the scale has also been extended and “excessive” polypharmacy, defined as the concurrent use of ten or more drugs, is also studied [49, 59, 70].

#### *Prescribed – dispensed – ingested*

Drug use, multiple medications and polypharmacy can be measured either as the number of drugs that are prescribed, dispensed, or ingested (consumed). The prescribed drugs reflect the prescribers’ recommended drug therapy of prescription drugs. Data regarding prescribed prescription drugs is available from doctors’ or health care institutions’ medical registers.

The volume of dispensed drugs reflects the drugs that the patient actually purchased from the pharmacies. Studies from different countries have shown that approximately 95-97% of all prescriptions are dispensed from a pharmacy [71, 72] (Figure 7). Data regarding dispensed prescription drugs is usually available

from pharmacy registers, either as aggregated sales statistics or individual-based data.



*Figure 7. Approximate share of prescribed drugs that are dispensed and taken according to drug therapy, dispensed but not taken according to drug therapy, or not dispensed [22, 72].*

Patients' adherence to prescribers' drug therapy is known to depend on several factors, including the number of medicines and the frequency of administration, side effects, and treatments alternatives [9, 73]. The adherence to therapy increases with the patient's age, and if the prescriber follows up the therapy [74]. The adherence to therapy also increases, if the patient regards the therapy as important and if the medication regime is designed after accounting the patients' existing routines [75]. Moreover, adherence is related to the acquisition cost of medication for patients [9].

Cost-related medication non-adherence may differ amongst countries due to the different health insurance and social security systems. In the US, up to 32% of older patients took less medication than prescribed to avoid cost [76] and in Sweden 1% of the total population and 4% of single parents with children did not have a prescription filled to avoid cost [3]. Studies from developing countries have reported that 90% of patients buy a three day supply, or less, of antibiotics making compliance with the recommended dosage impossible [77, 78].

## Occurrence

### Occurrence of prescription drugs, OTC drugs, CAM and dietary supplements use

#### *Prescribed drugs*

Prescribing medications to a patient is the most common therapy in the health care [4]. Consequently, a substantial proportion of the population use at least one prescription drug during a year, e.g. 81% of Americans age 57-85 years take at least one prescription drug on a regular schedule [2] and two thirds of all individuals in Sweden received at least one prescription drug during 2006 [3].

#### *OTC drugs*

Studies from US indicate that 42% of all individuals age 57-85 regularly use OTC drugs [2]. Individuals over 65 regularly use 1.8 OTC drugs [79] and individuals over 75 regularly use 2.5 OTC drugs [62]. Elderly people regularly use one OTC drug for every 2-3 prescribed drugs [80, 81]. These reports all suggest that OTC drugs comprise a considerable proportion of the total drug consumption for large groups of individuals.

#### *Dietary supplements*

Different studies display large differences regarding the prevalence of the use of dietary supplements. In one study, the estimated prevalence of dietary-supplement use among US adults was 73% in 2002 [82], and another study claims that 49% of individuals age 57-85 regularly use dietary supplements [2].

In Sweden, approximately one fourth of all individuals, age 16-84, and 22% of men and 33% of women, regularly use dietary supplements [83]. In Finland, a study indicated that a third of all men and half of all women used dietary supplements [84].

#### *CAM*

Studies also display large differences regarding the prevalence of the use of CAM, e.g. 40% of Americans 18 or older used some form of alternative medicine in 2007 [58] and 58% of patients in a university geriatrics primary care practice and a veterans medical clinic in US used some form of CAM [85].

In a survey of CAM in the Scandinavian countries, a prevalence of ever-use of CAM was 34% in Norway, 45% in Denmark, and 49% in Sweden [86]. In a sample survey in 1999 from Sweden, 31% reported having taken a CAM product the preceding two weeks. The use of CAM remedies was reported to be

more frequent in women than in men, and more frequent in people with high than with low levels of education [87].

However, according to WHO, the use of CAM is far more prevalent in other parts of the world than in US and Europe. If also non-medication therapies are included (e.g. acupuncture, manual therapies and spiritual therapies), CAM accounts for 40% of total delivered health care in China and four fifths of the population in Africa use CAM to meet their health care needs [45].

### **Occurrence of drug use, multiple medication and polypharmacy**

The observed occurrence of drug use in a population is dependent on the true occurrence and on the measurement, which has been applied in the estimates. Certain studies apply a point prevalence approach and display the number of individuals of different ages and gender having used a drug during a certain day or week. Other studies display the use of different types of drugs during longer study periods, e.g. 2-12 months. In addition to the large variations in the time periods, studies of multiple medication and polypharmacy have been conducted on the basis of different definitions, e.g. more than 2, 3, 4, 5, 6, 7, 9 or 10 drugs. Studies have been performed in different settings, e.g. out-patients, patients admitted to hospitals or nursing homes, patients with different ages, or with a focus on patients with different medical conditions, e.g. psychiatric diseases. The majority of the studies have been conducted in small samples of elderly individuals, but some have been population based. Due to the large variation in study settings, there is also a large variation in results regarding the prevalence of multiple medication and polypharmacy. Furthermore, there are also large differences in the types of drugs included in the different studies. As mentioned earlier, CAM and dietary supplements are seldom included. Many studies also focus on drugs for chronic therapy and, therefore, exclude as needed drugs, topical drugs and drugs for short time use such as antibacterials [63, 88, 89]. Other studies include only subsidized medication [27, 64] (Table 3).

#### *Drug use*

In the US, a total of 81% of individuals at least 18 years old regularly used some kind of drugs in 1999, and 50% used at least one prescription drug [1]. In 2005/06, 91% of all individuals aged 57 through 85 years regularly used at least one medication, 81% used at least one prescription drug, 42% used at least one OTC drugs, and 49% used a dietary supplement [2].

During 12 months in Denmark in 1994, a total of 58% of individuals age 16 and over used subsidized prescription drugs (oral contraceptives, sedatives and hypnotics were excluded in the study) [64]. In Sweden in 2008, two out of three individuals purchased at least one prescription drug [3].

**Table 3.** A selection of studies of drug use, multiple medication, and polypharmacy with different cut offs, data sources, length of study periods, age groups, and types of medications, and prevalence (%).

Cut off	Study	Data source		Study period					Age group	Type of medications				Prevalence %
		Inter-view	Regi-ster	Day 1	Week 1 2	Month 3 6 8 12	DP	OTC		CAM	DS			
≥1	[27]		X	X					16-	X(1)				21
≥1	[64]		X					X	16-	X(1)				58
≥1	[69]	X			X				65-	X	X			95
≥1	[52]		X				X		0-	X				60
≥1	[1]	X			X				18-	X	X	X	X	81
≥1	[62]	X		X					75-	X	X	X	X	97
≥1	[2]	X			X				57-85	X	X		X	91
≥1	[24]	X			X				77-	X	X			88
≥2	[27]		X	X					16-	X(1)				10
≥2	[64]		X					X	16-	X(1)				29
≥2	[61]		X				X		65-	X				42
≥3	[62]	X		X					75-	X	X			60
≥4	[63]		X					X	75-	X(2)				n i
≥5	[30]	X			X				77-	X	X			42
≥5	[59]		X			X			75-89	X				57
≥5	[35]			X					15-	X				47
≥5	[27]		X	X		X			16-	X(1)				1
≥5	[64]		X					X	16-	X(1)				5
≥5	[62]	X		X					75-	X	X	X	X	34
≥5	[1]	X			X				18-	X	X	X	X	25
≥5	[2]				X				57-85	X	X		X	51
≥6	[61]		X				X		65-	X				4
≥6	[26]	X			X				64-	X				25
≥6	[88]	X		X					70-	X(3)	X(3)			54
≥6	[69]	X			X				65-	X	X			51
≥7	[67]		X	X					65-	X	X			46
≥9	[69]	X			X				65-	X	X			22
≥10	[64]		X					X	16-	X(1)				3
≥10	[67]		X	X					65-	X	X			21
≥10	[59]		X			X			75-89	X				18
≥10	[1]	X			X				18-	X	X	X	X	5
≥20	[52]		X			X			0-	X				0.3

(1)= Only subsidized drugs (no contraceptives, sedatives or hypnotics) and drugs with establish DDD (no dermatological, ophthalmological, otological or antineoplastic drugs). (2)= Chronically prescribed drugs. (3)= Chronically prescribed drugs and OTC remedies in daily use. n i = no information.

### *Multiple medication and polypharmacy*

In 1998/99, a total of 25% of the population aged 18 and above in the US had taken five or more drugs a week (prescription drugs, OTC drugs, CAM and dietary supplements) and 5% had taken ten or more [1]. In 2005/2006, a total of 29% of all individuals aged 57 through 85 in the US regularly used at least five prescription drugs. Among prescription drug users, the concurrent use of OTC drugs was 46% and there was 52% concurrent use of dietary supplements [2].

In 1994 in Denmark, a total of 5% of individuals 16 and over used five or more subsidized drugs and 3% used ten or more subsidized drugs [64].

In the total population in Sweden, 20% of women and 13% of men had five or more dispensed prescription drugs during six months in 2005, 3% of men and 6% of women had ten or more dispensed prescriptions in the same time period [52].

To summarize, the knowledge regarding individual use of prescription drugs appears to be fairly good, but there is little knowledge as regards the individual use of OTC drugs, CAM and dietary supplements. Consequently, there is also a lack of knowledge concerning individuals' combinations of the different types of medications, e.g. how many individuals of different ages and gender combine prescription drugs, OTC drugs and CAM, in conjunction with or without dietary supplements.

If the pattern expands to also include individuals with multiple medication or polypharmacy, the uncertainty of the prevalence of various strata becomes even greater. The large variations in age groups, cut offs, study periods and types of medications between studies make it difficult to compare results.

## Consequences

The use of medication is intended to have a beneficial effect on patient health and the quality of life. However, the use of medications does not only have beneficial effects on humans. The use of medications, and especially the use of multiple medications, is also associated with the risks of negative consequences.

### **Adverse drug reaction (ADR)**

Many medications may result in an adverse drug reaction (ADR), defined as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" [90]. ADRs are usually classified as mild, moderate, severe or lethal. ADR can also be classified into six different types; "dose-related (Augmented, also known as "Type A"), non-dose-related (Bizarre, also known as "Type B"), dose-related and time-related (Chronic), time-related (Delayed), withdrawal (End of use), and failure of therapy (Failure)." [91]. Whether an ADR will occur and how severe it will be, vary with regard to the drug and the individual's specific circumstances.

#### *Hospitalization due to ADR*

ADR represents a substantial proportion of all admissions to hospitals and a sizable proportion of the health care costs. A review of 25 studies indicates that approximately 5-6% of hospital admissions were associated with ADRs [92].

In Sweden, admission to hospitals due to ADR has increased from 6% during the 1970's to 11-13 % after year 2000 [93] and a study from 2008 indicated that 27% of all admissions in the medical emergency department at a university hospital in Stockholm were caused by ADRs [94]. Almost all ADRs are well-known pharmacological (type A) reactions being, at least theoretically, preventable [95].

#### *Deaths*

Deaths caused by ADRs are estimated to be the fourth most common death cause in US hospitals [96]. A study from Norway indicates that 18% of deaths in departments of internal medicine were caused by ADRs [97]. A recent study from Sweden estimates that ADRs cause 3,000 deaths each year in Sweden, corresponding to approximately 3.3% of all deaths [98].

## Interactions

The effect of a medication can be influenced by other medications that the individual may be taking (drug-drug interaction), by food, beverages or supplements that the individual is consuming (nutrient-drug interactions), and by another disease in the individual (disease-drug interactions).

### *Drug-drug interactions*

Drug-drug interactions include prescription drugs, OTC drugs, and CAM, and can be classified in a mechanistic manner [99].

Another classification of drug-drug interactions is Duplication, Opposition/antagonism and Alteration. Duplication occurs when an individual inadvertently takes two drugs with the same active substance or two drugs with the same effect. The result may be unwanted side effects. Two drugs with opposing effects may also interact and cause a reduction of the desired effect of one, or both, drugs. Alteration is when a drug may alter the manners in which the body absorbs, distributes, or metabolizes another drug.

Drug-drug interactions can also be classified on the basis of clinical relevance into type A, B, C, or D (Table 4) [100]. 70% of all interactions are Type C (dose adjustment may be needed) or D (the combination should be avoided) [101].

**Table 4.** Classification of drug-drug interactions after clinical relevance [100].

Interaction classification	Clinical relevance
Type A	Probably no clinical relevance
Type B	Clinical relevance not completely assessed
Type C	The interaction may modify the effect of the drug, however this can be mastered by individual dose adjustment, and /or by determination of the plasma concentration of the drug
Type D	The interaction may have serious clinical consequences, such as severe adverse effects, no effects, or the modified effects may be difficult to control by individual dose adjustment.

Drug-drug interactions can also be classified as major, moderate, or minor depending on the severity of the outcome [102].

Theoretically, the risk for drug-drug interactions increases exponentially with the number of ingested drugs [28, 103], e.g. for five drugs there are ten possible one to one interactions, for ten drugs there are 45, for 15 drugs there are 105

and for 20 drugs are 190 possible interactions (Figure 8). Also, studies have displayed a strong association between the number of dispensed drugs and the probability of potential interactions [104].

There are several databases on the market supporting the prescriber to detect any potential interaction, e.g. SFINX [105].

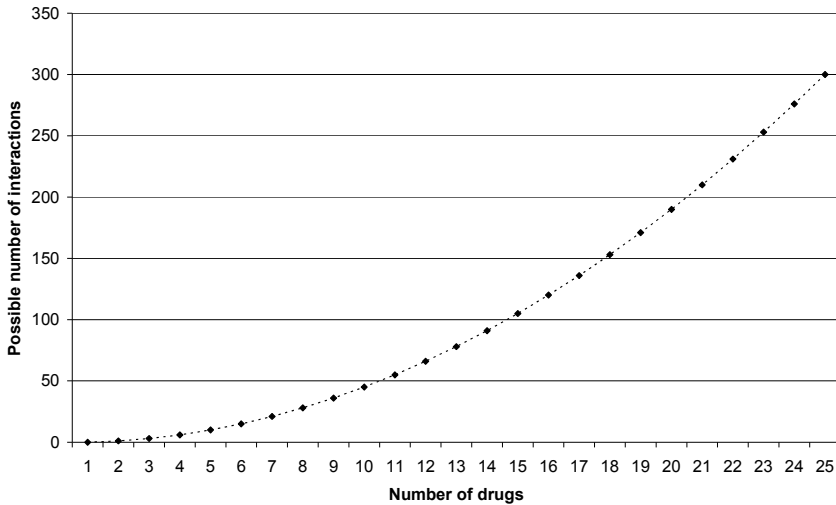


Figure 8. The number of possible one to one drug interactions with increasing number of drugs.

#### *Nutrient-drug interactions*

Nutrient-drug interactions include herbs and vitamins, which can interact with drug-metabolizing enzymes. One well known example is St. John's worth that can interact with several important medications [101]. Colas, coffee, and chocolate containing caffeine are known to possibly interact with certain antibiotics, and grapefruit juice and alcohol are also known to interact with certain drugs [101].

#### *Disease-drug interactions*

Disease-drug interactions occur when a disease is worsened due to a drug given for a reason other than to treat that disease. Potential disease-drug interactions are common in hospitalized elderly patients [106]. To prevent disease-drug interactions, there are clinical guidelines regarding drugs and drug classes the physician should avoid prescribing to patients with certain diseases [107]. Disease-drug interactions have been categorized on the basis of clinical importance in a 5-point Likert scale (from 1 = definitely not serious to 5 = definitely serious) [108].

## **Medication errors**

Drug use and multiple medications are also associated with the risk of medication errors. A medication error is a failure in the treatment process that might result in harm to the patient. Medication errors may occur in deciding which medicine and dosage regimen to use; writing the prescription; manufacturing the formulation; dispensing the formulation; administering or taking the medicine; and monitoring the therapy. Medication errors can be classified as knowledge-, rule-, action- and memory-based errors [19]. Medication errors can lead to serious consequences but are often trivial [19].

## **Non-adherence to drug therapy**

Patients' adherence to drug therapy is essential in optimizing the disease treatment, and non-adherence is associated with poor health outcomes [109-111]. The use of multiple medications and polypharmacy is commonly associated with non-adherence and it is assumed that the rate of non-adherence increases with an increasing number of prescribed drugs [23, 27-29, 31].

## **Inappropriate prescribing**

There exist several criteria for classifying inappropriate prescribing, almost all with the focus on elderly individuals' drug use; e.g. "Beers criteria" [112], "IPET" [113], "START" [114], "STOP" [115], "McLeod" [116] and "MAI" [117]. Furthermore, studies have been conducted which apply a combination of several of the more well known criteria [118].

Two of the most frequently applied criteria are the Beers criteria and Medication Appropriateness Index (MAI). Beers' Criteria originally included a list of drugs to be avoided in the elderly nursing home population but have successively been updated and modified to be used in community-dwelling elderly too [119]. Medication Appropriateness Index (MAI) measures the overall prescribing quality in 10 separate areas, without any specific list of drugs to be avoided [117].

According to Beers' Criteria, the prescription of potentially inappropriate medications to older people is highly prevalent in the United States and Europe, ranging from 12% in community-dwelling elderly to 40% in nursing home residents [120].

## **Underuse of medication**

Studies of polypharmacy have shown that the use of many different drugs is often associated with inappropriate medication use and underuse. In a sample study from the US, 64% of outpatients, age 65 and older with five or more medications, were not using one or more indicated medication [33].

In a study from the Netherlands, a relationship between polypharmacy (patients with five or more drugs) and underprescribing was also noted. Of patients with polypharmacy, 43% were undertreated in comparison with 14% of patients using four medicines or less, and the probability of underprescribing increased with the number of drugs [66].

## **Medical cascade effects**

Multiple medications are also associated with the risk of “medical cascade” effects or “prescribing cascades”. The prescribing cascades are initiated when an ADR is misinterpreted as a new medical condition, leading to the prescription of additional drugs. Thereafter, a new adverse reaction may occur that can be mistakenly diagnosed as a new medical problem, which may lead to additional number of prescriptions of medications [4, 32].

## Aims of the thesis

The overall aim of this thesis was to investigate the occurrence and development of drug use, multiple medication, and polypharmacy in an entire national population by using individual-based data on dispensed drugs.

The specific aims addressed in the five different studies are summarized below.

1. To estimate the prevalence of dispensed drugs and multiple medications in an entire national population.
2. To assess polypharmacy in a population with an emphasis on regions.
3. To assess the prevalence and the therapeutic intensity of dispensed drug groups for individuals with multiple medications.
4. To estimate the acquisition costs of dispensed drugs for individuals with multiple medications in a national population.
5. To analyze the development of drug use and polypharmacy in an entire national population during a 4-year period.

# Materials and methods

## Materials

The five studies in this thesis are all based on data from the Swedish Prescribed Drug Register. This data cover different time periods between July 2005-Sept 2008, and the data has been analyzed with epidemiological measures and statistical methods (Table 5).

**Table 5.** Overview of the studies in the thesis.

Study	Period	Research question	n	Methods	Variables
I	Jan-March 2006	Estimate prevalence of drug use and multiple medication	4,108,730	Individual-based register study, prevalence, RR	Age groups, gender, ATC-groups
	Jan- June 2006		5,117,817		
	Jan-Dec 2006		6,146,676		
II	July-Sept 2006	Assess prevalence of polypharmacy with emphasis on regions	3,934,348	Individual-based register study, prevalence, polypharmacy index, age standardization, binary correlation	Age groups, gender, regions, 14 socioeconomic variables
III	Jan-Dec 2006	Assess prevalence and therapeutic intensity of dispensed drug groups for individuals with multiple medications	6,150,573	Individual-based register study, prevalence, RR, therapeutic intensity	Age groups, gender, ATC-groups, DDD
IV	Jan-Dec 2006	Estimate the acquisition cost of dispensed drugs for individuals with multiple medications	6,150,573	Individual-based register study, prevalence, cost ratio	Age groups, gender, ATC-groups, DDD acquisition cost
V	July-Sept 2005	Analyze trends in drug use and polypharmacy over 4 years	3,844,594	Trends from four individual-based register studies, prevalence	Age groups, gender
	2006		3,929,650		
	2007		3,964,455		
	2008		4,016,521		

## The Swedish Prescribed Drug Register

The Swedish Prescribed Drug Register is individual-based and contains data from all dispensed out-patient prescriptions at all Swedish pharmacies from July 1, 2005, including multi-dose dispensed prescriptions and legal Internet sales. The registration is mandatory and includes information on patient, drug, prescriber, and pharmacy (Table 6). All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. Measurement units for utilization are DDD. The Pharmacies Service Company (Apotekens Service AB) administers the data collection from all Swedish pharmacies. Information is transferred monthly from the Swedish National Pharmacy Register [121] to the Swedish Prescribed Drug Register at the National Board of Health and Welfare, which is responsible for maintaining the register. The registered data cover the entire Swedish population and can be linked to other registers by using the personal identification numbers. The use of the data in the register is, on the basis of a specific statute (SFS 2005:363), restricted to epidemiological investigations, research and the production of health care statistics.

**Table 6.** Information content in the Swedish Prescribed Drug Register.

Object	The Swedish Prescribed Drug Register
Patient	Personal identification number (Age, sex and unique identifier)
	Place of residence of the patient (County, municipality and parish)
Drug	Substance
	Brand name
	Formulation
	Package
	Amount
	Dosage
	Expenditure
	Reimbursement
Prescriber	Date of prescribing
	The practice (Primary health care center or hospital)
	The prescribers profession (e.g. GP, psychiatry or pediatrics)
Pharmacy	Date of dispensing

## **Study design (I-V)**

In the studies, all data was extracted from the Swedish Prescribed Drug Register. The data processing was undertaken anonymously without the personal identification number. Only gender and year of birth, originally embedded in the personal identification number, were recorded. The study population was stratified according to gender and age (10-year classes). The results were compared to the number of individuals per gender and age group in the Swedish population.

The definition of drug was the chemical entity or substance comprising the fifth ATC level.

### **Study I. Dispensed drugs and multiple medications in the Swedish population**

To estimate the prevalence of dispensed drugs and multiple medications in an entire population, a study was conducted including the individual-based data concerning dispensed prescription drugs in the entire Swedish population between January 1, 2006 and December 31, 2006. 6,146,676 individuals (outpatients) with dispensed prescription drugs at Swedish pharmacies January-December 2006 were included in the study (Table 5).

For comparison, two shorter study periods; a 3-month period (1 January – 31 March 2006) with 4,108,730 individuals, and a 6-month period (1 January – 30 June 2006) with 5,117,817 individuals were studied. The prevalence of five or more dispensed drugs ( $DP \geq 5$ ) when certain drug groups were excluded (sex hormones, antibacterials for systemic use, and psycholeptics) was also studied.

The values applied were the number of individuals (all, women and men) and the number of dispensed prescription drugs (substance) per individual.

### **Study II. Regional variation of polypharmacy**

To analyze polypharmacy with respect to regions, a study was conducted including the individual-based data concerning dispensed prescription drugs in the entire Swedish population between July 1, and September 31, 2006. 3,934,348 individuals (outpatients) with dispensed prescription drugs at pharmacies in the 21 regions of Sweden July-September 2006 were included in the study (Table 5).

The correlation between the regional variation of the prevalence of polypharmacy and a set of selected regional socioeconomic variables was tested; the proportion of individuals aged  $\geq 70$ , life expectancy, the unhealthy rate in age 24-64, the proportion of men and women in the working population age 20-64, the proportion of individuals with high and low income, average level of education, and the working physicians per 100,000 individuals.

The values applied were the number of individuals (all, women and men), place of residence (county) and the number of dispensed prescription drugs (substance) per individual.

When applying a weighted polypharmacy index (see below), outliers were excluded, defined as individuals with more than 25 different substances dispensed during the 3-month study period. Thereby, 1,112 individuals, corresponding to 0.03% of all individuals with  $DP \geq 1$ , were excluded.

### **Study III. Prevalence and therapeutic intensity of dispensed drug groups for individuals with multiple medications**

To assess the prevalence and the therapeutic intensity of dispensed drug groups for individuals with multiple medications, a study was conducted including the individual-based data concerning dispensed prescription drugs in the entire Swedish population between January 1, 2006 and December 31, 2006. 6,150,573 individuals (outpatients) with dispensed prescription drugs at Swedish pharmacies January-December 2006 were included in the study (Table 5).

The values applied were the number of individuals (all, women and men), the number of DDD per individual and the number of dispensed prescription drugs (substance) per individual.

All dispensed drugs at the fifth ATC level were categorised and displayed as sets of 86 therapeutic drug groups, according to the second level in the ATC classification.

### **Study IV. The acquisition cost of dispensed drugs for individuals with multiple medications**

To estimate the acquisition costs of dispensed drugs for individuals with multiple medications in a national population, a study was conducted including the individual-based data concerning dispensed prescription drugs in the entire Swedish population between January 1, 2006 and December 31, 2006. 6,150,573 individuals (outpatients) with dispensed prescription drugs at Swedish pharmacies January-December 2006 were included in the study (Table 5).

The acquisition cost was measured in the Swedish currency “Svenska kronor” (SEK) and on the basis of 2006 prices.

The values applied were the number of individuals (all, women and men), the number of DDD per individual, the number of dispensed prescription drugs (substance) per individual and expenditure (acquisition cost in SEK) per dispensed drug (substance).

### **Study V. Increasing polypharmacy**

To analyze the development of drug use and polypharmacy in an entire national population during a 4-year period, a study was conducted including the individual-based data concerning dispensed prescription drugs in the entire Swedish population during four 3-month periods (July, August and September) 2005-2008. 3,844,594 (2005), 3,929,650 (2006), 3,964,455 (2007) and 4,016,521 (2008) individuals (outpatients) with dispensed prescription drugs at Swedish pharmacies July-September, 2005-2008, were included in the study (Table 5).

The values applied were the number of individuals (all, women and men), and the number of dispensed prescription drugs (substance) per individual.

## Methods (I-V)

### Prevalence of drug use, multiple medication and polypharmacy

In the five studies, drug use, multiple medication and polypharmacy were measured as prevalence - the proportion of individuals in the Swedish population getting prescriptions filled during the study periods. Depending on the objective of the study - drug use, multiple medication or polypharmacy - different cut offs for the number of dispensed drugs and different study periods were applied (Table 7).

#### *Study I*

As a definition for the individual drug use, one or more dispensed prescription drugs during a 12-month period ( $DP \geq 1$ ) were applied. The prevalence of drug use was defined as the proportion of individuals receiving one or more dispensed drugs during a 12-month period. As a cut off for multiple medications, five or more dispensed prescription drugs during a 12-month period ( $DP \geq 5$ ) were applied. The prevalence of multiple medications was defined as the proportion of individuals receiving five or more dispensed drugs during a 12-month period.

#### *Study II*

As a cut off for polypharmacy, five or more dispensed prescription drugs (substance) during a 3-month period ( $DP \geq 5$ ) were applied. For comparison, one or more dispensed prescription drugs ( $DP \geq 1$ ), "drug use", and ten or more dispensed prescription drugs ( $DP \geq 10$ ), "excessive polypharmacy", during a 3-month period were also applied. The prevalence of  $DP \geq 1$ ,  $DP \geq 5$  and  $DP \geq 10$  were consequently defined as the proportion of individuals who had  $\geq 1$ ,  $\geq 5$  or  $\geq 10$  drugs dispensed respectively during a 3-month period.

#### *Study III*

The utilization of drugs was defined as number of individuals (patients) exposed per 1,000 inhabitants (PAT/TIN). As a cut off for multiple medications, five or more dispensed prescription drugs during a 12-month period ( $DP \geq 5$ ) were used. For comparison and analysis one or more, ten or more and fifteen or more dispensed prescription drugs during a 12-month period ( $DP \geq 1$ ,  $DP \geq 10$ , and  $DP \geq 15$ ) were also applied. The prevalence of  $DP \geq 1$ ,  $DP \geq 5$ ,  $DP \geq 10$  and  $DP \geq 15$  was consequently defined as the proportion (%) of individuals receiving  $\geq 1$ ,  $\geq 5$ ,  $\geq 10$ , and  $\geq 15$  dispensed drugs, respectively, during a 12-month period.

#### *Study IV*

As a cut off for multiple medications, five or more dispensed prescription drugs during a 12-month period, ( $DP \geq 5$ ) were applied. For comparison and analysis, one or more ( $DP \geq 1$ ), ten or more ( $DP \geq 10$ ), and 15 or more ( $DP \geq 15$ ) dispensed prescription drugs during a 12-month period were used. For comparison, selections of individuals, groups of individuals with 1-4 ( $DP1-4$ ), 5-9 ( $DP5-9$ ), 10-14 ( $DP10-14$ ), 15-19 ( $DP15-19$ ), and 20 or more ( $DP20-$ ) dispensed prescription drugs during a 12-month period were also used.

#### *Study V*

The prevalence of dispensed drugs was defined as the proportion of individuals receiving one or more dispensed drugs ( $DP \geq 1$ ) during any of the four 3-month periods. As a definition of polypharmacy and excessive polypharmacy, five or more ( $DP \geq 5$ ) and ten or more ( $DP \geq 10$ ) respectively dispensed prescription drugs for an individual during the study period was applied. The prevalence of polypharmacy and excessive polypharmacy was defined as the proportion of individuals receiving five or more and ten or more dispensed drugs, respectively, during any of the four 3-month periods.

#### **Relative risk**

In study I, relative risk (RR) was measured as the relative prevalence for women vs. men for  $DP \geq 5$  during the study periods. For gender comparison in study III, the women-men prevalence ratio (all with  $DP \geq 5$ ) for different drug-groups was calculated. As cut-offs, a prevalence ratio of 0.7 and 1.5 was applied (Table 7).

#### **Therapeutic intensity**

In study III, therapeutic intensity was measured as DDD/1,000 inhabitants per day (DDD/TID) and DDD/per individual for individuals with  $DP \geq 1$ ,  $DP \geq 5$ ,  $DP \geq 10$ , or  $DP \geq 15$  (Table 7).

#### **Cost ratio**

For gender comparison in study IV, a cost ratio was measured as the ratio between average acquisition cost per DDD for women, and average acquisition cost per DDD for men, for individuals with  $DP \geq 5$ , and  $DP \geq 10$ .

#### **Indices**

As a measure for comparing the prevalence of polypharmacy between regions, a polypharmacy index, for which the national prevalence equals index 100, was used in study II. The polypharmacy index for each region was thereafter

calculated as the regional prevalence divided by the national prevalence\*100. As an improvement of the “straight” polypharmacy index, a weighted polypharmacy index was constructed in which the differences in the prevalence of different number of dispensed drugs in a population were taken into account.

**Table 7.** Applied definitions of drug use, multiple medications, polypharmacy, excessive polypharmacy, relative risk, therapeutic intensity, cost ratio and indices, in study I-V.

<b>Study</b>	<b>I</b>	<b>II</b>	<b>III</b>	<b>IV</b>	<b>V</b>
<b>Drug use</b>					
DP≥1 during 3 months	X	X			X
DP≥1 during 6 months	X				
DP≥1 during 12 months	X		X	X	
<b>Multiple medications</b>					
DP≥5 during 6 months	X				
DP≥5 during 12 months	X		X	X	
DP≥10 during 12 months			X	X	
DP≥15 during 12 months			X	X	
DP≥20 during 12 months				X	
<b>Polypharmacy</b>					
DP≥5 during 3 months	X	X			X
<b>Excessive Polypharmacy</b>					
DP≥10 during 3 months			X		X
<b>Relative risk, RR</b>					
Relative prevalence for women vs. men for filling a prescription	X		X		
<b>Therapeutic intensity</b>					
DDD/individual, DDD/1000 inhabitant				X	
<b>Cost ratio</b>					
Ratio between average acquisition cost per DDD for women and men				X	
<b>Indices</b>					
A straight polypharmacy index			X		
A weighted polypharmacy index			X		

## **Ethical considerations**

The use of data from the Swedish Prescribed Drug Register for research is regulated by Swedish law (SFS 2005:363) in order to protect the personal integrity. In addition, permission from ethical research committees is required. Only non-identifiable data were used in this thesis and studies I-V were approved by the Regional Ethical Review Board in Linköping, Sweden (Dnr M117-08).

## Results (I-V)

### Study I: Dispensed drugs and multiple medications in the Swedish population: an individual-based register study

To estimate the prevalence of dispensed drugs and multiple medications in an entire national population, the study used individual-based data on dispensed drugs. A total of 6.2 million individuals received at least one dispensed drug (DP $\geq$ 1) during 12 months in 2006 corresponding to a prevalence of 67.4%; 75.6% for females and 59.3% for males. Individuals received on average 4.7 dispensed drugs per individual (median 3, Q1-Q3 2-6); females 5.0 (median 3, Q1-Q3 2-7), males 4.3 (median 3, Q1-Q3 1-6). The prevalence of multiple medications (DP $\geq$ 5) was 24.4% for the entire population. The prevalence increased with age. For elderly 70-79, 80-89, and 90+, the prevalence of DP $\geq$ 5 was 62.4, 75.1, and 77.7% in the respective age groups (Figure 9). A total of 82.8% of all individuals with DP $\geq$ 1 and 64.9% of all individuals with DP $\geq$ 5 were <70. Multiple medications were more frequent for females (29.6%) than for males (19.2%). Sex hormones and modulators of the genital system excluded, reduced the relative risk (RR) for females vs. males for DP $\geq$ 5 from 1.5 to 1.4. The prevalence of DP $\geq$ 1 increased from 45.1 to 56.2 and 67.4%, respectively, when the study period was 3, 6, and 12 months respectively and the corresponding prevalence of DP $\geq$ 5 was 11.3, 17.2, and 24.4%, respectively.

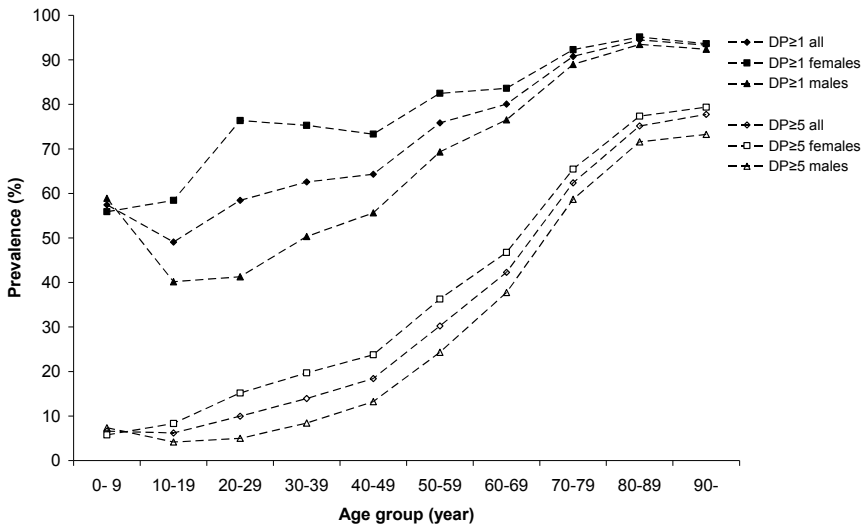


Figure 9. Prevalence (%) of DP $\geq$ 1 and DP $\geq$ 5 related to gender and age in Sweden in 2006 (Study I).

## Study II: Assessment of regional variation in polypharmacy

To assess polypharmacy in a population with emphasis on regions, the study applied individual-based data for all dispensed prescription drugs (DP) during a 3-month study period in Sweden 2006. The national prevalence of polypharmacy, DP $\geq$ 5, was 10.5% (inter-regional variation 9.1 to 12.1%). The regional variation in the prevalence of polypharmacy was largest for the age groups  $\geq$ 90 (45.6 to 59.1%), 80-89 (46.1 to 53.4%), and 70-79 (33.1 to 38.0%). The national prevalence of excessive polypharmacy, DP $\geq$ 10, was 2.2% (inter-regional variation 1.9 to 2.6%). The regional variation in prevalence of excessive polypharmacy was largest for the age groups  $\geq$ 90 (9.8 to 22.3%), 80-89 (11.4 to 17.1%), and 70-79 (7.0 to 9.4%). Fairly strong positive correlations between polypharmacy and the age group  $\geq$ 70 were found for men and women ( $r=0.84$  for men and 0.71 for women). A novel weighted polypharmacy index indicated regional differences in the internal distribution of the prevalence of dispensed drugs for individuals with polypharmacy (Figure 10).

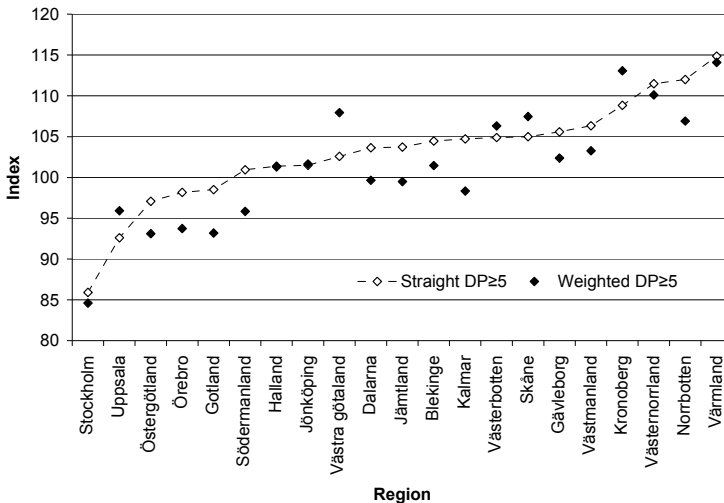


Figure 10. A straight and a weighted polypharmacy DP $\geq$ 5 index, for different regions in Sweden 2006. National mean = index 100 (Study II).

### Study III: Prevalence and therapeutic intensity of dispensed drug groups for individuals with multiple medications: a register based study of 2.2 million individuals

To assess the prevalence and the therapeutic intensity of dispensed drug groups for individuals with multiple medications, the study analyzed the individual-based data of all dispensed out-patient prescriptions in Sweden in 2006. For the 2.2 million individuals with  $DP \geq 5$ , the drug groups with the highest prevalence were antibacterials (48.2%), analgesics (40.3%), psycholeptics (35.9%), antithrombotic agents (33.4%), and beta blocking agents (31.7%). The prevalence increased with age for e.g. analgesics, psycholeptics, antithrombotic agents, and diuretics, and decreased with age for e.g. antibacterials, drugs for obstructive airway diseases and antihistamines for systemic use (Figure 11). Substantial differences in prevalence between women and men were observed for several drug groups, e.g. thyroid therapy (13.3 vs. 3.6%), psychoanalectics (26.3 vs. 18.2%), drugs used in diabetes (9.1 vs. 15.7%), and lipid modifying agents (18.1 vs. 30.7%). Generally, the therapeutic intensity increased with increasing number of dispensed drugs. For a third of the most common drug groups, the therapeutic intensity increased with an increasing age above the age group 60-69.

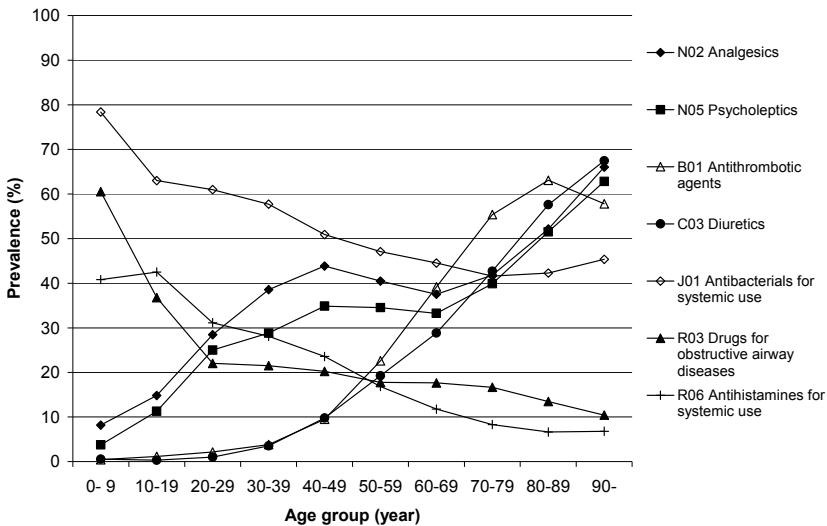


Figure 11. The prevalence for the dispensed ATC-groups: analgesics, psycholeptics, antithrombotic agents, diuretics, antibacterials, drugs for obstructive airway diseases, and antihistamines for systemic use for individuals with  $DP \geq 5$  in different age groups in Sweden in 2006 (Study III).

## Study IV: Acquisition cost of dispensed drugs for individuals with multiple medications – a register-based study

To estimate the acquisition cost of dispensed drugs for individuals with multiple medications in a national population, the study analyzed individual-based data of all dispensed drugs in Sweden in 2006. The total acquisition cost of dispensed drugs in Sweden in 2006 was SEK 23.2 billion (corresponding to EUR 2.5 billion 2006). Individuals with  $DP \geq 5$  (24.5% of total population) accounted for 78.8% of the total drug cost, and individuals with  $DP \geq 10$  (8.6% of population) and  $DP \geq 15$  (3.0% of population) accounted for 46.3% and 23.2% respectively (Figure 12). Individuals with  $DP \geq 5$  younger than 70 (corresponding to 64.9% all individuals with  $DP \geq 5$ ) accounted for 64.7% of the total acquisition cost for all with  $DP \geq 5$ . The highest total drug cost for individuals with  $DP \geq 5$  was displayed in the age group 60-69 followed by 70-79 and 50-59, 21.5%, 19.8%, and 17.4%, respectively. The average acquisition costs per daily defined doses (DDD) generally decreased with increasing age. For individuals with  $DP \geq 5$ , the average cost per DDD decreased from SEK 8.04 to SEK 2.27 (-72%) for the age group 10-19 to 90 and above. The highest average cost per DDD was observed for individuals with  $DP \geq 10$ . The drug cost for women with  $DP \geq 5$  (corresponding to 60.9% all individuals with  $DP \geq 5$ ) represented 56.0% of the total cost. Men with  $DP \geq 5$  (corresponding to 39.1% all individuals with  $DP \geq 5$ ) represented 44.0% of the total cost.

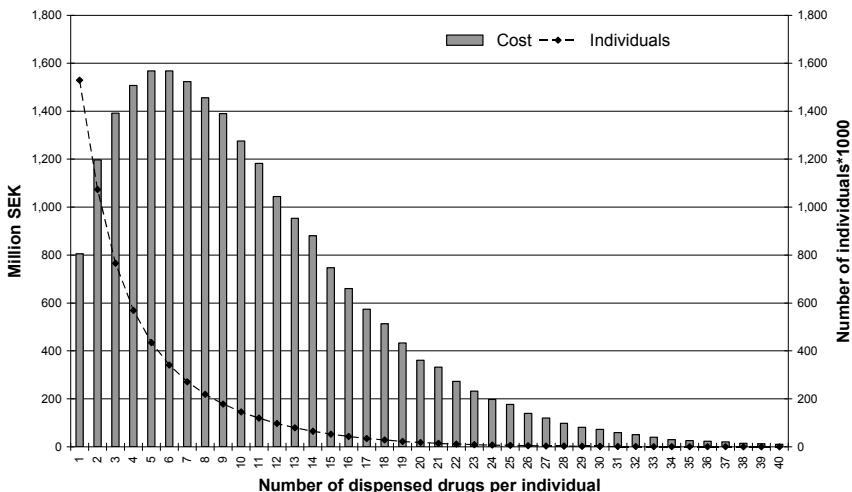
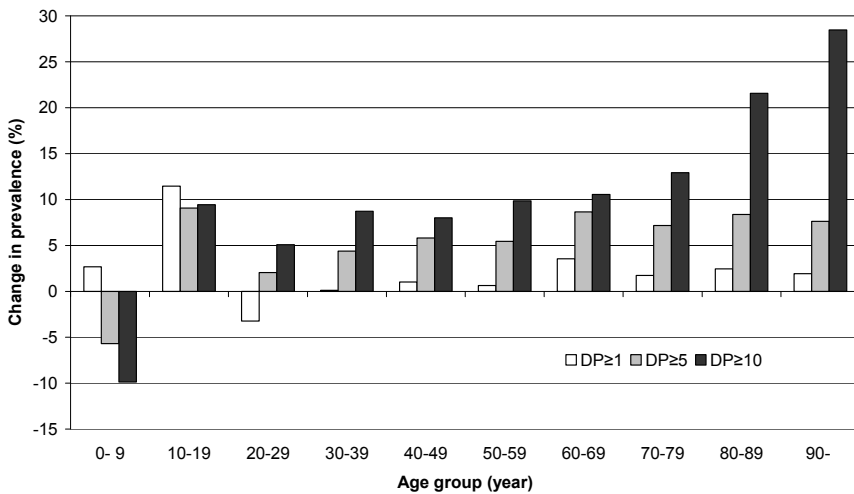


Figure 12. Acquisition cost and number of individuals with different number of dispensed drugs in Sweden in 2006 (Study IV).

## Study V: Increasing polypharmacy – an individual-based study of the Swedish population 2005-2008

To analyze the development of the prevalence of drug use and polypharmacy in an entire national population during a 4-year period, individual-based data on dispensed drugs during a 3-month period during 2005-2008, from the Swedish Prescribed Drug Register was used. During 2005-2008, the prevalence of drug use (DP $\geq$ 1) in the entire Swedish population increased by 2.3% (from 0.426 to 0.436). The prevalence of polypharmacy (DP $\geq$ 5) increased by 8.2% (from 0.102 to 0.111), and the prevalence of excessive polypharmacy (DP $\geq$ 10) increased by 15.7% (from 0.021 to 0.024). With exception for the age group 0-9 years, the prevalence of polypharmacy and excessive polypharmacy increased in all age groups. The prevalence of excessive polypharmacy displayed a clear age trend, with the largest increase for the age groups 70 years and above (Figure 13). Generally, the increase in the prevalence of polypharmacy was about twice as high for men as for women. The mean number of dispensed drugs per individual increased by 3.6% (from 3.3 to 3.4), during 2005-2008.



*Figure 13. The change (%) in prevalence of dispensed drugs (DP $\geq$ 1), polypharmacy (DP $\geq$ 5), and excessive polypharmacy (DP $\geq$ 10) in different age groups in Sweden during 2005-2008 (Study V).*

## Discussion

### **Prevalence of drug use, multiple medication, and polypharmacy in an entire population**

The presented prevalence level of drug use and multiple medication in the entire Swedish population can be deemed to be rather high; two thirds of all inhabitants use at least one prescription drug, and one out of four individuals uses five or more different drugs during a year. However, in comparison with the few available studies, Sweden seems to have approximately the same prevalence of drug use as other countries in the Western society [1, 64].

### **Age structure of drug use, multiple medication, and polypharmacy**

Drug use, multiple medication, and polypharmacy increase with age, but the studies underline that multiple medication and polypharmacy are relevant not only as regards the elderly; two out of three individuals with five or more dispensed drugs during 12 months, and half of the individuals with polypharmacy – five or more drugs during three months – were under 70. The regional variation of polypharmacy correlated with age, in that polypharmacy increased with increasing age, which is in line with previous studies [64].

The traditional focus on the drug use of the elderly and the efforts to achieve more appropriate drug therapy for elderly seems most relevant since elderly use more drugs and are more vulnerable for medications due to the natural ageing. However, we should also remember that today's middle age population will become the elderly in the future, and they will probably have an even higher prevalence of polypharmacy than the elderly of today, if not a drastic decrease in drug use will occur in the future.

### **Gender structure and drug use, multiple medication and polypharmacy**

The studies presented in this thesis confirm that women have a higher prevalence of drug use, multiple medication, and polypharmacy than men [64]. However, this is not a constant quota; between 2005 and 2008 the relative risk for women vs. men of receiving a prescription drug, of receiving five or more and ten or more drugs all decreased due to the relatively larger increase in polypharmacy and excessive polypharmacy for men. It remains to see if the present trend will continue.

## **The drug mix for individuals with multiple medication**

The most commonly dispensed ATC-groups for individuals with multiple medication were to a large extent also the most commonly dispensed ATC-groups for all individuals with drug use. This indicates that individuals with multiple medication have the same characteristic diseases and drug use as all drug users, but in addition, they also use drugs for other diseases. Nearly half of all individuals with five or more different drugs during 12 months received at least one cure of antibacterials and were also dispensed analgesics. In contrast to the present study, previous studies of multiple medication or polypharmacy, have often focused on drugs prescribed to be taken regularly and have, therefore, not reported the high use of as needed and temporarily used prescription drugs [63, 88]. Thereby, the potential risks regarding multiple drug use may have been underestimated.

## **The acquisition cost for drugs dispensed to individuals with multiple medication**

That individuals with ten or more dispensed drugs accounted for nearly 50% of the acquisition costs of all dispensed drugs in Sweden reflects that these individuals are prescribed large proportions of all DDD. In the perspective that the concurrent use of ten or more drugs in a medical context might be regarded as an excessive and inappropriate drug therapy, the proportion of the drug costs seems remarkable. Thus, interventions to reduce the number of prescription drugs for the small group of patients with many different drugs seems well motivated, and may consequently also give a substantial reduction of the total drug costs. Furthermore, the reduction of the number of prescription drugs will also reduce the risks for ADRs, and interactions.

## **Development of drug use and polypharmacy**

The increase of the prevalence of polypharmacy and excessive polypharmacy during 2005-2008 followed two different lines. The efforts to reduce the prescription of antibacterials, especially to children, are according to recent reports successful in Sweden [122] and has a direct impact on the prevalence of polypharmacy among the 0-9 year age group. It is also possible that the health care efforts to reduce the prescription of unnecessary generic duplications among the elderly have been successful. However, such change was not able to be measured in the present studies which only counted the number of different substances prescribed.

In contrast, polypharmacy might increase due to increased prescriptions. In order to fill the gaps in the medical arsenal towards earlier non-treated diseases, novel medications are successively introduced. Also many new clinical guide-

lines, which often recommend several drugs for a single medical condition, have been introduced. For patients with multiple diseases, guidelines might then result in several different “kits” of drugs being added on top of each other [10, 57, 123]. As multiple diseases are most common among the elderly, it seems logical that the prevalence of excessive polypharmacy had the largest increase in the elderly age groups.

### **Collection methods**

Data on drug use can be extracted from sale statistics, registers or can be provided directly by the patients in interviews. It is also possible to combine data on an individual’s drug use with other medical or socioeconomic data. The studies in this thesis can be seen as examples of studies that can be conducted on the basis of individual-based register data of dispensed drugs from an entire population.

When using individual-based drug registers or interviews, it is possible to change the focus from all individuals in a population to the individuals who actually use the drugs. It is also possible to select strata of individuals with different gender, age, and socioeconomic status from all users of a certain drug. Furthermore, it is possible to focus on the individual’s total use of different drugs.

With the individual-based register data on dispensed drugs, it is possible to calculate potential risks such as drug-drug interactions. For studies concerning other potential risks, such as ADRs and non-adherence to drug therapy, researchers must rely on interview methods.

One advantage with registers is that the data are already collected. Usually, the register is of high quality, it often covers large populations and it can provide data at low costs. The main disadvantages with individual-based register studies are that OTC drugs, CAM and dietary supplements are not included and that it is not known if the individuals actually ingested the dispensed drugs.

An additional condition that reduces the high precision of data on prescription drugs from registers is that, in real life, a substantial proportion of all adults borrow or share someone else’s prescription drugs [124, 125].

### **Measurements and study periods**

In study I-V, drug use, multiple medication and polypharmacy were all measured in terms of prevalence of certain numbers of dispensed drugs during a certain study period. The cut off for drug use was one or more drugs. The cut offs for multiple medications and polypharmacy were five, ten or 15 different drugs during different time periods. The prevalence is a rough measurement since it

gives no information about the variation in the distribution of the number of dispensed drugs above the decided cut off. The advantage with the prevalence measurement is that it is easy to understand and it is a standard measurement used in almost all studies of drug utilization. Thereby, the presented prevalence values in studies I-V can be compared to previous studies.

With the access to data on the actual number of dispensed drugs for each individual, it is possible to develop evaluation measurements for drug therapy that go beyond the traditional prevalence of individuals above a certain cut off limit. The presented novel weighted polypharmacy index in study II is an evaluation measurement, which reflects the exponentially increasing risks with increasing number of medications. The weighted index is a quality indicator, which can detect and evaluate differences in drug therapies between hospitals, regions and countries, and over time. The index has both advantages and disadvantages compared to traditional prevalence measurements, and needs to be tested more in future studies.

For the concept of polypharmacy, it is mostly unknown whether the patients have used all of the different dispensed drugs concomitantly. Many drugs are taken regularly but several, like antibiotics, are meant to be taken periodically and other drugs, such as certain analgesics, are meant to be taken only when needed. Moreover, what does concomitant mean in this context? Certain regularly used drugs are prescribed to be taken daily, some drugs two or three times a week, a few drugs once a month or even once every third month. Therefore, the periodical use of drugs has an impact on the number of individuals within the definition of polypharmacy during a study period. Consequently, the prescribed dosing interval, the patients' true consumption interval and the drugs in-vivo duration, all have an impact on the analysis of the magnitude of polypharmacy and the associated risks at a national level.

However, studies of polypharmacy display many different lengths of study periods. Some previous studies have in addition to a short study period focused on chronically prescribed drugs only and thereby e.g. not included antibacterials and analgesics, two of the most commonly used groups of prescription drugs. If the purpose of a study is to evaluate individuals' drug use, it seems appropriate to have a study period length that includes an individual's all available drugs. Therefore, a 3-month study period that includes all types of medications appears to be favorable.

# Conclusions and implications

## Conclusions

The main conclusions of the studies:

- The prevalence of dispensed drugs and multiple medication was extensive in all age groups and was higher for females than for males. Multiple medication should be regarded as a risk in terms of potential drug-drug interactions and adverse drug reactions in all age groups (I).
- Regional differences in the prevalence of polypharmacy could partly be explained by the regional age distribution in Sweden. The use of a novel weighted polypharmacy index indicated regional differences in drug therapy for individuals with polypharmacy (II).
- The number of drugs used, not only increased the potential risks associated with multiple drug use, but also the potential burden of an increased therapeutic intensity, especially for the elderly (III).
- Individuals with multiple medications accounted for nearly 80% of the acquisition cost of dispensed drugs, and individuals with ten or more drugs accounted for almost half of the cost. In order to reduce the risks for ADRs, interactions and inappropriate drug use, interventions with a focus on the reduction of the number of prescription drugs for the group of patients with many different drugs may, therefore, also result in a substantial reduction of the total drug cost (IV).
- In spite of reported efforts to reduce polypharmacy, the prevalence of polypharmacy and excessive polypharmacy and the mean number of drugs per individual continued to increase year-by-year in Sweden 2005-2008 (V).

## Implications

The presented prevalence of drug use and multiple medications in the studies of this thesis seems high, but if generic duplications, in-hospital medications, OTC drugs, dietary supplements and CAMs were included, the prevalence would probably have been even higher. As the potential risks with drug use and multiple medication - adverse drug reactions, interactions and non-adherence - involve all types and sources of medications, there is a need for a broader perspective on drug use than just prescription drugs.

### *Need of more information*

For physicians, it is of fundamental value to have up-dated information of the patients' actual use of all types of drugs. However, for the clinical outcome, it is also of great interest for physicians to know which of the prescribed drugs the patient did not take, and why. Health care politicians and planners have a dual focus; How can health care increase the efficacy of drug therapy from its current low level? What can be done to reduce the vast amount of resources spent on drugs patients probably never will use?

Physicians should be informed of all medications that their patients actually consume or do not consume, and should help their patients to make informed decisions appropriate to their medical care. Therefore, there is a need to develop methods to collect information about individuals total drug use from different sources which can cope with the well-known problems with register data and interview data. Moreover, other more advanced operational modes are needed, e.g. the participation of clinical pharmacologists or pharmacists in medication reviews in order to contribute to a more appropriate prescribing, especially for patients with several different physicians.

### *Monitoring and guidelines*

Today, the majority of studies regarding drug utilization have their focus on inappropriate drug use among elderly individuals. The patterns of multiple medication and polypharmacy in an entire national population as described in this thesis may, therefore, to a large extent be unknown to many physicians and health care stakeholders. Since two thirds of all individuals with multiple medications today are under 70 and the prevalence of polypharmacy is increasing in all age groups - except amongst children, due to the intervention success in the reduction of prescribed antibiotics to children - it should be important to monitor the development of drug use in all ages. In the future, today's large volume of individuals with multiple medications in the 50-60 year range will become the new elderly, probably with an increased use of medications compared to the elderly of today.

In this thesis, it is suggested that the introduction of new clinical guidelines might further contribute to increase the observed overall increase in polypharmacy, especially among the elderly, as the new guidelines may recommend several different drugs for each disease to individuals with multiple diseases. If this assumption is correct, it is urgent that the future development in medicine must include clinical guidelines for individuals with multiple diseases.

The individual based register studies of dispensed prescription drugs provide high quality data regarding drug use, multiple medication and polypharmacy. Results that are based on registers are without sample, recall, and interview bias. The presented patterns of prescribed drug use in an entire population could serve as a basis for further research, even if in-hospital medication, OTC drugs, dietary supplements, and CAMs are not included.

#### *Need of standards and future aspects*

In studies of drug utilization, there are large variations in the measurements used for drug use, multiple medication, and polypharmacy. There are also several different classifications, criteria, and scales for the different consequences of drug use and multiple medication, e.g. adverse drug reactions, drug interaction and inappropriate drug use. Obviously, there is a need for standards to enable better comparisons of drug use and its consequences between countries, regions, and other health care settings, and to examine trends in drug use over time.

The major advantages of individual-based register studies are that they can enlighten physicians and health care stakeholders concerning the complex patterns of multiple drug use in the entire population. The registers can be used as a base for interventions in order to create more appropriate and balanced prescription of medicines to individuals with multiple diseases. Register-based studies are also vital when interventions should be evaluated. Furthermore, the results from register-based studies can be used for educational purposes for professional health care personnel.

The development of the Swedish Prescribed Drug Register has created a unique base for pharmacoepidemiological studies. When drug consumption patterns for the entire population can be identified in detail, further steps may follow in which the analysis should expand, in line with the WHO definition of drug use, to also include the effects of drug use in a national perspective. The individual-based register of dispensed drugs can be combined with a large number of medical registers and socioeconomic variables and can provide science and society with vital knowledge of the effects of the increase in individual's drug consumption during recent decades.

## Acknowledgements

This PhD study was carried out 2007-2010 during my employment at PricewaterhouseCoopers in Uppsala, Sweden. Before this PhD project, I was 2004-2006 hired by the National Corporation of Pharmacies (Apoteket AB) as manager of the project which developed and implemented the Swedish National Pharmacy Register, which is the data source of the Swedish Prescribed Drug Register. During this project I became interested in multiple drug use. I presented a research proposal concerning multiple medications to my project initiator Stefan Carlsson, honorary doctor, CEO at Apoteket AB, who became interested and supported the proposed studies. Therefore, I wish to express my profound gratitude to Stefan Carlsson for his great interest in and support of my studies.

The idea to use the planned studies of multiple medications in a PhD project originated from my supervisors Göran Petersson, Professor Health informatics, MD, PhD, and Head of the eHealth institute at the Linnaeus University (formerly University of Kalmar) and Bengt Åstrand, M Sc Pharm, PhD, adjunct senior lecturer, School of Natural Sciences at the Linnaeus University. They both introduced the idea, and me, to Sven Tågerud, Professor of Pharmacology, PhD, School of Natural Sciences at the Linnaeus University, who became my third supervisor.

I wish to express my profound gratitude to my supervisors, who have supported and encouraged me during this study. Their interest in the study never failed, and they were always available for discussions. Their support has been of vital importance for the completion of my PhD project.

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