Refill Adherence to Long-Term Drug Treatment with a Focus on Asthma/COPD Medication

KRISTIN KRIGSMAN
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Abstract

Most patients are non-adherent with their medication sometimes, i.e. that they do not always use their medicines as prescribed. This might result in both under- and overuse and can lead to therapy failure, resulting in both unnecessary suffering and high costs. Therefore, medication adherence should be as high as possible.

The aims of this thesis were to investigate the refill adherence to long-term drug treatment, especially for patients with asthma and chronic obstructive pulmonary disease (COPD), and to study treatment gaps for patients with undersupply and drug costs for patients with oversupply. Further aims were to compare different methods for assessing refill adherence and analyse whether the same patient has the same refill adherence pattern to two different chronic drug treatments, i.e. diabetes and asthma/COPD.

The thesis shows that satisfactory refill adherence (80-120% of the prescribed dose) was 57% for repeat prescriptions with long-term drug treatment; undersupply was 21% and oversupply 22%. Patients with undersupply were without drugs more than half of the prescribed treatment time and the median oversupply for 90-100 days dispensation interval was 28 days. Patients who were exempt from charges had significantly higher oversupply than non-exempt patients and that leads to unnecessary cost for society. The level of satisfactory refill adherence for repeat prescriptions dispensed for asthma/COPD was on average 30%. The same low level was displayed for the elderly, where undersupply was more common than oversupply.

Assessments of refill adherence during a one-year period gave the same results irrespective of whether the repeat prescriptions were from an individual pharmacy record database or were manually collected at a pharmacy.

Patients with concomitant use of diabetes and asthma/COPD drugs do not have the same dispensation pattern for both drug types.

The introduction of patient profiles as a new approach to complement the calculated refill adherence needs to be further studied in larger and more divergent populations. In the future, the new national pharmacy record database in Sweden has opened up for larger studies and will be valuable when studying patterns of drug utilization.

Keywords: asthma, chronic disease, COPD, diabetes, pharmacy record database, prescription, refill adherence

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urn:nbn:se:uu:diva-8094 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-8094)
“Drugs don’t work in patients who don’t take them”

C. Everett Koop, MD.
former US Surgeon General
LIST OF PUBLICATIONS

The thesis is based on the following papers, which will be referred to by their Roman numerals:


IV  **Krigsman K**, Moen J, Nilsson JLG and Ring L. Refill adherence by the elderly for asthma/COPD drugs dispensed over a ten-year period. (submitted)


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¹ Andersson’s surname is now Krigsman
CONTENTS

DEFINITIONS ........................................................................................................... 10

INTRODUCTION ..................................................................................................... 13

BACKGROUND ..................................................................................................... 15
  Definition of adherence .................................................................................. 15
  Factors influencing adherence ...................................................................... 16
    Reasons for non-adherence ....................................................................... 17
    Consequences of non-adherence .............................................................. 19
    Interventions to improve adherence ......................................................... 20
  Adherence to long-term treatment – asthma/COPD .................................... 21
  Measuring adherence ................................................................................... 22
  Pharmacy records ......................................................................................... 26

AIMS OF THE THESIS ........................................................................................ 28

METHODS ............................................................................................................. 29
  The Swedish pharmacy and drug reimbursement system ......................... 29
  Prescriptions ................................................................................................ 29
  Settings .......................................................................................................... 30
    County of Jönköping .................................................................................. 30
    County of Jämtland ................................................................................... 31
  Assessing refill adherence .......................................................................... 31
  Data sources .................................................................................................. 33
    Papers I-II ................................................................................................ 33
    Papers III-V .............................................................................................. 33
  Statistical analysis ....................................................................................... 35
  Ethics .............................................................................................................. 35

RESULTS .............................................................................................................. 36
  Satisfactory refill adherence ....................................................................... 36
    All drugs for long-term medication ......................................................... 36
    Drugs for asthma/COPD .......................................................................... 38
  Undersupply .................................................................................................. 39
    All drugs for long-term medication ......................................................... 39
    Drugs for asthma/COPD .......................................................................... 39
  Oversupply ..................................................................................................... 40
All drugs for long-term medication .....................................................40
Drugs for asthma/COPD......................................................................40
Refill adherence to two long-term therapies ............................................40
Costs of oversupply for patients exempt and non-exempt from charges .42
Factors influencing adherence.................................................................43
  Gender .................................................................................................43
  Age.......................................................................................................43
  Treatment time.....................................................................................43

DISCUSSION...............................................................................................44
  Overview of studies included in the thesis...............................................45
Methodological considerations.................................................................45
  Pharmacy records ................................................................................45
  Settings ................................................................................................47
  Assessing refill adherence ................................................................47
  Asthma/COPD .....................................................................................48
Adherence and non-adherence to chronic drug treatment .......................49
  Satisfactory refill adherence .................................................................50
  Undersupply.........................................................................................51
  Oversupply...........................................................................................52
Refill adherence over a one-year period compared to that over a four-year period .........................................................................................52
Refill adherence to two long-term therapies ............................................53
Costs of oversupply for patients exempt and non-exempt from charges .54
Factors influencing adherence.................................................................55
Improving patient adherence....................................................................56

CONCLUSIONS ..........................................................................................58

FUTURE ASPECTS.....................................................................................59

SAMMANFATTNING PÅ SVENSKA .......................................................61

ACKNOWLEDGEMENTS..........................................................................64

REFERENCES .............................................................................................66
### ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic Obstructive Pulmonary Disease</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined Daily Dose</td>
</tr>
<tr>
<td>ECHO</td>
<td>Economic, Clinical and Humanistic Outcomes</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>MEMS</td>
<td>Medical Event Monitoring System</td>
</tr>
<tr>
<td>OR</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the counter</td>
</tr>
<tr>
<td>PACT</td>
<td>Prescribing Analysis and Cost Tabulation</td>
</tr>
<tr>
<td>RCR</td>
<td>Refill Compliance Rate</td>
</tr>
</tbody>
</table>
| SEK          | Swedish Krona (currency), conversion rate  
2007-06-01; 100 SEK = € 11 and 100 SEK = US$ 15 |
| WHO          | World Health Organization |
DEFINITIONS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence</td>
<td>“The extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” [1].</td>
</tr>
<tr>
<td>Anatomical Therapeutic</td>
<td>Classification system for drugs administered by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway [2].</td>
</tr>
<tr>
<td>Chemical classification</td>
<td></td>
</tr>
<tr>
<td>Compliance</td>
<td>“The extent to which a person’s behaviour (in terms of taking medications, following diets, or executing life-style changes) coincides with medical or health advice” [3].</td>
</tr>
<tr>
<td>Concordance</td>
<td>Focuses on the consultation process rather than on a specific patient behaviour, and it has an underlying ethos of a shared approach to decision-making rather than paternalism [4].</td>
</tr>
<tr>
<td>Defined Daily Dose</td>
<td>The (at any given time) assumed average maintenance dose per day for a drug used for its main indication in adults. Technical unit administered and decided by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway [2].</td>
</tr>
<tr>
<td>Oversupply</td>
<td>Refilled drugs covering &gt;120% of prescribed treatment time.</td>
</tr>
<tr>
<td>Patient profile</td>
<td>A graph for each individual patient that shows the date of each dispensation and the time period covered by the dispensed drugs.</td>
</tr>
<tr>
<td>Term</td>
<td>Description</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Primary non-adherence</td>
<td>Prescriptions issued to patients by their doctor, but never registered at the pharmacy for dispensing [5].</td>
</tr>
<tr>
<td>Repeat prescription</td>
<td>Patients with long-term treatment normally get several prescriptions in succession. In this thesis the term repeat prescription includes all prescriptions for the same patient and the same drug, during the study period. However, in Paper III, the term repeat prescription was referred to as prescribing.</td>
</tr>
<tr>
<td>Satisfactory refill adherence</td>
<td>Refilled drugs covering 80-120% of prescribed treatment time.</td>
</tr>
<tr>
<td>Undersupply</td>
<td>Refilled drugs covering &lt;80% of prescribed treatment time.</td>
</tr>
</tbody>
</table>
INTRODUCTION

Many patients do not use their medicines as prescribed. Patient adherence, i.e. how well patients follow agreed recommendations of medical treatment, has most likely been an issue for as long as pharmacotherapy has existed, and it was described by observers as far back as Hippocrates. The problem of non-adherence has been described worldwide and is seen in all parts of the population independent of age, gender, race, education or socioeconomic status [4]. Furthermore, non-adherence is observed in all types of diseases, i.e. acute and chronic, serious and non-serious and in relation to both symptom-alleviating and other drug treatment [1]. The fact that many patients do not use their medications as prescribed has been the focus of a vast amount of research and has given rise to much debate over the last three decades [4]. In the literature, non-adherence to long-term medication therapy has been reported among approximately half of all patients [1].

Non-adherence is a complex phenomenon that concerns practically every medical and non-medical treatment. Horne [6] reported that patient adherence to drug therapy is influenced by many factors related to how the patients judge the necessity of their treatment relative to their concerns. These factors comprise illness perceptions (symptoms), background beliefs (negative orientation to drugs in general) and contextual issues (view of others). Horne’s conclusion was that there is no typical non-adherent patient; most patients are non-adherent part of the time [6]. From a patient-centred perspective the meaning of medication in everyday life is more one of self-regulation than of compliance [7].

Non-adherence may involve both under- and oversupply of dispensed prescriptions. The proportion of dispensed prescriptions might be compared with either the proportion actually prescribed or with the actual drug consumption [1]. It is important to improve adherence in order to achieve improved clinical outcomes as well as reduced health care costs [8-12]. A meta-analysis [13] showed that good adherence to drugs as well as to placebo was associated with lower mortality. It was concluded that good adherence to drug therapy may be a surrogate marker for an overall healthy behaviour. However, adherence to drug therapy might not always be appropriate. A requirement for keeping up adherence is that the underlying prescribing is appropriate and furthermore that the patients have enough information to
make their own informed decisions of whether to follow the prescribed treatment or not.

In this thesis, the focus will be on refill adherence to long-term drug treatment and on different methods for assessing refill adherence. Adherence to medical treatment will be approached from a general perspective, emphasising long-term treatments, especially adherence to treatment of asthma and chronic obstructive pulmonary disease (COPD). Asthma/COPD were selected since adherence to these treatments has been found to be particularly low and improved adherence results in decreased morbidity [12] and mortality [1]. Moreover, the prevalence of these diseases in Sweden is currently high and increasing [14], which further contributes to the importance of gaining a greater understanding of adherence to asthma/COPD drugs.
BACKGROUND

Definition of adherence

The first and hitherto most common term for describing the phenomenon of patients not taking their medications as prescribed is “compliance”. In 1976 Sackett and Haynes published one of the first books on compliance [15], and this was followed by a more comprehensive book in 1979 entitled “Compliance in Health Care” [3], in which the state of the art in compliance research was summarized. Compliance was defined in a general way as “the extent to which a person’s behaviour (in terms of taking medications, following diets, or executing life-style changes) coincides with medical or health advice” [3]. The term compliance is associated with the traditional patient-physician relationship in which the patient is a passive responder to the physician’s authoritarian recommendations. Based on this view, non-compliance may be interpreted as patient incompetence if the patient does not follow the instructions or shows deviant behaviour.

An alternative, more modern term is adherence. The definition of adherence according to the World Health Organisation (WHO) is [1]; “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider”. Consequently, adherence and compliance refer to the patient’s behaviour in relation to the treatment and are measured in the same way. However, the term adherence indicates the patient’s behaviour in relation to the therapy, the provider’s behaviour in relation to the therapy, the patient/provider relationship as well as the environmental conditions in which the patient and provider must operate individually and together [1]. Adherence attempts to emphasise that the patient is free to decide whether to adhere to the doctor’s recommendations or not and that failure to do so should not be blamed on the patient [3]. The term adherence indicates that concordance between patient and provider is believed to increase adherence and is separated from the term compliance through the view of this phenomenon.
The term concordance represents an even greater step towards a deeper understanding between patients and physicians, and denotes a process of prescribing and medicine-taking based on partnership between patient and prescriber (including others, such as pharmacists and other carers) [4]. The term was introduced in 1997 [16]. Concordance is fundamentally different from both compliance and adherence. It focuses on the consultation process rather than on a specific patient behaviour, and it has an underlying ethos of a shared approach in decision-making rather than a paternalistic structure. Concordance gives the patients the opportunity to be involved in decision-making, and the doctor’s task is to ensure that the patients have enough information for making the decisions, and to support them in solving any problems they might have. This decision-making method should have a positive impact on treatment behaviour, and health outcomes may be improved [4].

In this thesis the term adherence will be used to describe patients’ medication behaviour, since the term has a more positive approach to the treatment than compliance. The focus will be on assessing refill adherence, which refers to the proportion of dispensed medicines in relation to issued prescriptions.

Factors influencing adherence

Adherence and non-adherence are complex phenomena that probably are eternal human issues. The average rate of non-adherence to chronic medication has been estimated to be about 50% [1]. Even in clinical trials the average non-adherence rates have been reported to be 22-57% among patients receiving treatment for chronic diseases [17-20]. Many studies of adherence and non-adherence have been published, but relatively few Swedish studies have estimated the proportion of adherence (see below). A Swedish literature review (ABLA II) focusing on adherence within the Swedish health care system was published in 2001 [21]. In the conclusion the authors strongly recommend that the Swedish health care system improve drug adherence, e.g. through feedback from the pharmacies to the physicians, education efforts for physicians, nurses and pharmacists, research and high-quality workmanship. Various theses in Sweden have also been presented reporting results on cardiovascular disease, glaucoma and Human Immunodeficiency Virus (HIV) patients, and present reflections on medicines, and on adherence from a general practice perspective [22-29]. There are few assessments of adherence to chronic lifelong treatment based on longitudinal studies and none have assessed the degree of adherence to different drug therapies at a national Swedish level. It is therefore of interest to assess patients’ long-term adherence in a Swedish setting and to do so, psychometrically sound and feasible methods are needed.
Many studies consider drug acquisitions covering 80% or more of the prescribed treatment time to indicate satisfactory adherence. However, non-adherence may involve both undersupply/underuse and oversupply/overuse. Underuse of medication seems to be more common than overuse [1]. It is less common to define an upper cut-off point of satisfactory refill adherence, above which there is an oversupply or overuse. This is probably because data on oversupply are difficult to interpret, since the patient could have had the drugs dispensed because of exemption from charges or the patient might want to have drugs available in several locations – at home, at work and at the vacation home. However some studies define satisfactory adherence as equal to dispensed refills covering 100±20% [30-32].

Reasons for non-adherence

There is always a reason for reduction or discontinuation of patients’ prescribed medications [33]. Many of the reasons are behavioural and non-adherence is therefore often classified by the patient’s intent, as unintentional or intentional [34].

Unintentional non-adherence occurs when a patient wishes to adhere but is prevented by forgetfulness or inability, e.g. misunderstanding the regimen, language barriers in doctor-patient communication or incorrect device technique e.g. the inability to inhale medicines correctly [35-37]. Unintentional factors are associated primarily with age and clinical variables like depression, anxiety and number of years of condition [34]. Among elderly patients factors such as concurrent diseases, multimedication (polypharmacy) and increased liability to adverse drug reactions may increase the tendency of non-adherence [38]. The most frequently reported reason among younger persons for taking too little medication is forgetfulness. This is according to a study examining 195 college students’ adherence, beliefs and attitudes towards physicians, medicines, illness and health [39].

Intentional non-adherence follows an active decision by the patient. This means that the decision not to take the medication or to take a lower or higher dose than prescribed is consciously made [34, 35]. Intentional non-adherence is associated with individuals’ beliefs and cognitions [34]. Effective prescribing must also take into account the patients’ beliefs, expectations and adherence behaviour. The theories of adherence behaviour to drug treatment have been developed from health behaviour in general and different health behaviour models have been used to study patient adherence, e.g. the Health Belief Model [40], the Theory of Reasoned Action/the Theory of Planned Behaviour [41, 42] and the Transtheoretical Model of Behaviour Change [43]. All of these models describe the medication behaviour as being
a result of both internal and external factors like attitude, perceived severity, perceived barriers, beliefs about outcomes, benefits, costs and motivation; the models have successfully been implemented in patient adherence studies [44-46]. One study [46] showed that some variables from the Health Belief Model and the Theory of Reasoned Action, i.e. barriers, benefits, belief strength, outcomes evaluation and behavioural intention, had a significant relationship with adherence [46]. Another study [44] found a correlation between patients’ overall compliance levels and a composite of patients’ level of health belief motivation (Health Belief Model). The highest levels of correlations between the areas of compliance and the motivators occurred with cues to action [44]. Accordingly, health behaviour models contribute to a greater understanding of patients’ adherence.

Concerning intentional non-adherence Labig et al. [39] found that 25% of the students studied were likely to stop taking their medicines as soon as they felt better and 9% were likely to stop early if their medications did not seem to help. Fear of perceived short- or long-term side-effects may cause some patients to reduce or discontinue their medication [47-49]. Inadequate knowledge and negative attitudes towards the treatment, such as lack of trust in the safety and efficacy of the medication [49, 50], complexity of the regimens, conflict between treatment recommendation and daily life [48] and lack of readiness before initiating the treatment [51] are considered to be barriers for adherence. Feeling well without treatment and lack of trust in health care providers constitute other barriers [48, 49]. Several studies have also shown that increased user costs decrease drug use [52-55]. Piette et al. [54] showed that two-thirds of chronically ill older patients never told a clinician in advance that they planned to underuse prescribed medication because of cost, and one third never raised the issue of cost. Their reason for not talking about their medication cost problems was that nobody had asked them and most patients reported that they did not think their doctors could help them with these problems. This background illustrates the importance of studying the relations between exemption from charges and the economic consequences of drug oversupply.

Elderly people (65 years and older) in Sweden comprise 17% of the Swedish population [56]. Age might have an impact on adherence and younger patients tend to have lower adherence than adults and elderly patients [57-62]. In addition, there are also problems specific to old age [63, 64]. Many elderly have multiple chronic diseases and they are the greatest consumers of prescription drugs. They consume approximately 43% of all prescription medicines, reflecting 37% of the medication cost [65]. Adherence to treatment is essential for everyone, but might be especially important for the well-being of elderly patients, and is thus a critically important component of care [38]. However, the prevalence of cognitive and functional impair-
ments in elderly patients increase their risk of poor adherence [66-68]. Multiple co-morbidities and complex medical regimens further compromise adherence [63, 64, 68, 69]. Age-related changes in pharmacokinetics and pharmacodynamics make this population even more vulnerable to problems resulting from non-adherence [38].

Thus non-adherence always has an underlying cause. It is the health care professional’s responsibility to identify whether a patient is adherent or not and to identify the cause of any non-adherence [33]. This is important since the consequences of non-adherence can be quite profound.

Consequences of non-adherence
Health care providers should always consider the possibility of poor adherence as an explanation for therapy failure. However, in many studies the relationship between inadequate adherence and therapy outcome are poorly documented. In publications where it has been documented, however, non-adherence is associated with both increased morbidity [12, 70] and mortality [13, 71].

In turn, non-adherence leads to increased use of health care service [70, 72]. For example, a significantly higher risk of hospitalization was found among patients with type 2 diabetes who did not obtain at least 80% of their oral antihyperglycaemic medication across a one-year time frame [73]. In the USA [74], the total cost of drug-related morbidity and mortality was estimated at $177.4 billion in 2000, a substantial part of which was due to non-adherence. Thus, non-adherence is a serious medical and economic problem for society [74]. Furthermore, non-adherence can lead to therapy failure and have negative effects on patients’ health. For example, patients who were taking >80% of prescribed statins doses were significantly associated with a lower risk of recurrent myocardial infarction [70]. In conclusion, it is of the utmost importance to keep adherence as high as possible both from an individual patient’s perspective and from a social perspective.

Sokol et al. [72] conducted a retrospective cohort study and evaluated the impact of medication adherence on health care utilization and cost for four chronic conditions (diabetes, hypertension, hypercholesterolaemia and congestive heart failure), all major drivers of drug spending. For diabetes and hypercholesterolaemia they conclude that high levels of medication adherence were associated with lower disease-related medical costs. The hospitalization rates were significantly lower for patients with high medication adherence in all four conditions [72].
Only patients with high adherence are included in some clinical trials since patients with poor adherence reduce the ability to detect treatment effects [75]. This means that adherence rates in clinical trials may overestimate the levels of adherence observed in clinical practice. Consequently, any benefit detected in the trials from a particular treatment can be generalized only to other patients who are also likely to adhere to the treatment program. Most patients are non-adherent part of the time and the physicians have therefore no evidence for a treatment’s effectiveness for these patients [75]. The treatment may have the greatest potential for reducing disease burden in non-adherent patients [76].

It is important to study the consequences of non-adherence further, especially in order to be able to design effective interventions for the purpose of improving adherence.

Interventions to improve adherence

It is vital to try to enhance adherence by emphasizing the value of a patient’s treatment, by focusing on patient motivation and readiness, and by making the regimen simple and customizing the regimen to the patient’s lifestyle [9]. According to a Cochrane review [77], interventions that were found to have an impact on adherence in long-term treatment included combinations of more convenient care (e.g. provision at the worksite), information (e.g. written material), reminders, self-monitoring, reinforcement, counselling, family therapy and other forms of additional supervision or attention by a health care provider (physician, nurse, pharmacist and others). However, even the most extensive interventions promoted only minor improvements in adherence and treatment outcomes. The review [77] showed that only 26 of 58 interventions for long-term treatments reported in 49 randomised controlled trials were associated with improved adherence, and only 18 of these 58 interventions led to improvements in treatment outcomes. Their conclusion was that the study design was usually inadequate.

To obtain improvements in adherence and treatment outcomes it is important to evaluate the interventions in relation to several outcomes. These outcomes may be both intermediary (e.g. improved adherence) and final outcomes (e.g. clinical value) [78]. The Economic, Clinical, and Humanistic Outcomes model (ECHO) depicts the value of a pharmaceutical product or service as a combination of traditional clinically-based outcomes and more contemporary measures of economic efficiency and quality of life [78]. Safety and effectiveness are no longer the only salient attributes; the effect on total health resource utilization, cost, and quality of life must also be evaluated [79].
Adherence to long-term treatment – asthma/COPD

It has been shown that adherence to treatments of chronic conditions is non-optimal, and furthermore that adherence to asthma/COPD treatments is particularly low. However, improved adherence results in decreases in both morbidity [12] and mortality [1]. The refill adherence among patients with asthma/COPD drugs has not been studied previously in Sweden. Therefore, it is of interest to assess the long-term adherence to asthma/COPD drugs and to inform health care professionals about how patients follow their prescribed treatments.

Asthma and COPD are chronic diseases and therefore treatment is likely to continue over many years. Asthma affects people of all ages whereas COPD mainly affects older people. The influence of gender on asthma changes with age; childhood asthma is more common in boys, while women are diagnosed with asthma more frequently than men [80, 81]. COPD is more common among men than among women [82], which may be related to differences in smoking history. However, after adjusting for previous smoking, women appear to develop more severe airflow obstruction than men [83, 84]. Several environmental factors also contribute to the onset of both asthma and COPD. The prevalence of asthma and COPD varies from 1 to 13% [85, 86] and in Sweden the prevalence of physician-diagnosed asthma is about 8% based on all ages [87]. The prevalence of COPD is 14% in northern Sweden (20-69 years old) according to the European Respiratory Society (ERS) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [88]. According to WHO, COPD is the fifth leading cause of death in the world [89].

To differentiate the diagnosis between asthma and COPD, clinical considerations like risk factors, patient age, symptoms and spirometry are used [90]. Indicators of asthma are family history, allergy, a seasonal variability of symptoms, wheezing, younger age and reversibility [91], while COPD is more associated with an age of over 45 years [92], current or past smoking, cough with sputum production and non-reversibility [90].

The treatment goal for asthma is that the patient should be free from symptoms and have no limitation of daily activities, normal lung function, no emergency visits, satisfactory quality of life and no dangerous side-effects of the treatment [93]. Swedish and international guidelines recommend daily use of short-acting bronchodilator agents and anti-inflammatory medicines or a combination of a long-acting bronchodilator and an inhaled corticosteroid for patients with persistent asthma [93, 94]. The goal for COPD treatment is to reduce symptoms and improve quality of life. The treatment usu-
ally consists of anticholinergics, inhaled corticosteroids and long-acting bronchodilators [93].

Adherence to preventive therapy, like inhaled corticosteroids, is especially problematic since the patients do not notice an immediate effect of taking the drug [35]. Many international studies show that adherence to asthma and COPD medication is generally poor and that only 40-80% of the asthma medications [10, 57, 59, 95-99] and 45%-60% of the COPD medications [100-102] are used as prescribed. Poor adherence to regular use of inhaled corticosteroids is considered to be an important causal factor in the increased morbidity and mortality of asthma patients [11, 103-107]. Moreover, elderly patients with asthma and/or COPD who receive inhaled corticosteroids and also adhere to their treatment plan have lower rates of hospitalization [108]. Among elderly asthma patients, the combination of inhaled corticosteroids and long-acting beta-adrenoreceptor agonists decreases mortality and hospitalization to a greater extent as compared to either treatment alone [108].

In real life, many patients use multiple drugs for different diseases, especially middle-aged and elderly people. It is a more complex endeavour for patients with more than one chronic disease to achieve an optimal drug treatment. The psychological basis for patients’ adherence and non-adherence has interested several researchers [6, 50, 109]. For example, Vég [109] proposed that the patients’ attitudes to diabetes and its treatment are associated with adherence behaviour. The study shows that if a patient has an attitude that will promote or diminish adherence to one chronic drug treatment this can also be observed for the patient’s treatment for a second chronic disease. Consequently, a patient with two chronic diseases would be expected to show the same adherence to the drugs for both diseases. This hypothesis would imply that a patient with concomitant use of, for example, asthma/COPD and diabetes drugs would show the same adherence pattern to both drug treatments. This has, however, not been studied, so it would be of interest to compare refill adherence patterns for asthma/COPD and diabetes drugs. This would help to further inform health care providers about patients’ adherence behaviour.

Measuring adherence

Ideally, adherence should be measured at the actual point of consumption, i.e. ingestion adherence, which is the final assessment goal. However, it is rarely possible to assess ingestion adherence. Therefore most studies rely on more easily performed intermediary measurements, or proxies for ingestion adherence. There are several different methods available (Table 1), but there is no golden standard despite a vast range of empirical studies about pa-
tients’ adherence. Instead, for high accuracy it is recommended to use a combination of methods [110]. The methods available to assess adherence may be grouped into direct and indirect methods.

Examples of direct methods include direct observation of the patient, e.g. in clinical trials where the patients may be directly observed taking their medications, and monitoring a biological marker or the drug level in blood or urine. Biological markers are non-toxic, stable, easily detected compounds (e.g. phenol red) that can be added to medications. Drug levels in serum or urine are not appropriate to use if the drug has a short half-life, since the patient may be non-adherent until shortly before a clinic appointment and return to non-adherent behaviour after the clinic visit [111].

Proxy methods, i.e. indirect methods used to measure adherence, are for example self-reporting, pill count, electronic monitoring (Medical Event Monitoring System, MEMS) and use of pharmacy records [110, 112]. Self-reporting via questionnaires, interviews or diaries is the easiest and most common method. Pill count is the comparison between the amount of medication remaining in the patient’s medication container and the amount that should have remained if the patient had been fully adherent [110]. Pill count as well as self-reporting tends to overestimate actual adherence behaviour. MEMS is a device that contains a microprocessor to record the time and date of when the patient obtains a dose of medication by registering when an inhaler is used or a pill box opened [113]. The use of pharmacy records allows the researcher to study early discontinuation of therapy and the dispensation of medication in a manner other than that prescribed, i.e. refill adherence.
Table 1. Methods for measuring adherence [1, 9, 110, 112, 113].

<table>
<thead>
<tr>
<th>Methods of measuring adherence</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug level in biologic fluids</td>
<td>▪ Objective</td>
<td>▪ For drugs with short half-life, only events shortly before measuring can be detected</td>
</tr>
<tr>
<td></td>
<td>▪ Possible to compare with standardized relationship regarding drug concentration and effect</td>
<td>▪ Risk of “white-coat adherence”, i.e. the patient is more adherent shortly before the visit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Individual variation in metabolism and volume of distribution can over- or underestimate adherence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Expensive</td>
</tr>
<tr>
<td>Biological markers</td>
<td>▪ Objective</td>
<td>▪ Only yes/no response; no level of adherence</td>
</tr>
<tr>
<td></td>
<td>▪ Provide objective proof that the patient ingested a dose of the drug</td>
<td>▪ Individual variation in metabolism and volume of distribution can over- or underestimate adherence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Expensive</td>
</tr>
<tr>
<td><strong>Indirect methods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reporting</td>
<td>▪ Easy to use</td>
<td>▪ Accuracy and validity is instrument-dependent, e.g. the wording of questions might affect patients’ responses</td>
</tr>
<tr>
<td></td>
<td>▪ Patients can provide information about circumstances and motives affecting non-adherence</td>
<td>▪ Cognitive or memory limitations might impact the assessment</td>
</tr>
<tr>
<td></td>
<td>▪ Most commonly used method that allows for comparison between studies</td>
<td>▪ Overestimation of adherence due to factors like social desirability</td>
</tr>
<tr>
<td></td>
<td>▪ Inexpensive</td>
<td></td>
</tr>
<tr>
<td>Methods of measuring adherence</td>
<td>Advantages</td>
<td>Disadvantages</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pill counts</td>
<td>Objective</td>
<td>Accuracy varies widely, i.e. the patient can discard drugs before the pill count</td>
</tr>
<tr>
<td></td>
<td>Easy to use</td>
<td>No information about medication timing</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td>Overestimation of adherence due to e.g. dumping pills</td>
</tr>
<tr>
<td>MEMS</td>
<td>Continuous data</td>
<td>The drug container may be inconvenient or can be lost</td>
</tr>
<tr>
<td></td>
<td>Date- and time-specific regarding drug intake</td>
<td>The patient may accidentally or purposefully open the drug container without taking the drug or take the wrong amount of the medication</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Underestimation of adherence if patients used pill box (e.g. Dosett) or other storage device</td>
</tr>
<tr>
<td>Pharmacy records</td>
<td>Objective</td>
<td>Requires a comprehensive system for collecting pharmacy records information, otherwise the dataset will be incomplete</td>
</tr>
<tr>
<td></td>
<td>Feasible in large populations</td>
<td>A dispensed prescription is not equivalent to ingestion of medication</td>
</tr>
<tr>
<td></td>
<td>Longitudinal data</td>
<td>Overestimation of adherence due to e.g. changes communicated by the physician, but not recorded on the prescription</td>
</tr>
<tr>
<td></td>
<td>Accurate measure in a comprehensive pharmacy system</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-invasive</td>
<td></td>
</tr>
</tbody>
</table>


Pharmacy records

Pharmacy records are useful for assessing refill adherence for large numbers of patients with chronic diseases, since patients’ drug use is lifelong and may thus be measured over a long period of time. The assessments based on pharmacy record measurements have been shown to correlate positively with the results based on other measurement techniques like self-reporting, drug plasma level and clinical outcome data such as diastolic blood pressure [114-116], although this approach tends to overestimate adherence [110, 114, 117]. The use of pharmacy records offers an accurate measure of overall adherence, provided that the refills are measured at several points in time [30, 114, 118, 119]. This method measures dispensed drugs and therefore an upper limit for actual drug intake. The use of pharmacy records to assess medication adherence has increased dramatically with the introduction of centralized computerized refill records [58, 120-123]. There is a clear distinction between the data provided by databases on prescribed drugs, like the British Prescribing Analysis and Cost tabulation (PACT) data [124], and databases on dispensed drugs. Not all prescriptions issued are dispensed at the pharmacy, and hence pharmacy records do not necessarily equal primary non-adherence. A British study indicated that 20% of prescriptions never reach a pharmacy [125]. The patients with the highest rate of prescriptions not dispensed had low education and socioeconomic levels, and the prescriptions not dispensed were often for psychotropic drugs and antibiotics. In Sweden, studies show that between 10-14% of repeat prescriptions never reached a pharmacy [126, 127]. For asthma prescriptions the corresponding proportion was 20% [126]. If adherence is to be compared to what was prescribed, this primary non-adherence should be considered. The number of countries with individual pharmacy record databases from which refill adherence could be assessed is increasing [128-130] but the practice is still rare. Sweden has a few pharmacy record databases, in the county of Jämtland [131], in Tierp [132] and since July 2005 a national pharmacy record database on dispensed drugs [129]. These databases contain data with patient identities for all dispensed prescriptions in the respective geographic areas.

The common goal of all refill adherence measures is to reflect the continuity of medication usage and to capture the timeliness and the frequency of refilling [133]. There are many different ways of assessing adherence using pharmacy records [114, 134, 135]. In a recent review 11 measures of calculating refill adherence were identified [134]. These are the following: the Single Interval Measure of Medication Acquisition (CSA); Continuous

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2 Swedish Prescribed Drug Register
Measure of Medication Acquisition (CMA); Compliance Rate (CR); Dates Between Fills Adherence Rate (DBR); Continuous Measure of Medication Gaps (CMG); Continuous Multiple Interval Measure of Oversupply (CMOS); Medication Possession Ratio (MPR); Refill Compliance Rate (RCR); Medication Possession Ratio, modified (MPRm); Medication Refill Adherence (MRA); and Proportion of Days Covered (PDC). These measures differ substantially, but three parameters characterize all refill adherence measure, i.e. continuous versus dichotomous distribution, single versus multiple refill intervals, and assessment of medication availability versus gaps in treatment [114]. As a continuous variable, adherence is assessed repeatedly during a period, and this makes it possible to identify time intervals during which drug exposure deviates from the prescribed treatment. When adherence is used as a dichotomous variable, the individual or the dispensing pattern is simply categorized as either adherent or non-adherent. Regardless of whether adherence is based on a continuous or dichotomous variable, adherence might be calculated based on single refill interval, or based on multiple refill intervals. A single refill interval means that adherence is assessed between two consecutive refills and a multiple refill interval means that adherence is assessed between more than two refills. The third parameter focuses on the medication availability (i.e. the prescribed treatment time in relation to the time between the fills) or treatment gaps (periods of non-adherence) [114].

Refill adherence can be based on two different types of pharmacy records, i.e. data from a pharmacy record database and data from manually collected repeat prescriptions. A database registers and stores all dispensed drugs for the same individual over time in a well-defined area, e.g. Norway or the county of Jämtland [130, 131]. Patients’ refill adherence can therefore be assessed over several years. Manually collected repeat prescriptions contain information regarding the dispensed drugs for a separate prescription and the refill adherence can only be assessed for a shorter period, e.g. one year in Sweden. Countries without a pharmacy record database can only estimate refill adherence using manually collected repeat prescriptions. The number of countries with individual pharmacy record databases is still rare. It is therefore important if a one-year study period based on manually collected prescriptions might be comparable to estimating refill adherence based on database registers covering several years, since some countries estimate refill adherence only from manually collected repeat prescriptions. This will contribute to the establishment of reliable methods for measuring the level of adherence.
AIMS OF THE THESIS

The overall aim of this thesis has been to survey the refill adherence to long-term drug treatment in Sweden, with a special focus on assessing refill adherence for asthma/COPD prescriptions. A further aim has been to compare methods based on pharmacy records for the assessment of refill adherence. This thesis has the following specific objectives:

- To survey refill adherence among different patient groups with long-term medication therapy.
- To assess treatment gaps for dispensed repeat prescriptions with undersupply for long-term medication therapy, and to analyse the relationship between oversupply, drug cost and exemption from charges.
- To compare refill adherence for asthma/COPD prescriptions based on two different types of pharmacy records, i.e. data from a pharmacy record database and corresponding data from manually collected repeat prescriptions.
- To survey refill adherence retrospectively over a ten-year period for asthma/COPD prescriptions dispensed to elderly patients.
- To compare refill adherence patterns regarding concomitant use of diabetes and asthma/COPD medication during a three-year period and to investigate whether patient profiles comprise a feasible and reliable method to assess refill adherence.
METHODS

The Swedish pharmacy and drug reimbursement system

All Swedish pharmacies (about 950 community- and hospital pharmacies [136]) have been owned by the Swedish Government since 1970 and organized into one pharmacy chain, the National Corporation of Swedish Pharmacies (Apoteket AB) [137].

The drug reimbursement system in Sweden stipulates that all patients pay the full cost of drugs up to 900 SEK (approximately € 100) during a 12-month period. The out-of-pocket cost is then gradually reduced and the patients are exempt from further charges when they have paid a total of 1,800 SEK (approximately € 195) calculated from the time the first prescription was dispensed. This exemption means that patients receive free medications for the rest of the 12-month period [138, 139]. One criterion for drugs to be reimbursed is that at any dispensation the amount obtained covers a maximum of three months’ treatment. However, when two/thirds of the time that the original dispensation was intended to cover has elapsed, a new reimbursed dispensation is allowed [140].

Prescriptions

A Swedish prescription contains information regarding the patient’s age, gender, the drug name, the strength, amount and dosage prescribed, date of dispensed drug, as well as the prescriber’s name and affiliation. From the drug name the Anatomic, Therapeutic, and Chemical classification code (ATC) can be determined [2].

In the ATC classification system, the drugs are divided into different groups according to the organ system on which they act and according to their chemical, pharmacological and therapeutic properties [2]. In this thesis, analyses were done based on ATC groups since diagnoses are not available for all prescriptions.
In Sweden, a prescription is valid for one year from the date of issue [141]. A patient with a refill prescription can only fill the medicine for three months’ use at a time (in order to receive reimbursement), i.e. a maximum of four times during one year. This means that the prescription has four valid refills or iterations, i.e. it is a repeat prescription. For long-term treatment, repeat prescriptions are most commonly issued in Sweden. All drugs sold in Sweden are prepacked and Swedish pharmacists are not allowed to break the containers to dispense part of the packages. Further, most packages for long-term use contain medicines to cover a three-month treatment period.

Papers I-IV included repeat prescriptions with fixed dosage (e.g. one dose two times a day) which had been dispensed at least twice. Prescriptions with irregular dosage, e.g. two-three doses three times a day, and drugs dosed “as needed” were excluded. Paper V includes repeat prescriptions both with and without fixed dosage.

At the time of the studies included in the thesis, the routine at Swedish pharmacies was to write/print information regarding the date of dispensation and amount of drug dispensed on the prescription each time it was filled. A pharmacist can view previous dispensations made at any Swedish pharmacy for up to one year. A prescription, with the four maximum documented refills, can be seen as a record of a patient’s refill adherence during one year.

Settings

County of Jönköping (Papers I-II)

The studies reported in Papers I and II were performed using data from manually collected repeat prescriptions in the county of Jönköping. The county of Jönköping has 332,000 inhabitants, corresponding to 3.6% of the Swedish population [56]. It is located in the middle of the southern part of Sweden, and contains 2% of the Swedish land area [56] (Figure 1). There are 13 municipalities with 35 health centres, three hospitals and 33 pharmacies in the county [142]. The drug utilization in the county of Jönköping approximately equals the Swedish average (628 and 620 DDD per inhabitant, respectively, in the year 2000) [65].
The studies reported in Papers III, IV and V were performed using data from manually collected repeat prescriptions as well as repeat prescriptions from a pharmacy record database in the county of Jämtland. The county has a population of approximately 127,000 inhabitants [56] and is located in the middle of Sweden (Figure 1). Jämtland includes 8% of the Swedish land area, but only 1.4% of the population [56]. The county hospital in Östersund dominates the health care service, but there are also 30 health centres and 23 pharmacies [143]. The drug utilization in the county of Jämtland was 579 DDD per inhabitant in the year 2000 [65].

Assessing refill adherence (Papers I-V)

Satisfactory refill adherence for each repeat prescription, assessed either from manually collected repeat prescription or from a pharmacy record database, was defined as dispensed refills covering 100±20% (Papers I-IV) of the prescribed treatment time, calculated as shown in the formula:
This approach is called the Refill Compliance Rate (RCR) \[134\] and the cut-off point (100\pm20\%) used is based on previous studies \[30-32\].

In Paper V, satisfactory refill adherence was defined as \(>80\%\) of prescribed treatment time \[58, 73, 144\]. In all other papers, undersupply means that the patient had drug dispensed to cover \(<80\%\) of the prescribed treatment time and oversupply \(>120\%\) of prescribed treatment time.

A patient with 100\% refill adherence would be dispensed a drug for a treatment period of 100 days and then get back to the pharmacy to pick up a refill after 100 days (indicating no gaps between the fills). A divergence from prescribed treatment time of more than 20\% would either lead to a treatment gap, i.e. undersupply, or drug stockpiling, i.e. oversupply. To evaluate the extent to which each patient had their prescriptions refilled over time, the supply for each prescribing was analysed over the entire year as shown in Figure 2.

A new approach was introduced to assess refill adherence, i.e. “patient profiles” (Paper V). These profiles consist of a graph per patient with the date of each dispensation and the time period covered by the dispensed drugs along the x-axis and the different drugs along the y-axis. Patients’ dispensation

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**Figure 2.** Evaluation of refill adherence of a repeat prescription with 100 days’ prescribed treatment time. In the left graph the patient has satisfactory refill adherence, i.e. has medicine available during the whole period, whereas the patient in the right graph has undersupply because of a gap of 30 days in the middle of the period.
patterns and treatment persistency over time were assessed based on the graphs using visual inspection or “eyeballing”, which is a more direct method of analysis. All patient graph assessments were carried out by two independent raters and an inter-rater agreement was calculated. The final classification of refill adherence was determined by consensus.

Data sources

Papers I-II
The studies (Papers I-II) were performed using data from repeat prescriptions collected during one week of November 2002 at the 16 largest pharmacies in the county of Jönköping. All types of dispensed drugs were covered. No pharmacy record database was available in the county of Jönköping.

The pharmacy staffs were instructed to make photocopies of all repeat prescriptions (both sides) which had at least two dispensations and fixed dosing. The copies were de-identified at the pharmacies and sent to the research group. The refill adherence per dispensation was determined from each prescription.

In Paper II the treatment gaps were analysed as the number of days that the patients had no drug available for their treatment (refill adherence <80%). For patients with refill adherence >120% the cost of oversupply of each drug package dispensed was determined from the official Swedish drug price list of November 2002. To calculate the cost of oversupply, the number of days beyond 120% coverage for each prescription was multiplied by the cost per day. The costs were measured in Swedish Krona (100 SEK = € 11 (November 2002)).

Papers III-V
The studies (Papers III-V) were performed using data from the local pharmacy record database in the county of Jämtland. This database has been available since 1970 [131, 145]. Prescriptions dispensed to individuals born on the same four dates of each month are included, yielding a representative sample of 13% of the population (17 000 persons) [131]. The participation is voluntary and only prescriptions dispensed at a pharmacy in the county are registered. Tourists and other non-residents of the county are excluded from the database. The database contains information regarding medicine dispensations per individual, including prescribed drugs, doses, and date dispensed, amount of supplied drug and category of prescribing physician (or
nurse/dentist) [131]. The identities of the individuals and the doctors are confidential. Diagnoses are not included in the database.

Paper III includes prescriptions issued to residents of Jämtland for asthma/COPD drugs, adrenergics and steroids in combination for inhalation (ATC code R03AK) and glucocorticosteroids and anticholinergics for inhalation (ATC code R03B) dispensed in 2002 to individuals 10 years and older. Younger patients were excluded since these drugs can be dispensed for other indications. In this paper, both manually collected repeat prescriptions and prescriptions from the pharmacy record database with at least two dispensations and fixed dosage were included for the same year for comparative analyses in refill adherence. The manually collected repeat prescriptions were collected from filed prescriptions for 2002 at a large pharmacy in Östersund, the largest city in the county of Jämtland. Refill adherence for a four-year period 1999-2002 from the pharmacy record database was also determined.

Paper IV includes dispensed asthma/COPD drugs, adrenergics and steroids in combination for inhalation (ATC code R03AK), glucocorticosteroids (ATC code R03BA) and anticholinergics for inhalation (ATC code R03BB) from the Jämtland pharmacy record database for the period 1994-2003 to individuals 60 years and older. The refill adherence was analysed separately for the three drug types and in relation to repeat prescription characteristics like patient gender, age and treatment time.

Paper V includes patients 50 years and older who had both diabetes and asthma/COPD drugs dispensed during 2001-2003. Patients younger than 50 years were excluded since few of these patients used drugs for type 2 diabetes. Drugs included were insulin (ATC code A10A), oral antihyperglycaemic drugs (ATC code A10B), long-acting adrenergics (ATC code R03AC), combination products for inhalation, (ATC code R03AK), glucocorticosteroids (ATC code R03BA) and anticholinergics (ATC code R03BB). Drugs like insulin without fixed dosages were also included and the refill adherence was based on the assumption that the patients used one defined daily dose (DDD) per day. Short-acting selective beta-2-adrenoreceptor agonists (ATC code R03AC) were excluded since they are prescribed for use “as needed” and the refill adherence for these drugs could therefore not be determined. Refill adherence was determined from calculated refill adherence and from patient profiles.
Statistical analysis

Data were analysed using the Microsoft® Office Excel 2003 software and SPSS for Windows, version 12.0 [146]. A value of \( p<0.05 \) was considered significant in this thesis.

- z-test was used to determine the differences in refill adherence related to patient characteristics, type of drug and reimbursement level (Paper I).
- Median and interquartile deviation was used to illustrate under- and oversupply among repeat prescriptions with 90-100 days dispensation intervals (Paper II).
- Independent t-test was used when comparing differences in cost between exempt and non-exempt patients (Paper II).
- A 95% confidence interval (CI) was used to compare proportions in refill adherence (Papers III-V).
- Mann-Whitney test and a crude regression (univariate analysis) were used to compare differences in refill adherence between age, gender and treatment time (Papers IV-V).
- Logistic regression was used to determine which explanatory variables influence the refill adherence, while adjusting for covariates (Papers IV-V). Variables in the univariate analysis with \( p \)-values less than 0.1 were included in the logistic regression model (Paper V) [147].
- Cohen’s kappa was used to measure inter-rater reliability between the two raters (Paper V).
- Correlation coefficient was used to compare refill adherence to patients with diabetes and asthma/COPD drugs (Paper V).
- The Bland and Altman limits of agreement method was used to compare patients’ refill adherence to diabetes and asthma/COPD drugs (Paper V).

Ethics

According to Swedish regulations, no permission was needed from the Research Ethics Committee in relation to the studies included in Papers I and II because no personal identification was used on the prescriptions, only gender and age. The Regional Research Ethics Committee at Lund University (Dnr. 318/2004) approved the studies included in Papers III-V.
RESULTS

An overview of the results is presented in Table 2. Refill adherence was assessed as satisfactory, under- and oversupply, respectively. In general, for all long-term medication, satisfactory refill adherence was 57% and for asthma/COPD it varied between 28 and 42%. Undersupply was more common than oversupply for dispensed asthma/COPD drugs, whereas no difference was found between under- and oversupply for all drugs used in long-term medication. More details are presented below.

Table 2. Overview of the results from the included papers.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Period</th>
<th>Included drugs</th>
<th>Included repeat prescriptions (rp)</th>
<th>Satisfactory refill adherence (%)</th>
<th>Under-supply (%)</th>
<th>Over-supply (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &amp; II</td>
<td>Nov 2001-Nov 2002</td>
<td>All drugs for long-term medication</td>
<td>3636 (rp)</td>
<td>57</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>III</td>
<td>2002, 1999-2002</td>
<td>Asthma/COPD</td>
<td>285(^1), 490(^2) (rp)</td>
<td>35(^1), 28(^2)</td>
<td>42(^1), 43(^2)</td>
<td>23(^1), 29(^2)</td>
</tr>
<tr>
<td>IV</td>
<td>1994-2003</td>
<td>Asthma/COPD</td>
<td>819 (rp)</td>
<td>28</td>
<td>53</td>
<td>18</td>
</tr>
<tr>
<td>V</td>
<td>2001-2003</td>
<td>Diabetes/Asthma/COPD</td>
<td>56 (p)</td>
<td>68</td>
<td>32</td>
<td>---</td>
</tr>
</tbody>
</table>

\(^1\) Manually collected repeat prescriptions in 2002  
\(^2\) Pharmacy record database in 2002

Satisfactory refill adherence (Papers I-V)

All drugs for long-term medication (Papers I-II)

Among 3,636 copies of repeat prescriptions for long-term treatment, 57% were dispensed with satisfactory refill adherence. The differences were large between different drug groups and the most important drug groups are shown in Table 3 (Paper I).
<table>
<thead>
<tr>
<th>ATC code</th>
<th>Type of drugs</th>
<th>Number of prescriptions</th>
<th>Satisfactory refill adherence %</th>
<th>Undersupply/oversupply %</th>
</tr>
</thead>
<tbody>
<tr>
<td>G03A</td>
<td>Hormonal contraceptives for systemic use</td>
<td>42</td>
<td>81</td>
<td>12 / 7</td>
</tr>
<tr>
<td>C01A</td>
<td>Cardiac glycosides</td>
<td>44</td>
<td>75</td>
<td>9 / 16</td>
</tr>
<tr>
<td>H03AA</td>
<td>Thyroid hormones</td>
<td>100</td>
<td>71</td>
<td>13 / 16</td>
</tr>
<tr>
<td>N06AA</td>
<td>Non-selective monoamine reuptake inhibitors</td>
<td>30</td>
<td>67</td>
<td>20 / 13</td>
</tr>
<tr>
<td>C07AB</td>
<td>Beta blocking agents, selective</td>
<td>307</td>
<td>66</td>
<td>14 / 21</td>
</tr>
<tr>
<td>B01AC</td>
<td>Platelet aggregation inhibitors excl. heparin</td>
<td>285</td>
<td>63</td>
<td>14 / 22</td>
</tr>
<tr>
<td>M04A</td>
<td>Antigout preparations</td>
<td>40</td>
<td>63</td>
<td>20 / 18</td>
</tr>
<tr>
<td>C10AA</td>
<td>HMG CoA reductase inhibitors</td>
<td>212</td>
<td>62</td>
<td>11 / 27</td>
</tr>
<tr>
<td>A10B</td>
<td>Oral blood glucose lowering drugs</td>
<td>87</td>
<td>59</td>
<td>16 / 25</td>
</tr>
<tr>
<td>C09A</td>
<td>ACE Inhibitors</td>
<td>136</td>
<td>59</td>
<td>12 / 29</td>
</tr>
<tr>
<td>G03C</td>
<td>Estrogens</td>
<td>161</td>
<td>58</td>
<td>25 / 17</td>
</tr>
<tr>
<td>N06AB</td>
<td>Selective serotonin reuptake inhibitors</td>
<td>101</td>
<td>58</td>
<td>22 / 20</td>
</tr>
<tr>
<td>C03C</td>
<td>Loop diuretics</td>
<td>144</td>
<td>57</td>
<td>22 / 22</td>
</tr>
<tr>
<td>C03A</td>
<td>Thiazides</td>
<td>56</td>
<td>55</td>
<td>27 / 18</td>
</tr>
<tr>
<td>N03</td>
<td>Antiepileptics</td>
<td>51</td>
<td>55</td>
<td>25 / 20</td>
</tr>
<tr>
<td>N05A</td>
<td>Antipsychotics</td>
<td>31</td>
<td>52</td>
<td>32 / 16</td>
</tr>
<tr>
<td>A06</td>
<td>Laxatives</td>
<td>45</td>
<td>51</td>
<td>31 / 18</td>
</tr>
<tr>
<td>C09C</td>
<td>Angiotensin II-blockers</td>
<td>67</td>
<td>49</td>
<td>19 / 31</td>
</tr>
<tr>
<td>R03A</td>
<td>Adrenergic anti-asthmatics for inhalation</td>
<td>40</td>
<td>43</td>
<td>23 / 35</td>
</tr>
<tr>
<td>N02A</td>
<td>Opioids</td>
<td>31</td>
<td>42</td>
<td>29 / 29</td>
</tr>
<tr>
<td>A02BC</td>
<td>Proton pump inhibitors</td>
<td>93</td>
<td>39</td>
<td>37 / 25</td>
</tr>
<tr>
<td>M01A</td>
<td>Anti-inflammatory and antirheumatic products, non-steroids</td>
<td>67</td>
<td>39</td>
<td>37 / 24</td>
</tr>
<tr>
<td>R03B</td>
<td>Other anti-asthmatics for inhalation</td>
<td>47</td>
<td>34</td>
<td>40 / 26</td>
</tr>
<tr>
<td>M01AH</td>
<td>Coxibs</td>
<td>22</td>
<td>23</td>
<td>41 / 36</td>
</tr>
<tr>
<td>N06D</td>
<td>Anti-dementia drugs</td>
<td>5</td>
<td>20</td>
<td>20 / 60</td>
</tr>
</tbody>
</table>
The highest satisfactory refill adherence was 81% for hormonal contraceptives for systemic use and the lowest was 20% for anti-dementia drugs. Anti-asthmatics for inhalation (34%), proton pump inhibitors (39%) and anti-inflammatory and anti-rheumatic drugs (39%) all had low satisfactory refill adherence.

Repeat prescriptions dispensed to patients with full exemption from charges showed lower satisfactory refill adherence than prescriptions dispensed to patient without exemption from charges (51% and 58%, respectively; \(p<0.05\)).

**Drugs for asthma/COPD (Papers I, III-V)**

The satisfactory refill adherence for asthma/COPD drugs varied between 21 and 42%. Figure 3 presents the distribution of repeat prescriptions for inhaled corticosteroids in relation to refill adherence (Paper IV).

**Figure 3.** Distribution of repeat prescriptions for inhaled corticosteroids (n=569) in relation to refill adherence during the ten-year period of 1994-2003. Black bars represent prescriptions with satisfactory refill adherence, i.e. 100±20% of prescribed treatment time.

The comparison between manually collected repeat prescriptions and the pharmacy record database resulted in a tendency for a lower satisfactory refill adherence for manually collected repeat prescriptions (Paper III). A
longer study period does not seem to influence the level of satisfactory refill adherence (Table 4).

**Table 4.** Refill adherence for asthma/COPD medicines (ATC codes R03AK and R03B) estimated from manually collected repeat prescriptions and the pharmacy record database in the county of Jämtland, Sweden.

<table>
<thead>
<tr>
<th>Refill adherence</th>
<th>Data capturing methods</th>
<th>Manually collected repeat prescriptions % (year 2002; n=285)</th>
<th>Pharmacy record database % (year 2002; n=490)</th>
<th>Pharmacy record database % (1999-2002; n=858)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfactory</td>
<td></td>
<td>35</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Undersupply</td>
<td></td>
<td>42</td>
<td>43*</td>
<td>53*</td>
</tr>
<tr>
<td>Oversupply</td>
<td></td>
<td>23</td>
<td>29*</td>
<td>18*</td>
</tr>
<tr>
<td>Total non-adherence</td>
<td></td>
<td>65</td>
<td>72</td>
<td>71</td>
</tr>
</tbody>
</table>

* Significant difference in refill adherence between pharmacy record database 2002 and pharmacy record database 1999-2002 in undersupply and oversupply, $p<0.05$.

Undersupply (Papers I-V)

All drugs for long-term medication (Papers I-II)

The proportion of repeat prescriptions showing an undersupply in relation to long-term treatment was 21% ($n=762$) of all repeat prescriptions. In Paper I, the variation between different drug groups was approximately 11-40% (Table 3); HMG CoA reductase inhibitors had 11% undersupply and steroids for inhalation had 40% undersupply. For the repeat prescriptions with 90-100 days dispensation intervals, the median treatment gap per interval was $53\pm23$ (interquartile deviation) days (Paper II). Accordingly, this implies that non-adherent patients were without drugs more than half of the prescribed treatment time. Undersupplies for repeat prescriptions dispensed to patients with exemption from charges were lower than for those without exemption (16% and 22%, respectively; $p<0.05$).

Drugs for asthma/COPD (Papers I, III-V)

The variation in undersupply for included asthma/COPD drugs was 40-59%. The distribution of undersupply of inhaled corticosteroids is illustrated in Figure 3, where the level of undersupply is fairly constant down to the 5% refill adherence level. In Paper III, the comparison of undersupply during
one year between manually collected repeat prescriptions and repeat pre-
scriptions from a pharmacy record database indicated no differences, but the
comparison of one-year data to data for the four-year period showed an in-
creased undersupply with longer treatment time (Table 4).

Oversupply (Papers I-IV)

All drugs for long-term medication (Papers I-II)
In total, 22% (n=816) of the repeat prescriptions were dispensed with over-
supply and the variation between different drug groups was approximately
16-35% (Table 3). Cardiac glycosides and thyroid hormones were dispensed
with 16% oversupply whereas adrenergic anti-asthmatics for inhalation were
dispensed with 35% oversupply (Paper I). For the repeat prescriptions for all
drugs used in long-term medication with 90-100 days dispensation intervals,
the median oversupply per interval was 28±6 (interquartile deviation) days
(Paper II). There was a significantly higher oversupply for repeat prescrip-
tions dispensed to patients exempt from charges than for repeat prescriptions
dispensed to patients without exemption (33% and 19%, respectively; p<0.05).

Drugs for asthma/COPD (Papers I, III-IV)
The oversupply among repeat prescriptions for included asthma/COPD
drugs was 12-26%. The repeat prescription data from the pharmacy record
data base for one year indicate a higher oversupply than the manually col-
llected repeat prescriptions (29% and 23%, respectively; p>0.05) in Paper III
(Table 4). Comparing one-year to the four-year data from the pharmacy re-
cord database showed a higher oversupply to one-year (29%) than to four-
year (18%). In Paper IV, the differences in oversupply between combination
drugs for inhalation, inhaled corticosteroids and anticholinergics for inhala-
tion showed that there was a greater oversupply of combination drugs and
anticholinergics for inhalation than for inhaled corticosteroids.

Refill adherence to two long-term therapies (Paper V)
The pharmacy record database included 5,563 patients 50 years and older in
2001. Among these patients, 93 individuals had dispensed drugs for both
diabetes and asthma/COPD during 2001-2003 and 56 individuals fulfilled
the inclusion criteria. For each of these an individual patient profile graph
was produced. In Figure 4, three representative patient profiles illustrate the
variation between the patients’ drug supply when using diabetes and asthma/COPD drugs.

Figure 4. Patient profiles for three individuals. Patient 1: Undersupply of all drugs. Patient 2: Satisfactory refill adherence to all three drugs, in contrast to the calculated refill adherence when this patient showed satisfactory refill adherence to glibenclamide and salmeterol but not to budesonide. Patient 3: Satisfactory refill adherence to diabetes drugs and undersupply of asthma/COPD drugs.
From the patient profiles it was concluded that 29 individuals had the same dispensation patterns (same dispensation interval) for both diabetes and asthma/COPD drugs. Most of these patients (86%) had satisfactory refill adherence and 14% showed an undersupply. Among the 27 patients with different dispensing patterns for both drugs, 93% showed a satisfactory refill adherence to the diabetes drugs and an undersupply of asthma/COPD drugs. The rest of the patients (7%) showed an undersupply of the diabetes drugs and a satisfactory refill adherence to asthma/COPD drugs. The inter-rater reliability for assessing refill adherence based on patient profile graphs was \( \kappa=0.80 \), which is consider to be excellent [148].

Refill adherence based on patient profiles showed that 89% (CI=81-97) of the patients were classified as having satisfactory refill adherence to diabetes drugs and 48% (CI=35-61) to asthma/COPD drugs. For calculated refill adherence the corresponding level was 68% (CI=59-77) to diabetes drugs and 42% (CI=32-52) to asthma/COPD drugs. There is a significant difference in refill adherence between diabetes and asthma/COPD drugs based on both methods. This is also the case for undersupply. The correlation coefficient and the limit of agreement method showed the same results; there is a difference between dispensation patterns for patients with concomitant use of diabetes and asthma/COPD drugs.

Costs of oversupply for patients exempt and non-exempt from charges (Paper II)

The included 3,636 repeat prescriptions had a total sales value of 5.1 million SEK (€ 0.55 million). The extra cost of oversupply for the 517 non-exempt patients was 99,000 SEK (191 SEK per prescription) and for the 299 exempt patients the cost was 131,000 SEK (438 SEK per prescription). Accordingly, the difference in cost of oversupply between exempt and non-exempt patients amounts to 32,000 SEK or 247 SEK (€ 27) per prescription.

An extrapolation to all of Sweden from our sample means that the additional cost of oversupply for exempt patients compared to non-exempt patients amounts to 142 million SEK (€ 15 million) per year. This corresponds to 0.6% of the total cost of all prescribed drugs in Sweden 2002 [149].
Factors influencing adherence (Papers I, IV-V)

Gender
When all drugs for long-term medication were considered, more repeat prescriptions were dispensed to women (60%) than to men (40%) (Paper I). There was no significant difference in satisfactory refill adherence between repeat prescriptions dispensed to men and women ($p>0.05$). Men had more repeat prescriptions dispensed with oversupply than women ($p<0.05$) and fewer repeat prescriptions with undersupply ($p<0.05$). These differences were not seen for asthma/COPD or diabetes drugs in Papers IV and V ($p>0.05$). Prescriptions dispensed to women were to a greater extent exempt from charges than prescriptions dispensed to men (Paper I).

Age
Younger people (30-39 years) seem to have lower satisfactory refill adherence and higher undersupply than older people (Paper I). In Papers IV and V, there were no differences in refill adherence between ages for diabetes and asthma/COPD drugs ($p>0.05$).

Treatment time
Paper IV determined that repeat prescriptions dispensed over a period of two-four years had higher satisfactory refill adherence ($p<0.05$), whereas treatment time for five-ten years showed no differences in refill adherence ($p>0.05$) as compared to zero-one years of treatment. In Paper V, there was no difference in refill adherence between different years of treatment times for patients with dispensed diabetes and asthma/COPD drugs ($p>0.05$).
DISCUSSION

No previous Swedish study has focused on adherence to different long-term drug therapies. Similarly, no Swedish study has assessed refill adherence to asthma/COPD drugs. Researchers and doctors have expressed a need for Swedish data since data from other countries cannot be directly applied to the Swedish situation [21]. This thesis is the first large study of adherence to long-term medication focusing on some of the most common drug therapies in Sweden. The results establish that the adherence pattern to long-term drugs in Sweden is similar to those reported from other countries. Furthermore, this thesis has contributed to methods development regarding assessment of refill adherence based on pharmacy records. Repeat prescriptions from a pharmacy record database have been compared with manually collected repeat prescriptions. In addition, this thesis introduced a patient profile approach as a new method to illustrate and assess patients’ refill adherence. Based on the pharmacy record database, it was possible to determine refill adherence pattern for concomitant use of two different chronic drug treatments.

The most important conclusion from this thesis is that satisfactory refill adherence to asthma/COPD medication in Sweden is low, on average 30%. The same pattern is displayed for repeat prescriptions dispensed to the elderly. These results are in agreement with results from international studies even if large variations have been reported (40-78%) [10, 95, 96]. Furthermore, it was shown that undersupply to asthma/COPD drugs is more common than oversupply. Refill adherence measurement during a one-year period gave the same results independently of whether the repeat prescriptions are from a pharmacy record database or are manually collected. When patients had concomitant use of diabetes and asthma/COPD drugs, the dispensation patterns differed for these drugs, i.e. they did not have the same adherence pattern to both therapies. For example, diabetes drugs were more associated with satisfactory refill adherence and the asthma/COPD drugs more with undersupply.
Overview of studies included in the thesis

Based on the aims of this thesis (presented on page 28), the studies included to assess refill adherence are illustrated in Figure 5. The results of the large study (Paper I) on refill adherence to all drugs used in long-term medication were the bases for all the subsequent studies in Papers II-V.

Figure 5: Overview of the studies presented in the thesis.

The focus on assessing refill adherence to asthma/COPD drugs was decided based on the results in Paper I that showed that refill adherence to asthma and/or COPD was low. To verify the results in Paper I, a larger number of repeat prescriptions for asthma/COPD drugs were studied in Papers III-V. Improving adherence to asthma/COPD drugs is likely to improve therapy outcome in these diseases. This thesis contributes new information regarding adherence and non-adherence to asthma/COPD treatments.

Methodological considerations

Pharmacy records

A number of limitations must be considered when pharmacy records are used to measure refill adherence. First, the level of refill adherence is influenced by previous prescriptions’ refills, i.e. before the first registered dispen-
ation included in the study. This could have involved both undersupply and oversupply. However, there was no possibility to verify patients’ earlier dispensations, but if this had been possible it might have shown that some patients would have been considered adherent instead of non-adherent and vice versa.

Second, only filed repeat prescriptions were manually collected at the pharmacy in Östersund. The prescription is filed when all refills are dispensed or the expiry date has passed. This means that repeat prescriptions which were dispensed only twice, and for which the patient did not return to the pharmacy to obtain the rest of the refills, are not included in the study. These patients could be more non-adherent due to fewer dispensations or they might have had a seasonal asthma.

A third factor that may distort the refill adherence measured from repeat prescriptions in Papers I-III is the possibility that the patients have used more than one prescription for the same drug at the same time. In such a case, a patient with satisfactory refill adherence would be classified as non-adherent with undersupply. Paper III shows that 11% of the individuals had used more than one repeat prescription of the same medicine during the same year. The majority of these patients showed an oversupply. Oversupply might be a problem and is likely to differ for different diseases. Among those with undersupply only 3% used more than one repeat prescription. For the determination of undersupply, this was therefore not seen as a problem. In Papers III-V, a reliable pharmacy record database was used where all dispensations are registered and this potential error is therefore eliminated.

Further, in Papers I and II, 16 pharmacies in the county of Jönköping collected the repeat prescriptions. We were informed that, due to lack of time, some of these pharmacies did not copy all repeat prescriptions. It could be estimated that approximately 33% of all repeat prescriptions dispensed at the participating pharmacies were collected. However, there is no reason to believe that this sample would omit prescriptions for any particular type of drug and we consider that 33% is a large representative sample of the bulk of prescriptions. The assessed refill adherence (Table 3) should therefore be valid.

Finally, some of the prescriptions in our studies (Papers I-V) may have been intended for temporary medication only. However, such information was not apparent from the prescription or from the Jämtland database. It could be assumed that the number of such prescriptions is small and should not influence the results.
Settings
The county of Jönköping was selected for collecting prescriptions for the studies in Papers I and II since the level of drug utilization in this county is close to Sweden’s average [65]. The month of November was selected because the drug sales in this month are close to one-twelfth of the sales for the whole year [65]. In Paper I it was therefore concluded that the sample of repeat prescriptions from the county of Jönköping would be representative of that of all of Sweden.

Some limitations should be considered in the comparison of refill adherence determined using a pharmacy record database with those from manually collected repeat prescriptions during the same time and in the same area. The aim of the study in Paper III was to compare data collection methods and not to compare different populations. Since the patients’ identities in the database are confidential, it was not possible to compare the drug dispensations registered in the database with those from the manually collected repeat prescriptions for the same individuals. To minimize a potential error the two data sets should be as similar as possible. The manually collected repeat prescriptions were obtained from the largest community pharmacy in the town of Östersund, the major city in the county of Jämtland. This pharmacy dispensed 21% of the total prescriptions of the county [65]. Since commuting to Östersund is common, the prescriptions dispensed by the participating pharmacy represent inhabitants from all over the county. Therefore, the manually collected repeat prescriptions were considered to be representative for the whole county and therefore comparable with corresponding data from the pharmacy record database.

The pharmacy record database in Jämtland contains only prescriptions dispensed in the county. Therefore, if patients had their drugs refilled outside the county, these dispensed drugs are not registered in the database. Since there is no major city in the vicinity of Jämtland, it was assumed that only few prescriptions were filled outside the county.

Assessing refill adherence
The level of refill adherence is influenced by numerous factors and therefore drug supply may diverge from medication use and under- and oversupply from under- and overuse. The dispensation pattern may also fluctuate over time for an individual patient.

In Papers I-IV satisfactory refill adherence was defined as a drug supply covering 80-120% of prescribed treatment time. Patients in Sweden may refill the prescription with reimbursement when two/thirds of the prescribed
treatment time has elapsed [140]. Hence, the definition of satisfactory refill adherence might perhaps more correctly have been defined as 67-133% of prescribed treatment time. But this would have hampered international data comparisons. The definition or cut-off points should instead be based on clinical relevance. Many of the studies about adherence in the literature have used the definition 80-120% of prescribed treatment time [30-32]. So far this definition is not based on clinical data. The level of acceptable divergence from the prescribed dose is likely to vary for different therapies. For most therapies the acceptable level of adherence has not been described in the literature. HIV therapy is an exception. Here the patients need to take a minimum of 95% of prescribed antiretroviral doses in order to avoid resistance development [150], even if this cut-off point could possibly be decreased today due to better medications. For diseases like asthma and COPD, lower levels of adherence than HIV are probably acceptable, but this has not been studied. The changes in recommended minimal intake of HIV therapy indicated that the level of satisfactory adherence should be evaluated at regular intervals, according to treatment changes. If we do not take into account different therapies’ cut-off points and also continuously revise them, how can we then properly assess adherence? Today’s assessments favour comparability at the expense of relevance. On the other hand, however, today’s assessments may not really be comparable since they may be based on irrelevant cut-off points for most treatments. At this time, the definitions of satisfactory adherence for most diseases are lacking and therefore 80-120% is the most reliable definition today.

The assessed refill adherence may be influenced by whether a patient is hospitalised and hence supplied with medication by the hospital. Such a patient could be considered non-adherent although the patient had satisfactory drug supply. Today in Sweden, most patients are normally hospitalised for less than one week, and then referred to other types of care with medication obtained from prescriptions. Therefore hospitalization should not be a major problem in the thesis.

Asthma/COPD

There are certain problems associated with the determination of refill adherence to asthma/COPD drugs since the diseases often have irregular dosage schedules. Therefore, many of the dispensations, both among the manually collected repeat prescriptions and those recorded in the database, were excluded since they were prescribed to be taken “as needed” or with irregular dosage (e.g. two-three doses two times a day). Therefore it was sometimes difficult to determine the refill adherence over a long period, as seen in Paper IV, where the aim was to analyse repeat prescriptions during a ten-year period although most of the repeat prescriptions were only analysed for a
period shorter than three years. In Paper V, where the refill adherence to drug therapies for patients with two chronic diseases was investigated, the use of insulin and long-acting adrenergics without fixed dosing were assumed to be one DDD per day. For most asthma/COPD drugs, except short-acting selective beta-2-adrenoreceptor agonists, there is a close agreement between prescribed daily doses and DDD [151] but for diabetes this has not been investigated. The doctors may also orally adjust the doses up or down without documenting this on the prescription. This may occur, for example, when the patient becomes ill and the patient can therefore deviate from the prescribed dose but still be adherent to the doctors’ oral advice. Patients can also change the dose on their own initiatives. No such information was available in these studies.

In the pharmacy record databases in Sweden and in most of the manually collected repeat prescription, information about diagnoses is not reported. Asthma and COPD share some characteristics but are in many aspects two separate conditions. Ideally, these conditions should be analysed separately, but this was not possible due to lack of diagnostic information in the database. However, the assumption is that the included drugs are prescribed for preventive treatment to patients with diagnosed asthma and/or COPD, since these drugs only have these indications approved in Sweden. Short-acting selective beta-2-adrenoreceptor agonists may be prescribed for other respiratory disorders than asthma/COPD, but they were excluded here.

Adherence and non-adherence to chronic drug treatment

Patients with chronic diseases can have different drug refill strategies and therefore also different adherence. A majority of the prescriptions were refilled close to the time when the last dose was estimated to be used (<68% of the repeat prescriptions in this thesis); others were undersupplied (21-59% of the repeat prescriptions) or oversupplied (12-29% of the repeat prescriptions). For the patient, adherence to drug therapy is of interest if the prescribing is proven to be beneficial. The right medication should be prescribed for the right person, in the right dose, at the right time, for the right condition and for the right reason. A meta-analysis concluded that good adherence to proven beneficial drug therapy is associated with lower mortality (Odds Ratio (OR) 0.55; 95% CI 0.49-0.62) than good adherence to harmful drug therapy (OR 2.90; 95% CI 1.04-8.11) [13]. Non-adherence to prescribed medication can sometimes be justified, e.g. if the patient gets side-effects and makes an intentional and rational decision not to follow through on the prescribed medication. In this connection, the concept of “intelligent non-compliance”
has been discussed [23]. The aim of all drug therapy is benefit for the patient, not adherence in itself.

Adherence to asthma/COPD drugs not only depends on when the drugs are taken, but also on how. Even if a patient has satisfactory adherence, the inhalation technique could be incorrect and inadequate amounts of the drug are delivered. In one study of inhaled drugs [37], the two most common errors made by patients were device-independent errors and included not breathing out before actuation of the device (29%) and failure to hold the breath for a few seconds after inhalation (28%). These errors were observed in 40-47% of the patients and some patients made more than one error. Accordingly, adherence may be improved by educating both patients and physicians in the correct use of inhaler devices.

Patients’ attitudes to drug treatment seem to influence adherence more than clinical and socio-demographic characteristics [4]. Lack of motivation and readiness before initiating the treatment are other factors that influence adherence [4, 51]. An important key to improving patients’ adherence behaviour is a patient-centred and open discussion at the start of the therapy including its complexity and the potential side effects, and other factors which may modify patients’ perception of the likelihood of adherence [46]. In this thesis, variables that could influence patients’ attitudes have not been studied since this was not the aim of the investigations.

Satisfactory refill adherence
The variation in satisfactory refill adherence between different types of long-term medications was large, ranging from 81% for contraceptives to 20% for anti-dementia drugs (Table 3). Women using contraceptives are probably highly motivated to have constant access to the drugs. Some drugs (serotonin reuptake inhibitors, AII blockers) had lower satisfactory refill adherence than related older drugs (tricyclic antidepressants, selective beta-blockers) despite allegedly fewer side effects, which should favour higher adherence [152, 153]. Anti-asthmatics for inhalation had low satisfactory refill adherence and this is in agreement with previous studies [10, 57, 95-98, 100-102]. In the literature, satisfactory refill adherence varies depending on drug treatment. A review analysed the level of satisfactory refill adherence to oral hypoglycaemic drugs and found a variation from 36% to 93% [154]. In another large drug group, antihypertensive drugs, 53% of the patients had satisfactory refill adherence [32]. In Paper IV, inhaled corticosteroids, anticholinergics and combinations of adrenergics and steroids all had low satisfactory refill adherence. The exceptionally low adherence rate for asthma/COPD treatment including steroids initiated detailed studies.
In Paper III, satisfactory refill adherence was compared for manually collected repeat prescriptions with repeat prescriptions from the pharmacy record database for 2002. The expectation was that repeat prescriptions from the database should have higher satisfactory refill adherence than for the manually collected ones, since the database registered and linked all dispensations for the individuals during the study period. The results in the study indicated the opposite, but the difference was not significant. One explanation could be that all manually collected repeat prescriptions were filed at the pharmacy in Östersund and therefore all refills were often dispensed on the prescription. Probably, if the repeat prescriptions were collected continuously as in Papers I and II, lower satisfactory refill adherence might be observed for manually collected repeat prescriptions than from the database.

**Undersupply**

Over 40% of the asthma/COPD drugs were undersupplied and therefore the patients could not medicate as intended by the prescribers. This is in agreement with several reports in the literature [59, 99]. In an international cohort study [99] with 8,829 subjects from 14 countries, only 17% had used inhaled corticosteroids on a daily basis at follow-up. Another study [59] showed that only 36% of the patients had used inhaled corticosteroids on a regular basis. Factors associated with underuse of inhaled corticosteroids were young age, non-white race, lower symptom severity, lower use of inhaled \( \beta \)-agonist and not possessing a peak flow meter [59]. Other explanations for undersupply include the possibility that some patients may be afraid to use steroids over long periods and may thus reduce or discontinue the treatment. Secondly, inhaled corticosteroids do not have an immediate effect and it is therefore more difficult to motivate the patients to be adherent. Some patients relieved from symptoms may believe that they have been cured of their asthma and therefore decide that they no longer need to take their medicine. Finally, non-adherence for elderly patients may increase with concurrent diseases, polypharmacy and sensitivity to adverse drug reactions [38].

Patients with undersupply of a drug most likely underuse their drugs. Patients with a refill adherence of 80% lack drugs for 18 days of a normal 90-day treatment period. This implies that the range defined as satisfactory refill adherence might inflict considerable gaps in the treatment. A treatment gap of 18 consecutive days could lead to therapeutic failure depending on the disease and treatment. For patients with HIV this is especially unsatisfactory [150]. For asthma/COPD, the therapeutic consequences of undersupply may be that the patients have more symptoms or adjust to unnecessary breathing problems or acquire more respiratory infections. The median medication gap for patients with undersupply reported in Paper II was 53 days of a 90-100 days’ treatment period. Many studies have shown that non-adherence is
strongly associated with increased morbidity [12, 70] and mortality [13, 71, 103], but in this study there was no possibility to explore the health consequences of low adherence. More attention should be directed toward developing solutions that reduce preventable morbidity, mortality and costs association with drug-related problems.

Oversupply

Oversupply is more difficult to interpret than undersupply. Therefore many studies do not indicate an upper level of refill adherence [58, 73, 144]. Oversupply can involve drug overuse and drug dependence that might lead to medical problems, but it can also involve patients giving their drugs to others. Another possible cause of oversupply is drug stockpiling, particularly for patients exempt from charges. Therefore, it is of interest to have an upper cut-off point for refill adherence, for instance to analyse the economic consequences of oversupply in relation to the reimbursement system. In Paper I, significantly higher oversupply was found for patients exempt from charges than for those who were non-exempt, 33% and 19% respectively. For some patients, the doctor might recommend increasing the dosage at some stage, e.g. during a cold when the patients has asthma. This would result in more frequent refills and be registered as oversupply. Moreover, for practical reasons patients with asthma/COPD might want to have several inhalers, at home, at work, at the vacation home and/or in the car. Such stockpiling is probably the most common reason for oversupply in this thesis.

Much of the dispensed medication is never used because of oversupply, side effects, changed treatment, low patient adherence or the patient’s death [155]. Therefore, some packages are returned to the Swedish pharmacies for destruction. The amount of returned drugs has been estimated to be about 4.6% of concomitant sales in volume with a value of 600 million SEK (€ 65 million) per year [156]. The stockpiling may thus be considerably larger than estimated here from the refill adherence of repeat prescriptions.

Refill adherence over a one-year period compared to that over a four-year period

A comparison of refill adherence in the pharmacy record database for a one-year and a four-year period might indicate if a one-year study period is acceptable for estimating refill adherence. As shown in Paper III the satisfactory refill adherence level for the four-year period does not differ from that of the one-year period. The one-year study period seems to underestimate
the proportion of undersupply and overestimate oversupply. Hence, over shorter time periods there is a risk of underestimating non-adherence.

Factors which contribute to the differences in under- and oversupply could be that some repeat prescriptions were dispensed outside the county of Jämtland and were therefore not registered in the database (no information). This is estimated as undersupply and might be more common during a longer time period. Oversupply can also even out over four years, since a one-year oversupply can be compensated by a one-year undersupply. Depending on the cut-off point when refill adherence is determined, the patient might either be adherent or non-adherent. Therefore, this study concludes that longer study periods represent a more reliable pattern of refill adherence than one year and give a better overview of patients’ refill adherence. We have been unable to find studies comparing refill adherence for two different time periods, but longitudinal studies of adherence showed an adherence level of 50-95% depending on drug type [58, 120, 121, 123], and the adherence decreased with increased number of treatment years [120, 121, 123].

In Sweden, for studies assessing refill adherence before the new national pharmacy record database was set up and in areas where a previous local pharmacy record database is not available, refill adherence information may be obtained from copies of the patients’ repeat prescriptions as in Papers I-II. This means that when estimating refill adherence before the year 2005, the vast majority of all estimations of refill adherence must be based either on manually collected repeat prescriptions, or on data from one of two local pharmacy record databases in the county of Jämtland [131] and in Tierp [132]. Some years in the future, when more data has been included in the national database, this will be a comprehensive data source for refill adherence studies.

Refill adherence to two long-term therapies

The patient profiles (Figure 4) for patients with concomitant use of diabetes and asthma/COPD drugs were used as a new approach introduced to complement the calculated refill adherence. These drugs, diabetes and asthma/COPD, were chosen since the drugs are specific for these two diagnoses and they are used in chronic lifelong diseases. It could be argued that the comparison is not justified since the two diseases are very different, as are the types of treatment. However, the aim was to evaluate whether the refill adherence related to one chronic disease differs from refill adherence for another chronic disease.
The patient profiles seem to increase the accuracy in the determination of each patient’s refill adherence over time (Figure 4, patient 2). In Paper V, the inter-rater reliability score (κ=0.80) indicated that the raters interpreted the graphs consistently and thus indicated a feasible and reliable method for estimating patients’ overall adherence. The refill adherence determined based on the patient profiles was in the same direction as the calculated refill adherence but showed a somewhat higher satisfactory refill adherence for diabetes drugs than for asthma/COPD. The reason could be that the patients consider diabetes to be a more serious disease than their asthma/COPD, since severity of the illness is one factor that influences adherence [40] and therefore patients follow the prescribed therapy more rigorously.

The initial hypothesis that patients with satisfactory refill adherence to diabetes drugs would also have satisfactory refill adherence to asthma/COPD drugs was not supported. But it must be taken into consideration that the sample size was small. However, the same pattern was also found in a study with concomitant use of antihypertensive and lipid-lowering medication where half of the patients did not have the same adherence to both therapies [157]. A patient who uses two different drug treatments may have different reasons to be adherent to the different drug therapies. Therefore, in addition to patients’ attitudes other factors like disease characteristics and type of treatment may contribute as well. This was supported by Bardel et al. [60].

Costs of oversupply for patients exempt and non-exempt from charges

Oversupply leads to additional costs and in the sample of patients in Paper II the extra cost of oversupply among exempt compared to non-exempt patients was 32,000 SEK or 247 SEK (€ 27) per prescription (Paper II). The extrapolation of this cost from the county of Jönköping to the whole of Sweden may be justified knowing that the level of drug utilization in relation to the population (628 and 620 DDD per inhabitant, respectively, in the year 2000) and the level of cost per inhabitant (2,428 and 2,508 SEK per inhabitant, respectively, in the year 2000) is approximately equal for these areas [65]. Such an extrapolation showed that in 2002 patients with exemption from charges and oversupply generated 142 million SEK (€ 15 million) higher drug cost than patients without exemption. We have been unable to find any similar studies.

Oversupply of drugs, both for exempt and non-exempt patients, will lead to increasing cost of destruction, since patients change medication, get side effects, have low patient adherence or die [155, 156]. Therefore, health care
professionals should advise the patients to fill their prescription as intended, and to avoid oversupply.

A drug reimbursement system has an effect on adherence, and the drug consumption decreases with increased co-payment [52, 53, 55, 139]. Papers I and II also showed that undersupply was more common for non-exempt patients compared to exempt patients \( (p<0.05) \). People with low incomes also have lower adherence due to drug cost [55, 158, 159]. However, when the pharmacy reimbursement system pays part of the total cost of the drugs consumed, both the quantity consumed and the price of the products dispensed increase [139]. The reimbursement system will thus restrict overconsumption and oversupply. An effective measure for decreasing pharmaceutical oversupply could be a small co-payment for all prescriptions, but it would have the disadvantage of leading to health problems for patients with low incomes. In conclusion, Papers I-II indicated that the reimbursement system in Sweden means better drug supply and hopefully better adherence at a low cost (142 million SEK = € 15 million). It is also important that clinicians take an active role in discussing patients’ medication cost problems to minimize non-adherence.

Factors influencing adherence

The gender ratio of collected repeat prescriptions (60% women) in Papers I-II was similar to the gender ratio of prescription customers at Swedish pharmacies [65]. In Paper I there was no difference in satisfactory refill adherence between prescriptions dispensed to men and women, but repeat prescriptions to women showed higher undersupply and lower oversupply than repeat prescriptions to men. In Papers IV and V these differences were not seen for diabetes and asthma/COPD drugs; in other words there was no difference between gender and refill adherence. Gender differences in refill adherence may therefore depend on the type of therapy, but a quantitative review of patients’ adherence research concludes that there is no relationship between gender and adherence among adults [57]. However, a relationship exists among paediatric patients; in paediatric samples, women are more adherent than men [57].

Satisfactory refill adherence to all drugs used in long-term treatment tended to be lower among younger patients than among adults and older patients, as shown in previous studies [57-62]. This may explain why there were no differences in refill adherence between ages in Papers IV and V, in which only patients 50 years and older were included. The results were expected, since younger patients have more irregular schedules than adults and thus it is more difficult for them to remember to take the drugs.
In Paper V there was no difference in refill adherence between different years of treatment times for dispensed diabetes and asthma/COPD drugs, whereas in Paper IV there was a difference for repeat prescriptions dispensed for two-four years but not for five-ten years as compared to zero-one years of treatment. Repeat prescriptions dispensed for two-four years of treatment time indicated higher satisfactory refill adherence than zero-one years. This means that no general trend in lower satisfactory refill adherence with longer treatment time was seen as could be expected [120, 121, 123, 157]. An explanation could be that the patients forget to use the drug or decide to take a lower dose than prescribed as time goes by (more than four years) and the refill adherence therefore decreases again.

Improving patient adherence

Improving adherence is a continuous and dynamic process [1]. This thesis has indicated that the level of refill adherence is low. There is no single activity that will improve adherence of all patients. For patients with asthma and COPD, simplification of therapy like reducing dosing frequency, combined inhalers, type of inhaler or memory aids might be sufficient for motivated and informed patients, while education or psychological counselling will be more appropriate for others [6, 35, 38, 160, 161]. Adrenergics plus steroids in a single inhaler is also cost-effective [162, 163]. One study [64] concludes that elderly patients need better information on medication and various aids to improve adherence. Individuals receiving three or more drugs, or drugs from several doctors, living alone, and with predementia symptoms should have special attention because of higher risk of non-adherence [64]. Adherence and satisfaction are expected to be optimized when the prescriber arranges many short visits instead of few and longer visits [164, 165].

The health care professionals may also contribute to better adherence. Studies show that health care professionals need to enhance their education and their co-operation in training asthma/COPD patients to monitor their disease, for example by adjusting the treatment according to symptoms [166]. Better listening and communication skills of the health care professionals can also improve the way in which they present information, motivate patients and reinforce progress [9, 167, 168]. Quality indicators are probably helpful for health care professionals to improve therapies [169]. Open-ended questions and providing reassuring messages helps patients feel that they are part of a partnership that is aimed at controlling their condition [168].
Other important factors are respect for patients’ health beliefs and involving them in the treatment decision [170]. This can foster an atmosphere of mutual responsibility and concordance over prescribed medicine taking [160]. This can all be included in the term “concordance” which is promoted as a tool to improve adherence [4]. An underlying expectation based on this thesis is that health professionals want to construct programs for improved drug adherence. The programs could for example contain a more open-ended discussion between provider and patient about the patient’s attitude and readiness for treatment. The lack of a match between patient readiness and the prescriber’s attempts at intervention means that treatments are frequently prescribed to patients who are not ready to follow the prescriber’s treatment. Health care professionals should be able to assess the patient’s readiness to adhere, and provide information and advice on how to do it. It is also important to follow up the patient’s progress at every contact and identify any misunderstandings that may arise.

A stronger commitment to a multidisciplinary approach is needed to make progress towards adherence. It comprises coordination of a range of actions from physicians, nurses and pharmacists but also from researchers, health planners and policy-makers.
CONCLUSIONS

- Among repeat prescriptions (n=3636) to patients with different long-term medications, 57% were dispensed with satisfactory refill adherence whereas 21% were undersupplied (<80%) and 22% oversupplied (>120%). The variation in satisfactory refill adherence between different types of medicines was large (20-81%).
- When repeat prescriptions for long-term medication were dispensed with undersupply, patients had drugs available half of the prescribed treatment time. Patients who were exempt from charges had a higher oversupply (33%) than non-exempt patients (19%), leading to unnecessary costs for society.
- The proportion of satisfactory refill adherence, under- and oversupply for repeat prescriptions from a pharmacy record database (n=490) as compared to manually collected repeat prescriptions (n=285), did not differ over a one-year period. However, refill adherence based on a one-year period seems to underestimate undersupply and overestimate oversupply, as compared to a four-year period.
- More than 50% of the repeat prescriptions for preventive asthma/COPD drugs dispensed to elderly patients showed an undersupply.
- Patients with concomitant use of diabetes and asthma/COPD drugs showed disparate dispensation patterns for their two drugs. The use of patient profiles seems to be a feasible and reliable (κ=0.80) method to complement the calculated refill adherence method, but it needs to be further studied in larger and more divergent populations.
FUTURE ASPECTS

New and exciting potentials for pharmacoepidemiological research were made possible with the new national pharmacy record database that was set up in July 2005 in Sweden [129]. This new register contains linked patient data for all dispensed prescriptions from the whole Swedish population, but does not include data on over-the-counter (OTC) drugs, herbal remedies or medications used in hospital. Furthermore, it does not include information on diagnoses [129]. This register represents one of the largest population-based pharmacoepidemiological databases in the world [129]. The new register has opened the door for studies on a national level and will be very valuable when studying patterns of drug utilization. The information from the register is possible to link to other epidemiological registers in Sweden such as the Hospital Discharge Register and the Cause of Death Register. This gives good opportunities to explore drug use and disease associations and also the risks, benefits, effectiveness and health economical aspects of drug use. For example, it would be possible to use the register to verify the results in this thesis at a national level. One option would be to further study the refill adherence to concomitant drug use. To validate refill adherence assessments, it is important to study how often prescribers have orally adjusted a patients’ dose due to disease fluctuation over time without this being recorded on the prescription. Knowledge about this improves the reliability of the calculated refill adherence. Future studies may also utilise the national register to study patient profile patterns in larger and more divergent patient populations.

The necessary levels of adherence to different treatments for achieving positive treatment outcomes are not well studied. In the area of Acquired Immune Deficiency Syndrome (AIDS)/HIV some studies have been conducted, and it has been shown that patients with HIV need to take a minimum of 95% of prescribed antiretroviral doses in order to avoid resistance development [150]. The corresponding percentages for optimal treatment outcome for asthma/COPD drugs or other chronic diseases are not reported in the literature. Further research is therefore needed to establish these necessary adherence levels to optimize treatment outcome without having to aim for a 100% adherence level. Another important aspect is to further evaluate the use of new technologies such as electronic reminders using cell phones and personal digital assistants to help patients improve adherence. In addition,
more complex and well-designed interventions to improve adherence need to be performed.

In Sweden, all persons get all their drugs refunded over a certain limit. The maximum annual out-of-pocket amount is 1,800 SEK (€ 195). There is a need for further studies to evaluate whether the current refunding system impacts drug use and its variation in different age groups, in different income levels and for different drugs. Moreover, the Swedish pharmacy monopoly is presently under discussion. The government has initiated a commission of inquiry to investigate how the monopoly can be abolished. If that happens both prescription drugs and OTC drugs may become more available and hopefully also at a lower price (the reimbursement system will probably remain in place). Furthermore the accessibility might change and there might also be potential consequences regarding pharmaceutical competence of drug distribution and patient safety issues. This could have an impact on adherence, making it important to evaluate the consequences of a deregulation.

Accomplishing concordance between patients and health care personnel such as doctors, nurses and pharmacists is the best approach to achieving good adherence. Therefore, it is important to feed back the results of well-designed interventions to stimulate health care professionals to create concordance at each patient encounter and how to use concordance as a tool to improve patient adherence. Further, patient adherence needs to be monitored and patients’ motivation and readiness to adhere must be addressed continuously. This thesis shows a complex adherence picture, i.e. a wide variation in dispensed prescriptions and hence in patients’ medication behaviour. Further analysis of this complex pattern needs to be considered in future studies.
Följsamhet har beskrivits som den ultimata absorptionsbarriären och det illustreras i följande citat av C. Everett Koop: ”Läkemedel verkar inte hos patienter som inte tar dem”. Bristande följsamhet till läkemedelsordinationer är ett välkänt problem och internationella studier visar att följsamheten är högst 50% vid långtidsmedicinering. I Sverige finns en del övergripande studier som fokuserar på kvaliteten på förskrivningen men inga svenska studier har hittills studerat uttagsföljsamheten på en nationell nivå.

Patienterna följer inte alltid läkemedelsordinationerna utan använder sina läkemedel utifrån den egna synen på behandlingen. Detta kan medföra både under- och överanvändning och leda till misslyckad terapi med onödigt lidande och sjukdom som följd. Oföljsamhet leder också till onödiga kostnader i form av förlopad arbetsinkomst, vårdbesök, inläggningar på sjukhus och att dyr medicin blir felanvänd eller oanvänd (kassation). Oföljsamhet kan ibland vara bra t.ex. om behandlingen inte är ändamålsenlig.

Detta är den första svenska studien av uttagsföljsamhet som studerar alla läkemedel för långtidsmedicinering och speciellt astma och kroniskt obstruktiv lungsjukdom (KOL). Det övergripande syftet med avhandlingen var att kartlägga följsamheten till läkemedel för långtidsmedicinering i Sverige med speciellt fokus på hur patienter hämtar ut läkemedel (uttagsföljsamhet) mot astma/KOL. Syftet var också att bidra med metodutveckling inom området läkemedelsutköp. Specifika syften var att uppskattta uttagsföljsamheten för olika patientgrupper med långtidsbehandling, undersöka under- och överutköp, om läkemedelskostnader påverkas av frikort, jämföra två olika datainsamlingsmetoder, äldres uttagsföljsamhet till astma/KOL läkemedel, se om patienter med två olika kroniska sjukdomar har samma utköpscensörer till båda läkemedlen och även undersöka om patient profiler är en bra metod för att uppskatta uttagsföljsamhet.

De första två studierna bygger på insamlade avidentifierade kopior av flergångsrecept från 16 apotek i Jönköpings läns landsting. Genom bestämmning av uttagsintervall fastställdes om patienterna hade läkemedel tillgängliga, så att de över huvud taget har kunnat vara följsamma till läkarens ordination. Uttagsföljsamhet beräknades genom att antalet dagar som ordinationen räckte dividerades med antal dagar mellan utköpen. Analyser genomfördes med
avseende på både under- och överutkøp. Tillfredsställande uttagsföljksamhet definierades som att patienten hämtat ut läkemedel så att det täckte 80-120% av den ordinerade behandlingstiden.

Resultaten visar att den genomsnittliga tillfredsställande uttagsföljksamheten för all långtidsmedicinering i Jönköpings läns landsting, var 57% (n=3 636). Vidare var underutkøpet 21% och överutkøpet 22%. Patenter som underutkøpte läkemedel hade bara läkemedel tillgängligt under halva behandlingstiden. Kartläggningen visar också att de som hade frikort överutkøpte läkemedel i högre utsträckning (33%) än de som inte hade frikort (19%) och detta leder till onödiga kostnader för samhället. Skillnaden i uttagsföljksamhet mellan olika läkemedelsgrupper var stor, högst uttagsföljksamhet uppmättes för medel för antikonception (81%) och lägst för demensmedel (20%). Astmaläkemedel för inhalation hade en låg uttagsföljksamhet (<40%).

De övriga studierna i avhandlingen baserades på läkemedelsutkøp hos ett representativt urval av 17 000 jämtlännings registrerade i den s.k. Jämtlandsstudien, en receptdatabas med individuppgifter. Läkemedel mot astma/KOL var i fokus för dessa studier. Uittagsföljksamheten bestämdes både genom att beräkna uttagsföljsamheten som i de två första studierna och genom introduktionen av s.k. patientprofiler. Dessa profiler illustrerar grafiskt hur varje patient hämtar ut sina läkemedel. Grafen visade datumen för varje utkøp och hur länge respektive utkøp räckte tidsmässigt.

Endast en tredjedel av patienterna med läkemedel mot astma/KOL hade en tillfredsställande uttagsföljsamhet i enlighet med läkarnas ordinationer. Detta gällde även för de äldre patienterna. Man kan därför anta att många patienter är underbehandlade. Vid jämförelse av registerdata med manuellt insamlade recept visar den manuella metoden på god validitet, åtminstone vid astma/KOL. Detta är av vikt för att kunna studera uttagsföljsamhet när registerdata inte är tillgängligt.

I Jämtlandsdatabasen var det 56 patienter som använde läkemedel mot både diabetes typ 2 och astma/KOL. Av dessa patienter hade 52% samma utkøpsmönster för både läkemedelsgrupperna och de flesta av patienterna hade en tillfredsställande uttagsföljsamhet. Resterande 48% hade därmed olika utkøpsmönster och det fanns ingen korrelation när det gäller utkøpsmönster för dessa läkemedel. Hypotesen att patienter med tillfredsställande uttagsföljksamhet till diabetesläkemedel också skulle ha tillfredsställande uttagsföljksamhet till astma/KOL-läkemedel kunde därför inte fastställas.

Sammanfattningsvis visade avhandlingen på att hälften av alla recept som hämtades ut för långtidsmedicinering hade en tillfredsställande uttagsföljsamhet medan motsvarande siffra för astma/KOL läkemedel var 30%. Resul-
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