Multiple Medicine Use

Patients’ and general practitioners’ perceptions and patterns of use in relation to age and other patient characteristics

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**Abstract**


There are widespread concerns about the increasing use of multiple medicines. The aims of this thesis were to identify older patients’ and general practitioners’ (GPs) attitudes to and experiences of multiple medicine use, as well as to describe patterns of multiple medicine use in different age groups in association with patient-related factors. An additional aim was to contribute to scientific methodological development by providing an empirical example of the application of the Lehoux, Poland, & Daudelin template for the analysis of interaction in focus groups. Data were collected via qualitative focus group discussions and from a cross-sectional community-based population survey conducted during 2001-2005.

The patients revealed co-existing accounts of both immediate gratitude that medicines exist and problems with using multiple medicines such as worrying whether multiple medicine use is 'good' for the body. The patient-doctor relationship coloured their attitudes towards their treatment and care.

The GPs at times felt insecure, though surrounded by treatment guidelines. Lack of communication with hospital specialists was perceived to reduce treatment quality, while influence of patient pressure was thought to contribute to the development of multiple medicine use. An interaction analysis helped in appreciating and clarifying the contexts in which results from the content analysis were created. Further discussion is needed on how to best report these results.

Different cut-offs are useful in defining multiple medicine use in different age groups. Vast majorities of users of multiple medicines were found to have unique medicine combinations. Multiple medicine use was found to be associated with morbidity and poor self-rated health across all age groups.

**Keywords:** Age groups, Focus group interaction analysis, General practitioners, Multiple medicine use, Patient-doctor communication, Patient-related factors, Polypharmacy

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To my parents, Trude and Jan Vidar
LIST OF PAPERS

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


III Moen J, Antonov K, Larsson CA, Lindblad U, Nilsson JLG, Råstam L, and Ring L. Multiple medicine use: factors of importance in different age groups. (Submitted)

IV Moen J, Antonov K, Nilsson JLG, Ring L. Interaction between participants in focus groups with older patients and with general practitioners. Qualitative Health Research. (Accepted)

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# ABBREVIATIONS

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<tbody>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical (classification system)</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>DRP</td>
<td>Drug-Related Problem</td>
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<td>EBM</td>
<td>Evidence-Based Medicine</td>
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<td>FQ</td>
<td>Further Education and Quality</td>
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<td>GP</td>
<td>General Practitioner</td>
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<td>IDU</td>
<td>Inappropriate Drug Use</td>
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<td>LTPA</td>
<td>Leisure Time Physical Activity</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<td>OTC</td>
<td>Over the Counter</td>
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<td>Rx</td>
<td>Prescription medicine</td>
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<td>SRH</td>
<td>Self-Rated Health</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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DEFINITIONS

In this thesis, the following definitions are used. Some of these may have other meanings in other contexts and publications.

ATC Classification  Anatomical Therapeutic Chemical Classification system for drugs administered by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway [1].

Body Mass Index  Calculated as body weight (kg)/height² (m²) using measured data and categorised into subgroups according to WHO as: underweight: BMI <18.5, normal weight: BMI 18.5-<25.0, overweight: BMI 25.0-<30.0, and obesity: ≥30.0 kg/m² [2].

Concordance  A process of prescribing and medicine taking based on partnership. The patient and the healthcare professional participate as partners to reach an agreement on when, how and why to use medicines, drawing on the expertise of the healthcare professional as well as the experiences, beliefs and wishes of the patient [3].

Drug-related problem  An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes, for example need for additional drugs, unnecessary drugs, or adverse drug reaction [4].

Focus groups  A form of group interview that capitalises on communication between research participants (interaction) in order to generate data (focus) [5].

Polypharmacy  Multiple medicine use defined by the number of medicines used or the administration of more medicines than are clinically indicated [6].
| Self-rated health | Self-perceived health status measured using the question: How would you rate your general health status? The response options are: excellent, good, fair, poor, or very poor. [7] |
INTRODUCTION

The best way to get rid of a problem is to hold it up to the bright light and look at it from all sides

- Andy Rooney

Life expectancy has never been higher than at present [8], but increasing life expectancy is not necessarily equal to a healthier population. The decline in mortality from many diseases, chiefly from cardiovascular diseases, means that more people will be living with chronic diseases; patients survive their illnesses [9]. Multiple chronic disease states must therefore be managed concurrently and over longer periods. Physicians must prescribe medicines for multiple diseases appropriately and at the same time avoid risks associated with multiple medicine use. These are inappropriate drug use [10], adverse drug events [11], drug-drug interactions [12], poor adherence [13], hospitalisation [14], mortality [15], and increased healthcare costs [16]. The concepts of multiple medicine use, inappropriate drug use, and polypharmacy are often used interchangeably. There are continuous discussions regarding the relationships between these concepts, and whether the term polypharmacy should be used at all. Some argue that the term is misleading and ambiguous [17]. Furthermore, because of the potential adverse outcomes of multiple medicine use, a negative connotation is linked to the concept. This has important implications since older patients have historically been undertreated for many chronic conditions [18]. Because older patients are more likely to become users of multiple medicines, research has so far focused on the concept in this patient population [19-27]. Additionally, research is mostly conducted using quantitative approaches focused on prevalence [19] and adverse drug reactions and/or drug-drug interactions [28, 29].

Despite the fact that multiple medicine use is related to adverse drug reactions and has therefore been warned about for over three decades, a solution seems hard to find [30]. Attention to under-, inappropriate, and overuse of medicines is salient in the research literature and prescribing quality has become an important issue in the assessment of health care quality in many countries, primarily related to older patients [31-35]. The long-term effects of these initiatives are unknown and multiple medicine use remains a major public health issue, indicating that the initiatives have had the wrong focus. The omission of the users’ perspective of multiple medicines as well as the
physicians’ perspective is unfortunate, given that they possess the experiential knowledge likely to help target interventions more accurately. Moreover, knowledge about multiple medicine use in the general population is scant.

Consequently, this thesis focuses on multiple medicine use based on the assumption that no well-intended and carefully executed intervention, aiming to reduce inappropriate multiple medicine use, will succeed if it is not performed in concordance with the patients and physicians experiencing it in everyday life. The perspectives are those of patients, i.e. elderly users of multiple medicines and a community-based population sample, and general practitioners (GPs). The limitation to GPs is based on primary health care’s role in managing the patients’ total medical care [36, 37], as well as on the fact that GPs are the largest prescriber group in Sweden and elsewhere in western Europe [38, 39]. The first two studies were explorative, using focus groups to search for patients and providers’ perspectives of multiple medicine use. Data from a community-based population survey was used in the third study to describe the patterns of multiple medicine use among people aged 30-75 in association with sociodemographic, lifestyle, and health status factors.

The fourth study in the thesis is a result of using focus groups as the data collection approach. The important distinguishing feature of focus groups, from for example one-on-one interviews, is the interaction between participants [5]. Thus, the data collected arise in the social context of an interactive process where people discuss issues and form opinions [40]. Although gaining knowledge about how this interactive process impacts on the processes and outcomes of focus groups has been stressed as pivotal, methods for analysing this interaction are less well developed and can be regarded as an emerging area of methodology [41]. Suggestions of analytical approaches have been put forward, even though this literature mainly focuses on analytic difficulties [41-44]. Other problems are lack of a thorough description of the framework on which the method is based or any manual for the actual analysis procedure [45, 46]. One solution is using a ‘congruent methodological approach’, where the group interaction data are analysed using the same methodological approach as for the focus of the discussions [47]. Another approach is to use the Lehoux, Poland, & Daudelin template [48]. To the best of the thesis author’s knowledge, this is the only attempt to provide a comprehensive template for analysis of interaction in focus groups. A careful analysis of the impact of the group interaction on the data pertaining to the focus will have impact on both the validity and relevance of focus group research results [49]. Study IV was therefore conducted in order to contribute to the methodological development of reporting interaction data in focus group study reports by performing an interaction analysis using the Lehoux, Poland, & Daudelin template [48].
Biographical account

The inseparability of researcher and self. [50]

I believe in the value of including a brief biographic account illustrating the researcher’s pre-understanding. Such personal information puts a human face on research results that have consequences for the persons whose lives are affected by the research [50]. Moreover, including a biographical account expands the way we address researcher bias, meaning that pre-understandings are not the same as bias, unless the researcher fails to take them into account [51].

I am a 29-year-old Norwegian woman with a Masters degree in pharmacy. During 1999-2001, I worked as an assistant at a nursing home on weekends and school holidays. Here I first came across the concept of multiple medicine use as I watched the nurses give the residents handfuls of medicines at each meal. Furthermore, the frustration I felt when I discovered how the residents were put to bed at eight and given a sleeping pill has been with me ever since.

During my Masters and PhD education, I worked at a local pharmacy, first as an assistant and later as a pharmacist. From this, I have learnt that it is not only older people who use many medicines simultaneously. Chronically ill people of all ages have to manage substantial numbers of medicines and demanding dosage schedules. The responsibility for the appropriateness of the medicines’ strength and dosing and further that the many combinations of different substances are compatible is overwhelming. As a member of the healthcare community, I feel that we do not have enough knowledge to secure a successful outcome for many patients. I also experience firsthand how many patients struggle with understanding the use of generics and how to handle prescriptions from different doctors.

Depending on how you define multiple medicine use I myself have some experience as I have been using two prescription drugs regularly for quite some time. I struggle with this two-pill regime daily; I sometimes forget one of them and worry whether I should stop using the other because of fear of side effects.

I was first trained in the quantitative tradition during my Masters education and discovered the qualitative methodology when preparing my research plan for this thesis four years ago. Learning to appreciate and use both methods has been one of the personally most valued fruits of my research education.
BACKGROUND

Terminology

‘Fall and rise of polypharmacy?’ These are the words of John L. Reid in an editorial commentary in Hypertension in 2007. He is referring to the fall and rise of the use of multiple drug combinations in individual tablets or capsules, as this is the original definition of the word polypharmacy dating back to the early 20th century. During the 1950s and 1960s there was an academic reaction against these combination products as the mixture was often developed based on dubious efficacy and rationale. Effective doses of medicines with established actions and mechanisms were encouraged and generations of medical graduates from the 1960s to the 1980s were presented with a view that polypharmacy was dangerous therapeutics and indefensible practice. Yet, there may be a new era of these combination products as the Lancet recently published a phase II double-blind, randomised trial studying the effects of a polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease [52].

However well intended and linguistically correct the original use of the word polypharmacy was, today it is the term for the overuse of medicines. Moreover, there is no consensus on the definition of this overuse, though it is usually defined in one of two ways [6].

One definition is the concomitant use of multiple medicines measured by a count of medicines. The number of medicines that defines polypharmacy is not established, and varies from two to over ten [19, 20, 53-57]. However, one of the most frequently used cut-off points is the concomitant use of five or more medicines [21, 22, 58-60]. Additionally, polypharmacy has been characterised as minor (2-4 medicines) and major (> 5 medicines) [54], or minor (2-3 medicines), moderate (4-5 medicines) and major (> 5 medicines) [20]. These types of cut-off definitions are usually used in European studies and are limited by the lack of a quality judgement of the medicines actually used.

The other definition of polypharmacy is the administration of more medicines than are clinically indicated [6], often called inappropriate drug use (IDU) [10] or inappropriate prescribing [61]. This implies that use of only
one medicine could be considered polypharmacy. There are primarily two approaches. The first is using predetermined explicit criteria for identifying medicines to avoid, especially for older people, like the Beers criteria [62] or by performing drug utilisation reviews [63, 64] using consensus opinion by drug therapy experts to define standards or explicit criteria for a single drug, class of drugs or group of drugs. The second approach utilises implicit methods based on review of individual medicines by experts in geriatric pharmacology without predetermined criteria [65]. Studies conducted in the United States most often define polypharmacy in this way.

Multiple medicine use

Measurements
Traditionally, multiple medicine use has been measured by interviews or questionnaires [66] that are influenced by recall bias and low response rate [67, 68]. However, one advantage is the possibility to include information on relevant independent variables like sociodemographic, health status, and lifestyle factors. The introduction of large individual prescription databases reduces the problem of recall bias and response rate [10]. It also gives population-based results as opposed to selected survey samples. The most significant limitation with prescription databases is the lack of information on the use of over-the-counter (OTC) and herbal drugs, relevant related variables, as well as actual intake of medicines by the patient at home [69].

Most studies on the occurrence of multiple medicine use have focused on older patients [19, 21, 27, 55, 66, 70-74] or other selected subgroups like outpatients/ambulatory patients [19, 21, 71, 75-77], hospitalised patients [72, 78-80], and nursing home residents [81-83]. Studies have also explored multiple medicine use in specific diseases such as psychiatric diseases [80], rheumatic diseases [78], asthma [84], and heart failure [85]. Knowledge about multiple medicine use in the general population is scarce [86]. This has important implications for when in the lifespan multiple medicine use is regarded a quality problem, and more importantly to whom public health resources are directed. It is found, though not acknowledged, that multiple disease states and not age per se are the real risk factors associated with adverse outcomes of multiple medicine use [87].

Additionally, ‘medicine use’ is defined either as prescription medicines (Rx) only [10] or Rx and OTC medicines [66]. It is reasonable to consider self-medication as a contributing factor to multiple medicine use. Further, medicines that were once prescription-only are now becoming available over the counter, and herbal medicine use increases. On the other hand, the inclusion
of OTC medicine in the multiple medicine use definition in some studies and not in others confuses the terminology even further. Moreover, there has not been any discussion of the appropriateness of inclusion of OTC or herbal medicine in the multiple medicine use definition.

Occurrence

The occurrence of multiple medicine use depends on the definition of multiple medicine use. Use of five or more Rx medicines has been reported to range from 4% to 39% among people aged ≥65 years [19-21, 88]. International and Swedish studies have found that the use of medicines and multiple medicine use are increasing among the elderly [19, 89]. American surveys on community-based elderly patients show an average daily use of two to nine Rx medicines [90]. In Sweden average prescribed medicine use is reported to have reached 5.4 medicines among elderly aged 75 years and older [10], with the largest increase amongst institutionalised elderly using an average of ten medicines [91-93]. Recent studies show that the same level of medicine use can be true for elderly living at home [91, 94]. This pattern is similar in other Scandinavian countries [19, 55].

The few studies covering total and/or younger populations [86, 95, 96] show diverging results based on different study samples. Bjerrum observed use of five or more Rx medicines by 1.2% of the population (aged >16 years) living in the county of Funen, Denmark [86], while Al-Windi observed use of four or more Rx medicines for 21.4% in a multiethnic Swedish general practice population [96]. Bardel et al. observed use of four or more Rx medicines for 12% of a middle-aged (35–65 years) female population in mid-Sweden [95], while Thomas et al. observed use of five or more Rx medicines for 9% in a community sample of men aged 56-75 years in south Wales [70]. The three first studies were cross-sectional and the general trend was higher prevalence of multiple medicine use among older age groups. The study by Thomas et al. showed a time-period effect as well, where for example the prevalence of multiple medicine use for men aged 60-64 years increased from 3.2% in 1984-1988 to 4.4% in 1989-1993 and 9.2% in 1993-1997.

Associated factors

Studies on patient factors associated with multiple medicine use are almost exclusively conducted on older people [19, 21-27], or a few selected subgroups of younger populations [70, 95, 96]. Generally, the use of multiple medicines increases with age and women are more likely to be users of multiple medicines [86]. Other important sociodemographic factors identified are educational level and marital status. Educational level was inversely related to medicine use in a middle-aged female population [95], while both
positive and negative correlations are found among older populations [66, 97]. Being single was related to multiple medicine use in a multiethnic general practice population [96], while it did not seem to have any effect on medicine use in a middle-aged female population [95]. Lifestyle factors studied in conjunction with multiple medicine use are body mass index (BMI), smoking, and alcohol consumption. Multiple medicine use has been found related to obesity in both younger and older populations [27, 70, 95], while there are no clear correlations with smoking and alcohol consumption [23, 27, 70, 95, 96]. Among older populations, being an ex-smoker is reported to be related to increasing medicine use [27]. The relationship between physical activity and multiple medicine use has not, to the thesis author’s knowledge, been studied. Predictors of multiple medicine use related to health status in older populations are poor health, number of co-morbid conditions, asthma, cardiovascular disease, diabetes, psychiatric conditions, and stomach disorders [20, 22-24, 26], while poor self-rated health (SRH) has been found related to multiple medicine use in younger populations as well [19, 23, 27, 70, 95].

Consequences
The distinction between multiple medicine use as a risk factor for IDU and as a quality problem per se is important, because a general condemnation of multiple medicine use ignores its potential benefits.

Optimal treatment
Individuals with several chronic conditions may need to be treated with multiple medicines. In addition, treatment regimens that include two or more different medicines for a single condition are increasingly promoted for the optimal management of many of the most prevalent chronic conditions [98, 99]. An individual with diabetes and hypertension will be labelled a user of multiple medicines when treatment guidelines are applied.

By being too preoccupied with reduction of multiple medicine use, one might fail to inform about lack of use of beneficial drugs [18, 100]. Underuse of medicines is an important and increasingly recognised problem among older people [18, 101]. Underuse is defined as the omission of drug therapy that is indicated [6]. Underuse is likely to have a negative relationship on health outcomes but this is not well described. Deservedly, recent studies have investigated underuse in some diseases, e.g. heart failure, myocardial infarction and osteoporosis [102-105], giving attention to the opposite pole of multiple medicine use.
Drug-related problems
The negative connotation that has been linked to the word polypharmacy is undoubtedly due to observed drug-related problems (DRPs) like unnecessary medicine use, adverse drug reactions (ADRs), and patient non-adherence in users of multiple medicines, which have led to hospitalisations and negative health outcomes [11, 13, 14, 28, 59, 71, 72, 90, 106-108]. The risk of DRPs is strongly associated with increasing numbers of medicines used [4, 109]. However, the definition of multiple medicine use as a definite number of medicines (i.e. five or more medicines) has been challenged as a suitable indicator for the risk of DRPs in clinical practise [4]. Viktil et al. found that the number of DRPs per patient was linearly related to the number of medicines used. Therefore, while it may be useful as an indicator for DRPs, a strict cut-off poorly describes the relationship between the number of medicines used and the risk of unfavourable health outcomes [4].

Inappropriate drug use
Multiple medicine use is also associated with higher likelihood of potential IDU, which is a significant but preventable safety concern [10, 15, 110]. IDU has been defined as the use of medicines that introduce a significant risk of an adverse drug-related event where there is evidence for an equally or more effective but lower-risk alternative therapy available for treating the same condition [61]. The definition further includes the use of medicines at a higher frequency and for longer periods than clinically indicated, the use of multiple medicines that have recognised drug-drug interactions [12] and drug-disease interactions as well as the underuse of beneficial medicines that are clinically indicated but not prescribed for ageist or irrational reasons [61]. Studies of elderly populations using different sets of explicit criteria have reported the prevalence of IDU to range from 3% to 40% [111]. Low education, advanced age, female gender, living in a rural area, and higher Charlson Comorbidity Index (which weighs the number and seriousness of comorbid conditions) scores are possible risk factors for IDU, in addition to multiple medicine use [112]. Consequences of IDU include higher likelihood of drug-drug interactions, ADRs, hospitalisations, poor quality of life and death [15, 113-115].

Increased costs
The major concern about using many medicines is the risk for DRPs, but also the possible excess consumption of public health service resources and excessive personal and public expenditures that follows [16, 116, 117]. This recognition has paved the way for programmes aiming at better medicine therapy along with cost saving. A Medication Therapy Management Program introduced in nursing homes in the United States was beneficial, based solely on medicine savings [83, 118].
Interventions

Because of the negative health outcomes for the patient and the inappropriate use of public health service resources as well as excessive personal and public costs that inappropriate multiple medicine use may cause, many researchers have focused on how to reduce the number of medicines [76, 101, 119]. Hajjar et al. reviewed randomised controlled studies published in the past two decades designed to reduce multiple medicine use in older adults [90]. Overall, three used prescriber education as the intervention. In one of these studies 12.5% of potentially inappropriate medicines were discontinued [75, 120, 121]. One study utilised a medicine grid to alert providers on how many medicines were being administered. This resulted in 0.92 medicines being reduced per patient in the intervention group compared with an increase of 1.65 medicines in the control group [122]. The last study evaluated the use of geriatric evaluation and management in inpatient and outpatient care. It found a significant reduction in inappropriate medicines in the intervention population compared to usual care [123]. It is important to notice that multiple medicine use may not be reduced if one improves inappropriate use by both discontinuing medicines and identifying underuse simultaneously [60]. Moreover, many studies of regimen simplification have failed to show increased satisfaction or acceptability by the patient or clinical improvements [124-128]. This suggests that there is more to medication problems than just large numbers of medicines.

The focus on older users of multiple medicines

Multiple medicine use is particularly difficult in older patients because of age-associated changes in pharmacokinetics and pharmacodynamics [129]. It is well known that older people experience more ADRs than younger patients [130, 131], of which most are preventable [132, 133]. Older patients may also have atypical presentation of ADRs, which may be confused with aging or disease progression [129, 134]. The use of multiple medicines may also affect geriatric syndromes with an increased risk of cognitive impairment [135], urinary incontinence [136], and falls [137]. There are therefore widespread concerns about both the high proportion and the quality of medicine use in older people [6, 61]. In the United States, for example, 12.5% of the population is over 65 years of age but consume 32% of all Rx medicines, account for 25% of medicine expenditure and for 30% of total national healthcare expenditure [61]. Similar figures are reported for Europe. In Ireland, people aged 65 years or more comprise 11% of the population but consume 47% of all Rx medicines [138]. The number of people over the age of 75 constitutes one tenth of the Swedish population, but they consume a fourth of all medicines [91].
The high prevalence of medicine use among elderly combined with the vulnerability of this patient group is surely the reason why almost all research on multiple medicine use and IDU so far has been conducted in this population. It is important to recognise, though, that age itself is a less important factor for ADRs than the complexity of care of the older patient, which includes the number of coexisting conditions and frailty [87, 131, 133]. Moreover, limiting the focus of multiple medicine use to older people narrows our understanding of the phenomenon and creates an illusion of optimal medicine use among younger patients.

Perspectives on multiple medicine use

From the patient’s point of view

There are many studies on experiences of medicine taking in different diseases and attitudes to medicines in general [139] but few focus on the user of multiple medicines, although multiple medicines occupy a central place in the way people with chronic morbidity manage their diseases [125, 140, 141]. The omission of this perspective in the scientific literature is important, given that these patients possess fundamental knowledge derived from lived experiences that can guide development of future interventions.

From a general perspective a considerable reluctance to medicine use and a preference for using as little as possible is salient among patients [139]. Medicines are seen as unwelcome but necessary and having a routine is recognised as the key to coping with multiple medicine regimes [139]. Occurrences of ADRs are key criteria in patients’ risk/benefit evaluations [142]. Additionally, as medicine use is equated with having a disease, people with conditions like asthma who do not accept their diseases are unlikely to accept their treatment [143].

Patients are increasingly encouraged to be active in managing their health, expressing their concerns and preferences, and in participating in medical decision-making [144, 145]. This is the effect of a high prevalence of chronic diseases with no overall gold standard treatment. Consequently many patients and health professionals believe that patients themselves should evaluate the risk-benefit ratio of alternative treatments [146, 147]. Furthermore, patients’ expectations regarding choices and decision-making together with easy access to health information via media like the Internet is important [146]. In addition, social movements such as the feminist movement and reports on flaws in governmental legislation or funding help patients challenge medical authority [146, 148, 149]. Patients’ actual preferences for involvement in decision-making is reported to be variable, likely to develop over time, change at different stages of the illness and to be highly complex [145].
From the general practitioner’s point of view

Prescribing medicines is a cornerstone of medical practice. Researchers have therefore studied how GPs choose between medicines in a therapeutic drug group [150], the factors associated with cost in prescribing [151], medicines and clinical problems associated with prescribing discomfort [152], and the influence of patients' hopes of receiving a prescription on GPs' perceptions and the decision to prescribe [153]. Recent Swedish studies include hospital doctors’ views of factors influencing their prescribing and secondary care doctors’ perceptions of appropriate prescribing [154, 155]. However, available research involving GPs’ perspectives on prescribing for users of multiple medicines is scant. Studies have focused on attitudes towards prescribing for single conditions [156, 157], the impact of co-morbidity on prescribing for single conditions [158], according to evidence-based medicine (EBM) [159], and clinical practice guidelines [160].

An important initiative for improving treatment quality is physicians’ adherence to treatment guidelines that incorporate available evidence-based knowledge regarding a given disease and provide recommendations, including the use of multiple medicines regimens, for the treatment of patients with a certain disease [99]. Even if the benefit of such guidelines is accepted, what is less clear is the long-term net benefit and potential harm associated with multiple medicine use due to adherence to each disease-specific guideline relevant for patients with multiple diseases [98]. There is very little evidence to guide prescribers in combining disease-specific guidelines for patients with multiple health conditions [161, 162]. Regardless, both quality assurance initiatives that encourage adherence to and monitoring of such guidelines as well as the push for financial incentives linked to performance will probably further increase their application [163, 164]. As there clearly is no way around the problem of multiple medicine use for GPs, it is important to find solutions that fit their every day clinical practice. Their perspective is therefore of utmost importance.

Public health relevance

The man who says it cannot be done should not interrupt the man doing it.

- Chinese Proverb

Since 1950, the worldwide proportion of people aged 60 years and older has increased from 8% in 1950 to 10% in 2005, and is expected to reach 22% in 2050 [165]. Global population aging is due to decreased mortality as well as fertility rates [166]. This is particularly critical in developing countries.
where the increase in absolute numbers of elderly is threefold, from 422 million in 2005 to an estimated 1.6 billion in 2050 [165]. In developed countries, the increase is more moderate, expecting a doubling of the population aged 60 years and older from 245 million in 2005 to an estimated 416 million in 2050. In Sweden, 25% of the total population is aged 60 years and older (December 31, 2008) [167] and this proportion is expected to reach 30% in 2050 [165].

It is reasonable to expect that as longevity continues to increase, both developed and developing countries will face the challenge of coping with chronic illness and consumption of multiple medicines. Irrational use of medicines is therefore a major public health problem worldwide. The World Health Organization (WHO) estimates that more than half of all medicines are prescribed, dispensed or sold inappropriately, and that half of all patients fail to take them as intended [168]. The overuse, underuse or misuse of medicines results in wasting scarce resources and widespread health hazards. Use of too many medicines per patient is among the examples of irrational use of medicines WHO gives, in addition to inappropriate use of antimicrobials, over-use of injections when oral formulations would be more appropriate, failure to prescribe in accordance with clinical guidelines, inappropriate self-medications and non-adherence to dosing regimes. Therefore, studies aiming to increase the quality of multiple medicine use have high public health relevance.
AIMS

The general aim of this thesis was to increase the overall understanding of multiple medicine use.

The specific aims were:

• To identify elderly users’ attitudes to and experiences of using multiple medicines

• To identify general practitioners’ attitudes to and experiences of prescribing for elderly users of multiple medicines

• To describe patterns of multiple medicine use in different age groups in association with sociodemographic factors, lifestyle and health status

In addition, the thesis is a contribution to scientific methodological development by

• Providing an empirical example of the application of the Lehoux, Poland, & Daudelin template for the analysis of interaction in focus groups.
METHODS

Framework

All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time.

- Sir Austin Bradford Hill

Research approaches have multiplied in recent decades, leaving the researcher with many choices. This thesis is grounded in a pragmatic claim on knowledge based on the assumption that collecting diverse types of data best provides an understanding of a research problem [169]. The thesis author was therefore not committed to any one system of philosophy and reality and hence was free to choose the methods, techniques, and procedures of research that best met her needs and purposes – to draw liberally from both quantitative and qualitative assumptions, approaches and data. The researcher acknowledges the differences between quantitative and qualitative methodologies but recognises, accepts and values their compatibility.

The study of multiple medicine use has predominantly used a quantitative approach focusing on older people, with few studies exploring experiences of multiple medicine use from a patient or healthcare provider perspective. The use in this thesis of both a qualitative hypothesis generating method, like focus groups, and a deductive quantitative method, like the survey approach, increases the possibility of capturing as many aspects of multiple medicines use as possible. Furthermore, inclusion of both users of multiple medicines, GPs and a population-based sample is a case of data triangulation [170]. This implies the use of multiple data sources, all with a similar focus, used to obtain differing views about a problem. New data is expected to contribute an additional piece to the puzzle, not confirm existing data from other samples [171]. For these reasons, and to help ensure the robustness of the conclusions, qualitative and quantitative findings are discussed in relation to each other wherever possible.
Table 1 provides a short methodological summary of the papers included in this thesis.

Table 1. Overview of papers included in the thesis

<table>
<thead>
<tr>
<th>Design</th>
<th>Ethical approval</th>
<th>Study population</th>
<th>Assessments</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Approved (DNR 06:159)</td>
<td>29 male and 30 female home-dwelling elderly (≥65 years) users of multiple medicines</td>
<td>• Interview guide (Appendix 2)</td>
<td>• Content analysis using the Framework approach • Consensus analysis</td>
</tr>
<tr>
<td>II</td>
<td>Approved (DNR 06:159)</td>
<td>31 GPs working at five public primary care centres and one private healthcare centre</td>
<td>• Interview guide (Appendix 3)</td>
<td>• Content analysis using the Framework approach • Consensus analysis</td>
</tr>
<tr>
<td>III</td>
<td>Approved (DNR 01-199O)</td>
<td>Randomised population sample of 2,816 individuals (30-75 years old)</td>
<td>• Patterns of multiple medicine use • Patient characteristics</td>
<td>• Chi Square • Binary logistic regression</td>
</tr>
<tr>
<td>IV</td>
<td>Approved (DNR 06:159)</td>
<td>The study population from studies I and II</td>
<td>• The interaction between the participants in the 18 focus groups in studies I and II (Appendix 4)</td>
<td>• Interaction analysis using the Lehoux, Poland, &amp; Daudelin template</td>
</tr>
</tbody>
</table>

Focus groups (Papers I-II)

Data collection was based on semi-structured focus groups. The most important tool during the sessions was the discussion itself, and the most important data was what emerged spontaneously in the groups. With this in mind, the moderator only interfered if a subject was not addressed at all or if the discussion came to a halt.
A purposive sampling strategy was used in order to recruit participants that would potentially provide rich and diverse data pertinent to the research question. The users of multiple medicines were recruited in and around one of Sweden’s largest cities by the thesis author at monthly meetings of the two largest senior citizens’ associations in Sweden. Inclusion criteria were Swedish-speaking, 65 years of age or older, currently using five or more medicines (including both Rx and OTC used daily and ‘as needed’ for chronic conditions), willingness, ability to comply with and understand study requirements, and sufficiently good hearing for group discussion. Each focus group contained members from the same local association. Therefore, some but not all participants knew each other beforehand. Those who volunteered to participate completed a questionnaire giving information about the medicines they were currently using (Table 2). The GPs were recruited as members of Further Education and Quality (FQ) groups through contact persons at five public primary care centres and one private healthcare centre in three large cities in Sweden. FQ groups are a special variant of collegial discussion between GPs working together at a healthcare centre [172].

Overall, 18 focus groups were conducted and saturation was reached on the research questions. A total of 29 men and 30 women participated in six male and six female patient groups. Same-gender patient groups were preferred in order to provide a secure environment for participants to talk about sensitive issues regarding medicines and accompanying diseases [45]. A total of 31 GPs participated in six focus groups; five groups consisted of 27 county-employed GPs and one private practitioner group of four doctors. The male and female distribution of GPs (15 and 16) was about equal, mean age was 54 years (range 33-63), and duration of practical work experience was 5-38 years (mean 22). There were between three and eight participants in each group.

Table 2. Users of multiple medicines

<table>
<thead>
<tr>
<th></th>
<th>Female (n=30)</th>
<th>Male (n=29)</th>
<th>Total (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>76 (67-88)</td>
<td>75 (67-87)</td>
<td>75 (67-88)</td>
</tr>
<tr>
<td><strong>Rx medicines used regularly (n)</strong></td>
<td>8 (4-15)</td>
<td>7 (3-11)</td>
<td>7 (3-15)</td>
</tr>
<tr>
<td><strong>Rx medicines used as needed (n)</strong></td>
<td>0.6 (0-4)</td>
<td>0.7 (0-5)</td>
<td>0.7 (0-5)</td>
</tr>
<tr>
<td><strong>OTC drugs (n)</strong></td>
<td>1 (0-10)</td>
<td>0.4 (0-3)</td>
<td>0.7 (0-10)</td>
</tr>
</tbody>
</table>

The patient focus groups were held at the senior citizens’ associations and the GP groups where the FQ groups usually met. The discussions lasted 1-1½ hours, were digitally recorded and transcribed verbatim for further analy-
sis. An experienced qualitative senior researcher moderated the groups, while the thesis author acted as an observer. The observers’ role was to take notes of both the non-verbal communication and of who was talking. The observer was also responsible for the digital recorder and other practical details.

After every session, the moderator and the observer discussed the nature of the session. This debriefing, based on the 12 questions by Stevens [45], was digitally recorded and used as a complement during analyses (Appendix 1).

Measurements

One interview guide for the patients and one for GPs were developed after carefully reviewing the literature, containing the following key issues (Appendices 2-3):

- Experiences of multiple medicine use
- Attitudes to multiple medicine use
- Benefit of multiple medicine use
- Risks of multiple medicine use
- Adherence

The interview guides were reviewed by members of the research team and tested in the first female patient, male patient, and GP groups. As no major changes were made these groups were included in the analyses.

Conventional content analyses

Due to the limited empirical literature and lack of a theoretical framework regarding experiences of users of multiple medicines and GPs, a conventional content analysis approach [173] using the framework approach [174] was chosen. No preconceived categories were used; rather the categories and their names came directly from the participants. Framework analysis includes five key analytical stages: familiarisation, identifying a thematic framework, indexing, charting, mapping and interpretation. The analysis was done with the NVivo 1.2 software (QSR International Pty Ltd., Melbourne, Australia).

Researcher triangulation was adopted. Data was first analysed independently by the thesis author and a colleague. Consensus was then reached through discussions on a single, unified version that both endorsed as the best representation of the data. Additionally, a senior researcher (the moderator) audited the consensus judgements to ensure that the results were anchored in the data and that important data had not been overlooked [175].
The community-based population survey (Paper III)

Paper III is based on data from the Skaraborg Project [176], collected between November 2001 and July 2005 in the municipalities of Vara and Skövde in south western Sweden. Vara is a small municipality with 16000 inhabitants, 95% of whom are native Swedish, and major forms of employment are light industry and farming. Skövde is a mid-sized town with 50000 inhabitants of whom 90% are native Swedish. The major employer is a car industry.

A randomised general population sample, aged 30-75 years, stratified by sex and five-year age groups, was invited to participate. Of the invited subjects 1811 individuals (81% response rate) from Vara and 1005 individuals (70% response rate) from Skövde completed the study. A deliberate three-fold number of participants in the 30-49 age groups were included from a preventive perspective as it reflects the circumstances in the initial stages of diabetes and hypertension.

The health survey included two visits to the study centre, including completing a structured self-administered questionnaire, an interview by a study nurse about previous medical history and ongoing medicine use, and a physical examination. Medicine use was defined as the use of Rx, OTC or herbal medicine regularly and as needed during the two weeks prior to the interview. The questionnaire included several items, among which questions about sociodemographic features, lifestyle and SRH were used in Paper III.

Dependent variable

Multiple medicine use was restricted to the use of Rx medicine. Individuals with quantities equal to or greater than the upper quartile were defined as users of multiple medicines. Among 30-49-year-olds, all analyses were performed both with and without hormonal contraceptives for systemic use (G03A). The dependent variable was dichotomised into 0=no multiple medicines use and 1=multiple medicines use, based on identified cut-offs.

Independent variables

The studied sociodemographic factors included gender, education, and marital status. Education was dichotomised into \( \leq 9 \) years of schooling (elementary or compulsory education) or \( >9 \) years of schooling (upper secondary and higher education). Marital status was divided into living alone or cohabiting/married.
The studied lifestyle factors included BMI, current smoking, alcohol consumption, and leisure time physical activity (LTPA). BMI was calculated as kg/m² and dichotomised into non-obese <30.0 kg/m² or obese ≥30.0 kg/m². Current smoking was dichotomised into No (never smoked/previous smoker) or Yes (current smoker). Alcohol consumption was divided into No (have not consumed alcohol during the previous 30 days) or Yes (have consumed alcohol during the previous 30 days). LTPA was dichotomised into Sedentary (seated leisure activities like reading and moderate leisure activities like walking) or Physically active (regularly for ≥ 2 hours/week).

Finally, the health status factors included were diabetes, hypertension, and SRH. Diagnosis of hypertension and diabetes were based on known diagnoses and new diagnoses made during the study visit [177-179]. SRH was graded by the participants as excellent, good, fair, poor, or very poor [7], and divided into Good (excellent or good health) and Poor (all others).

Statistical analyses

Separate univariate and multivariate analyses were performed for subjects between 30-49 years, between 50-64 years, and between 65-75 years. In univariate analysis, the differences in the distribution of categorical variables between users of multiple medicines and non-users were compared using the Chi Square Test. Logistic regression analysis was chosen for the multivariate approach and all variables were included in the analyses.

Associations are displayed as odds ratios (OR) with 95% confidence intervals (CI). All statistical tests were carried out at a significance level of α = 0.05. The data was analysed using SPSS statistical software for Windows XP (version 17.0, SPSS Inc., Chicago, 2008).

Group interaction analysis (Paper IV)

In Paper IV the Lehoux, Poland, & Daudelin template [48] developed for the analysis of the interaction in focus groups was applied to the 18 focus groups from Papers I and II (Appendix 4).

The template is based on a descriptive, sociological model of what happens in focus groups. Two sociological theories constitute the foundation on which this model is based. The first theory describes the participants’ dual problems of how they will function as a group, both regarding how they will establish a common ground in the first place and regarding how to contribute to the common ground afterwards [180]. The second theory states that a focus group discussion is shaped by four social contexts [40]: associational
– ‘the common characteristic that brings the participants together’, status – ‘the relative positions of the participants in local or societal status hierarchies’, conversational – when certain topics or personal experiences may seem incongruous because of, for example, individual power/status or because of cultural conversational norms, and relational – ‘the level of intimacy already established among the participants’. Associational and status contexts can be expected to influence the establishment of the common ground, while conversational and relational contexts can be expected to influence what the participants perceive to be appropriate contributions to the group as the interaction moves forward. Acting upon the foundation are the participants’ own motivations and expectations for joining a focus group and how they position themselves within the group, whether as knowledgeable and experienced or as potentially vulnerable advice-seekers. Additionally, the moderator and the extent to which he/she participates will play a role in the construction of the participants’ view.

The thesis author performed the analysis, while a senior researcher (the moderator) audited the results and consensus was reached on diverging issues. The patient and GP groups were analysed separately and then compared. The digital recordings constituted the main data source. The written transcripts and the debriefing notes (Appendix 1) were used as complements.
RESULTS

Perceptions of multiple medicine use (Papers I-II)

The focus group sessions were directed at elucidating the attitudes to and experiences of multiple medicine use from both the patients’ and the GPs’ perspectives. The discussions focused on the categories (with sub-categories) displayed in Table 3 and accounted for in detail in Papers I-II. The categories presented are not mutually exclusive; rather, they are evidence of the complex and overlapping nature of the users of multiple medicines’ and GPs’ perceptions. The same (sub-)categories emerged in separate analyses of male patients’ and female patients’ discussions. However, some statements were only made by one gender and this is stated clearly under the sub-category concerned. Here the results are presented as a condensed and entwined version comparing the patients with the GPs whenever possible. For quotations exemplifying raw data see the original Papers I-II.

Table 3. Perceptions of multiple medicine use

<table>
<thead>
<tr>
<th>Patients</th>
<th>GPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belief about medicines</td>
<td>Multiple medicine use</td>
</tr>
<tr>
<td>- Attitude to medicines</td>
<td>- Definition</td>
</tr>
<tr>
<td>- Definition of multiple medicine use</td>
<td>- Prevalence</td>
</tr>
<tr>
<td>- Benefit from medicines</td>
<td></td>
</tr>
<tr>
<td>- Adverse effects and interactions</td>
<td></td>
</tr>
<tr>
<td>Being a multiple medicine user</td>
<td>Treatment factors</td>
</tr>
<tr>
<td>- Thoughts and unanswered questions</td>
<td>- Risk-benefit evaluation</td>
</tr>
<tr>
<td>- Taking responsibility</td>
<td>- Considering interactions</td>
</tr>
<tr>
<td>- Adherence</td>
<td>- The importance of treatment guidelines</td>
</tr>
<tr>
<td>Relationship to the doctor</td>
<td></td>
</tr>
<tr>
<td>- Trust and distrust</td>
<td>External factors</td>
</tr>
<tr>
<td>- Access</td>
<td>- The patient</td>
</tr>
<tr>
<td></td>
<td>- Patient information leaflets and</td>
</tr>
<tr>
<td></td>
<td>generic substitution</td>
</tr>
<tr>
<td></td>
<td>- Other prescribers</td>
</tr>
<tr>
<td>The GP’s working environment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Occupational experience</td>
</tr>
<tr>
<td></td>
<td>- Consultation time</td>
</tr>
<tr>
<td></td>
<td>- Anxiety when deciding treatment</td>
</tr>
</tbody>
</table>
Definition
Both patients and GPs had problems defining multiple medicine use. The patients viewed the amounts they were currently using as many, regardless of the actual number. Moreover, the patients believed it was a matter of age; if a 20-year-old used seven medicines it was regarded as excessive. For the GPs, the relevance of the medicines for the patient was considered more important than the actual number. The GPs also struggled with deciding which medicines should be included in the count. Analgesics used as needed and topical treatment were excluded. Medicines that elderly patients continue to use from earlier adulthood were viewed as one important reason for why older people become users of multiple medicines.

Co-existing accounts among patients
The patients displayed co-existing positive and negative attitudes towards their medicines during the discussions. The initial statement was that they had no problems using multiple medicines; rather they were very grateful that they were able to live such rich lives despite diseases and medicine use. They acknowledged that they were ‘living on borrowed time’ because of their medicines, and this helped them endure adverse effects. Nevertheless, later in the discussions they revealed that they used the medicines because they ‘had to’ and that they would avoid them if they could. These statements were accompanied by emotions like worry, fear and uncertainty and were revealed during discussions about other factors like side effects or interactions.

Risk-benefit
The assessment of risk-benefit was seen by the GPs as particularly difficult in older patients because of the exclusion of elderly individuals with multiple diseases from clinical trials. Furthermore, treatment guidelines were viewed as ‘medicine generators’ leading to ‘kits’ of medicines per indication which are the same regardless of the patient’s other diseases. The male patients also noted this. Hence practising EBM through guidelines was regarded as difficult. The GPs stated that they adhere to and trust them because specialists write them, but at the same time they feel restrained and sometimes dictated to by the guidelines. Anxiety can appear when the GP’s conviction conflicts with either that of a specialist or the guidelines, resulting in fear of being reported for malpractice. The GPs would like to involve the patient more in the risk-benefit assessment – something they believed would increase the patient’s quality of life as well. The GPs discussed that a patient may perceive that a medicine is not worth its negative aspects but the respect for the treating doctor may prevent the patient from questioning the treatment. This is something they believe is likely to influence patient adherence. This seems reasonable since the patients were not convinced that benefits outweighed
risks like side effects and had many thoughts and unanswered questions not discussed with their doctors. Patients specifically discussed the need for more information, preferably from their doctors. They were generally worried about side effects of new medicines and what would happen if they missed a dose. Patients found interactions hard to understand and worried about whether their own medicine combinations were appropriate. GPs felt they were on thin ice regarding interactions with as few as three medicines. An important problem for the patients was how they would know which medicine had caused an adverse effect/interaction. However, they knew very well that the risk increases with the number of medicines they were using. Other issues brought up by the patients were medicines labelled ‘For the heart’. They did not understand why they used them, or why they used two or more such medicines simultaneously. In addition, not being able to stop treatment when the blood pressure was normal was a matter of great frustration and confusion.

Responsibility
The GPs believed that some patients are responsible for their multiple medicine use as they actively seek treatment. An informed patient who demands certain medicines that she/he has read about or that friends or relatives are using puts pressure on the GPs. The patients on the other hand felt a need to take responsibility for their own health ‘as no one else would do it for them’. They experienced resistance from the healthcare system, which they ‘had to work hard to get through’, for example reaching their doctors to make appointments or getting to see the same doctor. For women the consultation was a stressful event that often was over too quickly. The GPs acknowledged the problem of access and time as well, stating it as an important reason for medicines remaining in charts longer than was appropriate. They reported not having time to review the charts properly nor to request medical record reviews from clinical pharmacists. The patients sought continuity of care and personal relationships with their doctors, including a feeling of mutual understanding and trust. Men also believed it important to be curious and educate themselves in order to both inform doctors and question their actions. At the same time, the patients withheld information from their doctors regarding herbal drug use, smoking, reducing/increasing doses etc.

Adherence
Besides problems of having many medicines/dose intervals per day and forgetfulness, the GPs saw patient information leaflets and generic substitution as obstacles for adherence. The detailed adverse effect descriptions in the leaflets were considered primarily as disclaimers of responsibility by the industry, and GPs believed they scare the patient and negatively influence
patient adherence. The patients read them diligently and requested more information about positive effects as well. Both patients and GPs saw generic substitution primarily as a disadvantage that increases the likelihood of the patient taking both the original and the generic. Patients stressed the importance of being well informed by their doctor to avoid this confusion.

Doctor-patient relationship
The doctor-patient relationship affected how patients viewed their multiple medicine regimes. They had great faith in and respected ‘good’ doctors who took initiatives, listened, and gave ‘the right treatment’. Distrust in the healthcare system in general or in specific ‘bad’ doctors was due to poor experiences such as no follow-up, not being listened to, or conflicting advice given by different doctors. A general distrust in doctors’ knowledge about treating elderly patients with multiple diseases was stressed. Specialists were thought to have good specific knowledge but too little general knowledge, resulting in problems for the patients with multiple diseases. Moreover, poor communication between disciplines made the patients feel uncomfortable when transferred between primary and hospital care. They were afraid the doctors did not know of each other’s prescriptions. That patients see more than one doctor was acknowledged as an important contributing factor to multiple medicine use by the GPs. The GPs reported that they seldom contacted hospital specialists, as there is a perceived lack of routines for this as well as an informal understanding not to pursue a colleague’s motivations for prescribing. Hence, GPs rely on their own experience when changing a dose or discontinuing a medicine. Generally, the patients stated that they hoped the doctors had more knowledge than they did and that it is important to have faith in the treatment for it to work.

Interaction analysis (Paper IV)
Comparing the patients with the GPs one could say that GPs found a common ground in their belonging to the same profession, while the patients based their group discussion on sharing a common focus. The GPs, both as individuals and as group members, identified themselves as medical doctors in relation to the focus group discussions; targeting the different aspects of treating users of multiple medicines in a medical way. The patients chose an individual approach, using biographical narratives of lived experience to express their perceptions. However, the patients’ discussion did not resemble a traditional interview since the individual narratives most often produced a ‘follow-up’ narrative from another participant or contributions like agreement or disagreement, questions or advice that kept the discussion moving forward without any contribution from the moderator. It was an advantage that both the patients and
the GPs chose to establish their discussions based on the context they were most comfortable with and in which they probably ‘normally’ express similar perceptions. Both sets of focus groups resulted in equally rich data for the content analysis and it is therefore insignificant if the data emerged based on a common ground or a common focus. Straightforwardly, this argument is valid within an essentialist epistemological framework as content analysis was used to gather information about the focus of the discussions.

The patients used their narratives either to express experiences and corresponding attitudes as users of multiple medicines (contributing knowledge) or to uncover insecurity about illness or medicine treatment (seeking information). This provided a great variation in how the perceptions of the users of multiple medicines were displayed to the researchers – illustrating a category from multiple angles. However, three domineering participants (one male and two female in three separate groups) may have restrained the other participants, although the other participants mostly looked bored and ignored the domineering members’ monologues. Their narratives were often about non-relevant experiences in relation to the research questions, and when the moderator tried to break in, they were reluctant to change the subject. On the other hand, three male participants (in three different groups and not in the same male group as the negative domineering participant) acted as ‘positive dominators’ being somewhat more outspoken and encouraging the others to contribute. One of these ‘looked after’ a more passive member in his group, who could not follow rapid exchanges during the discussion due to a hearing aid not functioning optimally,

Driving, reserved, and hostile group dynamics was observed in the GP groups. Members covering almost all questions in the interview guide spontaneously and progressing almost entirely without the moderator interfering characterised the driving group. The interaction was constructive, emotional, and loud, ranging from total disagreement to consensus accompanied by many laughs. In contrast, three reserved groups mostly answered the moderator’s questions consecutively, interacting quietly and unemotionally and seldom disagreeing. The head of the healthcare centre participated in one of these groups, which might have silenced the others, though he himself never dominated the discussion. The moderator and observer felt that the underlying emotion in the hostile group was that the GPs felt the researchers were ‘out to get them’. There was a feeling of disapproval between the participants as the interaction was negative and limited.

The patients and the GPs positioned themselves very differently towards the moderator. In the patient groups, moderating was a matter of keeping the discussion on track with the research questions, especially in the groups containing dominant members, but also of handling direct personal questions.
The patients interacted directly with the moderator primarily as a pharmacist seeking information about diseases and treatment. When the moderator gently referred them to their regular pharmacist or GP, the participants seemed to realise intuitively that they were taking up time from the collective discussions and readily accepted it. In the GP groups, the GPs’ attitudes towards the moderator were either professionally superior or indifferent. Therefore, a social desirability factor leading participants to give answers they think are ‘right’ or sought by the moderator, was probably not present to any great extent. The only time the GPs actually interacted directly with the moderator was in the hostile group, patronising her and giving her a hard time to keep the discussion moving forward in a calm constructive way. Either way, limiting her interaction while still keeping the focus, the moderator seldom interfered with the collective story told by each group.

Heterogeneous multiple medicine regimes (Paper III)

Overall, 71% of the study participants used some kind of medicine, 51.5% used one or more Rx, 38.4% used one or more OTC, and 8.3% used one or more herbal medicine (Table 4).

Table 4. Distribution of medicine use in the total sample and by age cohort

<table>
<thead>
<tr>
<th>Age group, years</th>
<th>Individuals, No. (%)</th>
<th>Rx mean (range)</th>
<th>OTC mean (range)</th>
<th>Herbal mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-75</td>
<td>2816 (100)</td>
<td>1.3 (0-16)</td>
<td>0.5 (0-4)</td>
<td>0.1 (0-4)</td>
</tr>
<tr>
<td>30-49</td>
<td>1851 (65.7)</td>
<td>0.8† (0-11)</td>
<td>0.5 (0-4)</td>
<td>0.1 (0-3)</td>
</tr>
<tr>
<td>50-64</td>
<td>617 (21.9)</td>
<td>1.6 (0-16)</td>
<td>0.4 (0-3)</td>
<td>0.1 (0-4)</td>
</tr>
<tr>
<td>65-75</td>
<td>348 (12.4)</td>
<td>3.2 (0-16)</td>
<td>0.3 (0-3)</td>
<td>0.2 (0-3)</td>
</tr>
</tbody>
</table>

† The corresponding number is 0.7 when excluding G03A

Based on the upper quartile, the cut-offs defining multiple medicine use in the three age cohorts was ≥2 medicines among 30-49-year-olds (14.8% without G03A and 17.7% with G03A), ≥3 among 50-64-year-olds (23.5%), and ≥5 among 65-75-year-olds (25.9%).

Most of the users of multiple medicines had their own unique combinations of medicines, different from those of all other individuals (Figure 1).

When medicines were grouped on the second level of the ATC code, i.e. therapeutic subgroup, 76.3% (72.9% including G03A) of 30-49-year-olds, 97.9% of 50-64-year-olds, and 100% of 65-75-year-olds had their own unique multiple medicine regimes.

The three most frequently used medicine groups among users of multiple medicines in each age group are presented in Table 5.
Figure 1. Proportions of unique individual multiple medicine regimes. The medicines are classified according to the second level of the ATC code, i.e. therapeutic subgroup.

Table 5. The three most frequently used medicine groups among users of multiple medicines

<table>
<thead>
<tr>
<th>ATC class</th>
<th>Medicine group</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30-49 years using ≥2 medicines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Rx medicines:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G03A</td>
<td>Hormonal contraceptives for systemic use</td>
<td>33.8</td>
</tr>
<tr>
<td>N06A</td>
<td>Antidepressants</td>
<td>17.1</td>
</tr>
<tr>
<td>M01A</td>
<td>Anti-inflammatory and anti-rheumatic products, non-steroids</td>
<td>16.2</td>
</tr>
<tr>
<td><strong>30-49 years using ≥2 medicines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excluding G03A:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N06A</td>
<td>Antidepressants</td>
<td>19.3</td>
</tr>
<tr>
<td>N02B</td>
<td>Other analgesics and anti-pyretics</td>
<td>17.9</td>
</tr>
<tr>
<td>M01A</td>
<td>Anti-inflammatory and anti-rheumatic products, non-steroids</td>
<td>17.5</td>
</tr>
<tr>
<td><strong>50-64 years using ≥3 medicines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C07A</td>
<td>Beta-blocking agents</td>
<td>35.9</td>
</tr>
<tr>
<td>B01A</td>
<td>Anti-thrombotic agents</td>
<td>24.1</td>
</tr>
<tr>
<td>A02B</td>
<td>Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)</td>
<td>21.4</td>
</tr>
<tr>
<td>M01A</td>
<td>Anti-inflammatory and anti-rheumatic products, non-steroids</td>
<td></td>
</tr>
<tr>
<td><strong>65-75 years using ≥5 medicines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B01A</td>
<td>Anti-thrombotic agents</td>
<td>52.2</td>
</tr>
<tr>
<td>C07A</td>
<td>Beta-blocking agents</td>
<td>48.9</td>
</tr>
<tr>
<td>C10A</td>
<td>Lipid modifying agents, plain</td>
<td>42.2</td>
</tr>
</tbody>
</table>
Factors associated with multiple medicine use (Paper III)

In the univariate analyses being female, living alone, current smoking, sedentary LTPA, diabetes, hypertension, and poor SRH were associated with use of multiple medicines among 30-49-year-olds. When G03A was included, no association was found between marital status and multiple medicine use. Among 50-64-year-olds, being female, low education, obesity, sedentary LTPA, diabetes, hypertension, and poor SRH were associated with use of multiple medicines. Finally, being female, obesity, sedentary LTPA, diabetes, hypertension, and poor SRH were associated with use of multiple medicines among 65-75-year-olds. Users of multiple medicines did not use OTC and/or herbal drugs to an extent that differed from non-users of multiple medicines.

Table 6 shows the final logistic regression models for multiple medicine use among 30-49-year-olds, 50-64-year-olds, and 65-75-year-olds separately.

The final model among 30-49-year-olds included female sex, diabetes, hypertension, and poor SRH (Table 6). When health status factors were added into the multivariate analyses, sociodemographic factors, except for female sex and lifestyle factors no longer correlated with multiple medicine use.

The final model among 50-64-year-olds included female sex, current smoking, diabetes, hypertension, and poor SRH (Table 6). After adding health status factors, current smoking was the only lifestyle factor associated with multiple medicine use. If current smoking was divided into never smoked, ex-smoker, and current smoker (not associated with multiple medicine use in univariate analysis, P = 0.139), only ex-smokers were associated with multiple medicine use in the final model (P = 0.043, OR 2.0, 95% CI 1.02-3.73) as opposed to current smokers (P = 0.061, OR 1.9, 95% CI 0.97-3.55). Low education was no longer associated with multiple medicine use when lifestyle factors were added into the multivariate analyses. When SRH was excluded from the final model obesity remained borderline associated with multiple medicine use (P = 0.057, OR 1.6, 95% CI 0.99-2.59).

The final model among 65-75-year-olds included obesity, diabetes, and poor SRH (Table 6). Female sex did not remain associated when controlling for the other sociodemographic factors, BMI, and the health status factors.
Table 6. Multivariate analysis of factors associated with multiple medicine use in the final models in each age cohort

<table>
<thead>
<tr>
<th>Factors</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-49 years using ≥2 medicines&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2.1</td>
<td>(1.57-2.77)</td>
<td>0.000</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6.1</td>
<td>(2.95-12.40)</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.5</td>
<td>(3.39-9.01)</td>
<td>0.000</td>
</tr>
<tr>
<td>Self-rated health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>3.1</td>
<td>(2.37-4.17)</td>
<td>0.000</td>
</tr>
<tr>
<td>50-64 years using ≥3 medicines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3.4</td>
<td>(2.09-5.51)</td>
<td>0.000</td>
</tr>
<tr>
<td>Current smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.9</td>
<td>(1.05-3.46)</td>
<td>0.035</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6.6</td>
<td>(3.18-13.55)</td>
<td>0.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5.4</td>
<td>(3.34-8.71)</td>
<td>0.000</td>
</tr>
<tr>
<td>Self-rated health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>4.3</td>
<td>(2.74-6.77)</td>
<td>0.000</td>
</tr>
<tr>
<td>65-75 years using ≥5 medicines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30.0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30.0</td>
<td>2.3</td>
<td>(1.32-3.92)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.2</td>
<td>(1.22-4.06)</td>
<td>0.009</td>
</tr>
<tr>
<td>Self-rated health</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>3.1</td>
<td>(1.82-5.17)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

<sup>Note</sup>. OR = odds ratio. CI = confidence interval. P, statistical significance in logistic regression. <sup>a</sup>Not including G03A.
DISCUSSION

Methodological considerations
This thesis was designed to investigate multiple medicine use from different perspectives, i.e. those of patients, GPs and a community-based population sample.

Focus groups
Focus groups are increasingly used in health science to examine both patients’ and healthcare providers’ attitudes and experiences of a given topic, which is the focus of the discussion [5, 44]. As Papers I-II are exploratory in nature, the intention was not to generalise the results, but rather to collect information and come to some understanding of the attitudes and experiences of multiple medicine use. The purposive sampling technique supported the selection of participants who could best supply the information needed, not a random sample from a population. Patients and GPs in different settings may have different perceptions of multiple medicine use. The patients represent Swedish retired people living at home and managing their medicine regimes. They are able and willing to attend social meetings such as the senior citizens’ associations’ activities. The sample should include a wide range of backgrounds since one of the associations primarily attracts persons with longer formal education while the other primarily attracts blue-collar people. Since the GPs work according to the laws and guidelines of the Swedish healthcare system, the results might be transferable to similar contexts. As always, the generalizability is best judged in terms of logical inference and the credibility of the analyses [49]. The relevance of the qualitative studies is best judged in terms of how the results add new knowledge and increase the confidence with which existing knowledge is regarded. This can only be determined if both the content and interaction analyses are well documented.

The group interaction analysis
The Lehoux, Poland, & Daudelin template was easy to understand and apply to both the patient and professional focus groups (Appendix 4). The template originally focused on patients as participants. However, there are no reasons for not applying it to other participant categories, like professional groups,
since the sociological theories it is based on apply to participants of focus groups in general [40, 180]. Lehoux et al. define several questions to respond to under each main heading of the template. However, it is not possible, and probably not the intention of the template creators, to acknowledge all questions consecutively and mutually exclusively under each main heading. Especially, the moderator’s role needs to be discussed during related issues.

There were two important limitations of the template. The first was the difficulty of trying to identify the participants’ explicit and implicit purposes for participating. The participants were not asked directly what their purposes of participating in the studies were, and Lehoux et al. do not propose doing this. This information could have been collected through a questionnaire or interview before the focus groups. However, to give negative or critical motivations for research participation initially might be difficult for participants [181]. Afterwards their responses might be coloured by the experience itself, for example that they found the experience ‘therapeutic’.

Peel et al. have identified four motivations for offering to take part in qualitative health research relating primarily to patients as opposed to professional groups [181]. These are: (a) factors associated with the context of recruitment, (b) notions for altruism and ‘helping others’ because the research represents a ‘good cause’, (c) conceptualising the research context as inherently innocuous, or (d) viewing interviews as therapeutic. The recruiter (thesis author) experienced that some of the patients (especially the men) agreed in a somewhat patronising way to participate, saying, ‘Of course I will help you out’ and ‘You’re so young and cute’. The altruistic notion that ‘this is important research to conduct for the improvement of treatment for elderly people’ was also present. A likely implicit purpose is that the patients saw it as an opportunity to ventilate frustration, have questions answered, and learn how their peers cope as users of multiple medicines. One might also wonder if an implicit purpose for domineering participants was to dominate and show off their knowledge and experience, or if they just lack the social skills for participating in a group discussion.

The GPs’ purpose for participation seems more straightforward to identify due to the nature of the recruitment; participation depended on whether the contact person or the whole FQ group was positive to the research. In all but one group, the GPs appreciated that this was ‘an important issue they were supposed to put on the FQ agenda soon anyway’, and therefore it was no inconvenience or anything that felt alien to them. However, some GPs might have felt obliged to participate as the sessions occurred during a regular FQ meeting. In the exception group, there was a hostile climate from the beginning, giving the researchers the impression that the GPs felt supervised by the research team. There might be several underlying reasons for this cli-
mate, such as pre-existing relational problems and/or power issues in the FQ group, making it difficult for the GPs to interact constructively and freely in the focus group setting.

However, there is a very fine line between actually interpreting and using qualified guessing. If a retrospective interpretation of participation purpose adds valid information about interaction in groups is therefore questionable. There may be other issues more relevant to discuss based on such information than how it may affect the interaction in the groups, such as if the participants have been informed adequately before participation to be able to give an ‘informed consent’ [181]. One can wonder if the male patient who brought all his medicines for a review had fully understood beforehand what the research project was about.

The second limitation is not a limitation of the template but the likelihood of exceeding word limitations in scientific papers when trying to report both the results from the interaction analysis and the content analysis in one paper. A thorough discussion is needed among researchers conducting focus groups on how to best report the results of the analysis of interactions as well as how to avoid lengthy reports and insignificant contributions to the content analysis. A suggestion is to condense the results to only what contributes to the methodological validity regarding focus group research and to what contributes information about the relevance regarding the actual focus of the study. Still, a more generous word limit for focus group reports is needed if it shall ever be possible to report interaction analysis in the same paper as the content analysis.

Overall, conducting the interaction analysis using the Lehoux, Poland, & Daudelin template increased the confidence in the validity of the results of the content analysis through its detailed account of in which contexts the opinions were formed. Based on this an interaction analysis should always be performed when conducting focus group research.

Survey

Paper III is based on data from a community-based population survey used in many research papers [182-186]. The strengths of this survey include the large community-based population, the high participation rate and the well-characterised cohort. Furthermore, the inclusion of information about OTC and herbal medicine use in addition to Rx is unique. Another advantage of the survey technique is that persons are likely to report on medicines they actually use, as opposed to those bought, but not used.
Among the disadvantages of surveys is the difficulty of verifying the accuracy and the fact that social desirability cannot be ruled out [187]. The possibility for the participants to ask a research nurse for help when answering the questionnaire should have limited misunderstandings, though the nurse may also have affected the answers given.

Recall bias is likely to be limited as participants were asked to bring medicine containers and prescriptions to the interview. In addition, since use of medicines during the past two weeks was reported recall bias is likely to be limited. Earlier studies have reported high reliability and validity in surveys with self-reported medicine use [188]. Detailed information on the use of medicines collected can be difficult to obtain in surveys, as was the case in the Skaraborg survey. The decision to define package sizes of Rx medicines allowed sold OTC as Rx when taking a regular dose and as OTC when the dose was as needed may have both underestimated and overestimated Rx use.

Low response rates may introduce selection bias in survey research. A response rate of 76% is generally considered good but there is no information on the non-respondents in the Skaraborg survey. Healthier individuals might have been more likely to accept participation and thereby be overrepresented among the respondents, but the poor SRH that was found might imply that there was no such selection bias. Illness has been shown to be the most important contributor to non-response bias in health surveys [189].

Causality is central in epidemiology and the temporality criterion – that the cause must precede the outcome – has not been questioned [190]. Temporality between the independent variables studied and multiple medicine use could not be established in Paper III since the survey used was cross-sectional. Several alternative interpretations for the associations found are therefore possible. It may be that persons who are users of multiple medicines perceive and report the other studied factors to a different extent than others. The independent variables and multiple medicine use may also be related to a common third factor, a confounder, that mediates the associations found.

The risk for random error increases when the study sample is divided into the three age cohorts. The statistical power was consequently reduced, especially in the oldest age group (65-75 years). Furthermore, there might be other variables that are significant but that could not be detected due to missing data. However, the internal attrition due to missing data was low for all variables (range 0.05%-8.9%) and all variables were accounted for when building the models. Because the response rate was high, the total number of observations large, and missing data assumed random, listwise deletion was determined the most appropriate and conservative way to handle incomplete data.
Since only individuals between 30 and 75 years of age were included in the survey, the generalizability is limited to this age interval. Moreover, Vara and Skövde are part of a rural area in which income and educational levels are somewhat below and unemployment rates somewhat above the Swedish national average. In addition, the study cannot be generalised to other ethnic groups.

Multiple medicine use

Knowing is not enough; we must apply. Willing is not enough; we must do. – Goethe

Definition

This thesis, along with previous research, supports the idea that the use of multiple medicines is a different concept from inappropriate drug use (IDU) – hence abandoning the term ‘polypharmacy’. This is not controversial and should be easy to implement in future research and policy. Researchers need a general and operationally useful definition that helps in standardising the literature, in building a common platform for comparing and combining results, and for aiding in the development of effective and efficient intervention strategies to improve treatment outcomes. Whether multiple medicine use defined by a cut-off is useful in clinical practice will require more research and discussion. There is no question as to the clinical benefit of identifying IDU both for the health of the patient and for the cost of health care, but the clinical benefit of identifying multiple medicine use is not clear.

The GPs in Paper II spontaneously defined multiple medicine use as the ‘administration of more medicines than are clinically indicated’ and could not relate a cut-off to clinical reality. Identified barriers were the individuality of each patient and uncertainty about which drugs should be included in a count. For the patients in Paper I the number of medicines taken was irrelevant. Adequate knowledge about the treatment, achieved through a good doctor-patient relationship, and the absence of side effects determined the acceptance of their regimens. These results support the hypothesis that a cut-off point is nothing more than an arbitrary number created by researchers and not anchored in real life [4].

Nevertheless, a high number of medicines used per se were important for both the patients and the GPs. First of all, both patients and GPs acknowledged multiple medicine use as an important barrier for adherence, as previously reported in many studies [13, 106-108]. Secondly, the patients wondered how their bodies handled all the medicines they took, how the medi-
cines ‘worked together’, as they were very aware of the increased likelihood of side effects and interactions with increasing number of medicines [4, 10, 15, 109]. The GPs shared their worries, stating they were already on ‘thin ice’ when the patient reached three medicines. Furthermore, health status factors were the variables most strongly related to multiple medicine use in Paper III. This suggests that multiple medicine use is due to higher morbidity and not due to medicine over-consumption. Therefore, multiple medicine use in itself warrants extra patient attention through methods like proper information about diagnoses and the purpose of treatment, as well as close follow-up of medicine regime and adherence.

It is therefore not simply a question of measuring quantity or quality. Whether it is due to the focus in both scientific literature and media on ‘polypharmacy’ or an actual intrinsic precaution by the patients and GPs, multiple medicine use raises a red flag. The clinical benefit lies in warning healthcare providers and patients of possible DRPs. However, when shall we raise the red flag?

Remembering that multiple medicine use increases with age [54] and that there is a linear increase in DRPs with increasing number of medicines [4] researchers should avoid using a pre-defined cut-off, e.g. five or more drugs, intended to fit all categories of patients. Patients in Paper I acknowledged that the number of medicines defined as many were age-dependent. The younger the patients the sooner the number of medicines are regarded as excessive. With the intention of describing users of multiple medicines in different age cohorts more appropriately and deriving results more clinically relevant, a dynamic procedure was chosen in Paper III. Identifying individuals who used a number of Rx medicines equal to or more than the value of the upper quartile gave age-adjusted definitions of multiple medicine use. Thus, 30-49-year-olds were defined as users of multiple medicines when their use exceeded one Rx, 50-64-year-olds when their use exceeded two Rx medicines and 65-75-year-olds when their use exceeded four Rx medicines. The point is not that other researchers should use exactly the 75th percentile [191]. Isacson et al. used the 90th percentile on the distribution of number of prescriptions per person registered during a year in a pharmacy record database to define heavy users of Rx medicines [192]. They found that the 10% with the heaviest use accounted for more than 40% of total medicines prescribed. The fact that there was higher mortality among heavy users compared with non-heavy users shows the importance of studying the heaviest users of Rx medicines defined by age groups. Another aspect is the number of coexisting conditions and frailty that are pointed out as more important factors than age itself concerning DRPs [87, 131, 133]. Consequently, age-adjusted definitions of multiple medicine use may not be adequate and further sub grouping according to, for example, frailty, should be applied.
The GPs in Paper II thought that self-medication is an important reason for multiple medicine use among elderly. However, there is no consensus on the appropriateness of including self-medication in the multiple medicine use definition. Exclusion is largely a result of practical problems like the use of pharmacy record databases in which OTC and herbal medicine are not included, and the fact that herbal medicine cannot be classified according to the ATC classification system. The users of multiple medicines in Paper I reported minimal use of self-medication because of fear of interactions in combination with their Rx medicines. Likewise, Paper III suggests that herbal and OTC medicine need not be included in the definition of multiple medicine use since no association was found with multiple uses of Rx medicines.

Reviewing the patient’s medicine regime and recognising a DRP, whether it is an ADR or non-adherence, and identifying the inappropriate drug causing the problem is an obvious cause of action after a red flag alert. The results of this thesis stress two other important issues related to multiple medicine use. The first issue is the effect of the doctor-patient relationship on how the users of multiple medicines viewed their regimes. The second issue is the mismatch between extensive use of disease-specific treatment guidelines and the GPs’ insecurity when prescribing for more than one disease.

**Doctor-patient relationship**

The users of multiple medicines’ perceptions of their medicine regimes in Paper I depended on the interaction with doctors; more faith was reported in medicines provided by ‘good’ doctors. The health services’ place in lay perceptions of different diseases is currently being evaluated in the sociology of illness [193]. The users of multiple medicines categorised their doctors as ‘good’ or ‘bad’ based on previous experiences, irrespective of speciality or whether the doctor was a county-employed or private practitioner. The ‘bad’ experiences concerned access and time, concordance [3], and episodes revealing doctors’ limited knowledge about treating older patients with multiple diseases. Furthermore, the patients revealed extensive concerns about their medicines, diseases, and experiences from the healthcare system that they had not discussed with their doctors. Patients are known to withhold concerns about medicines from their healthcare provider [194], and practitioners may also block or fail to explore any concerns expressed [195]. Factors influencing patients’ medicine-taking behaviour are therefore not identified and addressed, which may lead to self-experimentation and poor adherence [140, 196] as well as to increased risk of poor quality of life [197], and unmet service needs [198]. In addition, patients who are less trusting of their prescribers have been found to have more unnecessary medicine use [110].
Supporting this, users of multiple medicines in all three age groups rated their health as poor in Paper III, suggesting that their health conditions are not adequately treated, or that they still feel in poor health despite assumed treatment goals to improve health. There might be relevant confounders such as disease severity that could not be controlled for in Paper III. However, it is well established that a person’s own appraisal of her/his general health is a powerful predictor of future morbidity and mortality, even after controlling for a variety of physical, sociodemographic and psychosocial health status factors [7]. Taken together this means that users of multiple medicines of all ages need attention aimed at revealing and alleviating their specific concerns and problems, as this has both immediate and future consequences for their well-being regardless of the conditions treated.

This might not be captured in the brief doctor-patient consultations. The users of multiple medicines in Paper I did not reveal their ‘private’ negative opinions until later in the focus group discussions [199]. Initially they expressed the ‘public’ positive account supporting today’s image of retaining good health through successful aging. Alternatively, they viewed their symptoms as normal in order to cope better and therefore normalised the significance of the medicine regimen on their everyday lives [200] – also called a response shift [201]. Another explanation is that disease symptoms and hence the use of multiple medicines are normal for older patients – an integral part of their biographies [202, 203]. In addition to limitation of time during doctors’ appointments, both patients and GPs mentioned lack of continuity of care as a barrier for a functional doctor-patient relationship [198]. However, there is little research examining fundamental barriers for concordance, such as whether exchange of views takes place during a consultation [204]. Analysis of consultations suggests that patients rarely initiate medicine-related topics and take a passive role when discussing medicines with healthcare providers [204]. Additionally, when doctors give information they rarely assess the patients’ understanding of it, despite acknowledging the importance of doing so [204]. Patient definition of ‘involvement’ has been identified as ‘caring relationship’, ‘person-centred approach’, and ‘receiving information’ rather than active participation in decision-making [198]. To secure concordance, healthcare providers need to be sensitive to both the patients’ ‘positive’ and ‘negative’ responses to illness and consequently medicine regime, and the communication needs an appropriate length and stability to capture both accounts.

It is equally crucial that doctors disclose and discuss their own concerns and views about medicines, although this does not always appear to happen [205]. The GPs in Paper II clearly stated insecurity when prescribing for users of multiple medicines, even though they are surrounded by treatment guidelines. They viewed guidelines as ‘medicine generators’ and were torn
between trusting them and finding them difficult to apply to their patients with multiple diseases. The most important concern for GPs was that their older patients with multiple diseases had clinical needs differing from those of younger patients with a single disease; they believed the guidelines to be based on the latter group [206]. As adhering to guidelines produces ‘kits’ of medicines per indication added on top of each other, thus generating multiple medicine use, the GPs felt they moved further and further away from the outcomes predicted by guidelines [98]. Consequently, the total treatment regime of users of multiple medicines was not considered EBM. The GPs were further torn between adhering to guidelines as they are used as a basis for quality assurance [163] and adjusting them for individual patients. Arguments against guidelines are the risk of ‘cookbook’ medicine and ‘deskilling’, threatening the doctor’s autonomy [207]. Supporters, however, believe that guidelines permit individual choices deviating from them and that formalising a professional group’s knowledge base will rather strengthen the doctors’ autonomy. Loss of professional autonomy is when a profession no longer controls access to the profession and is hindered from determining the required knowledge and skills for their own practice [208].

"The required knowledge" is just what the GPs lack when it comes to prescribing for patients with multiple diseases. This diminishes the clinical significance of EBM and consequently the safety net property of guidelines. Shifting from a disease-driven to a patient-driven focus is increasingly sought after in clinical research and practice, a result of the inherent tension between prescribing for the single disease and prescribing for the patient with multiple diseases [98].

There is no consensus about the constituent elements of concordance. Three aspects, though, have been identified from literature: (i) evidence that patients share their beliefs, experiences and preferences, (ii) information healthcare professionals ask patients to provide and (iii) balance of discussion between healthcare practitioners and patients [204]. Based on the results in this thesis a fourth aspect should be included, namely (iv) communication about the healthcare practitioner’s limited knowledge about treating patients with multiple diseases. Straightforwardly, this is because the (i)-(iii) aspects are based on the notion that the healthcare practitioner has the proper knowledge. Users of multiple medicines in Paper I had a strong desire for medical information, preferably from a doctor. They also placed the responsibility for medical decision-making on their doctors [209] despite their awareness of the doctors’ lack of knowledge about treating patients with multiple diseases. This was clearly illustrated when they reported that they hoped the doctor had more knowledge than they did and emphasised the importance of having faith in the treatment for it to work. The GPs on the other hand acknowledged the importance of patient pressure for whether doctors examine, prescribe, refer or investigate [210]. Patient pressure was negative when the
claims were based on misunderstandings, incorrect information, or personal wishes, but positive when the patient was seen as a partner in decision-making – that is, concordance. The GPs would especially like to involve patients more during risk-benefit analysis of items like preventive medicines, discussing pros and cons openly. As the users of multiple medicines clearly needed discussion partners to relieve their worries and the GPs clearly wanted a more open dialog about their insecurities, a thoughtful and strategic plan providing this communication would benefit patients’ medicine use [209].

Heterogeneous medicine pattern

For the GPs in Paper II, multiple medicine use is manageable one indication at a time. Consequently, a holistic approach applied to patients with multiple diseases, tailoring the treatment to each patient, demands a hierarchy of priorities. This might be one explanation for why most of the users of multiple medicines in Paper III had their own unique medicine combinations, different from those of all other individuals. This is consistent with results from a Danish population study [54], where the authors compared the medicine regimes with an ‘uncontrolled experiment with humans’ based on the unsystematic and sparse knowledge about effects of combining multiple medicines. Based on the cross-sectional data for three age groups in Paper III the findings suggest that the use of multiple medicines originates in the use of antidepressants and pain relievers, to which medicines for cardiovascular conditions and peptic ulcer are added consecutively. However, the heterogeneous pattern shows that just presenting information of the most commonly used medicines in a population oversimplifies the actual pattern of multiple medicine use. Moreover, it shifts attention away from the actual complex variation in individual users’ medicine regimens towards non-existent general trends. Future treatment guidelines for single diseases should not only incorporate evidence of combining medicines for that disease but should also acknowledge the substantial burden of multiple medicine use that characterises the contemporary medical management of a population with multiple diseases. This is a formidable task as the heterogeneous patterns make any clinical trial aiming to control for medicines prescribed for multiple diseases valid for only a limited number of patients.

Another explanation for the heterogeneous pattern is the increasing proportion of users of multiple medicines receiving care for multiple diseases by multiple specialists. The users of multiple medicines in Paper I felt uncomfortable when transferred between primary and hospital care because of poor communication between disciplines. They feared that doctors were unaware of each other’s prescriptions, which could lead to adverse clinical outcomes. The ‘inheritance’ of medicine from specialists was recognised by the GPs in
Paper II as an uncontrollable factor for the development of their patients’ multiple medicine use. Poor information transfer following hospital discharge is widely acknowledged to lower quality of care and cause adverse clinical outcomes [211]. Studies have found that GPs lacked information about a quarter of the prescribed drugs consumed by their patients [55]. Furthermore, patients with prescriptions from more than one doctor were more prone to multiple medicine use and to medicine combinations with a potential drug interaction [55]. It is difficult to express in writing the responsibility the GPs in Paper II felt for their patients’ total medicine regimes. GPs must therefore be empowered to manage the increasing proportion of users of multiple medicines receiving care for multiple diseases from multiple specialists. Additionally, inequities in prescribing rates, especially for cardiovascular medicines, have been highlighted both in Sweden and elsewhere [212, 213]. A possible explanation is so-called ‘treatment traditions’ among prescribers within a municipality [213]. However, this does not explain the heterogenous pattern described in Paper III.

Better registration of the patient’s total medicine regime and the implementation of a common database available to all physicians involved seem urgent. It is known that chronic multimorbidity is rarely adequately documented in present medical records [214]. Treatment of patients with multiple chronic conditions with several coexisting treatment methods through a number of different healthcare professional groups and within different organisational forms puts extensive demands on coordinated analysis and integrated medical record management [215]. An immediate, less extensive and expensive approach is to urge patients to provide their doctor and pharmacist with a comprehensive medicine list of all used Rx medicines, as well as OTC and herbal medicine use. The patients should also be urged to use only one pharmacy or pharmacy chain whose database is linked, to increase the likelihood of detecting IDU.

However, regardless of whether the goal is to establish concordance between patient and provider, improve treatment guidelines, or perform medicine list reviews, knowledge about patient populations most prone to becoming users of multiple medicines is important for specifying the target group for future interventions. As discussed above, users of multiple medicines, regardless of age, had higher morbidity and reported poorer SRH than non-users in Paper III. In addition, women were more likely to be users of multiple medicines until age 65, which is consistent with previous research [54]. One explanation put forward for extensive medicine use is women's reproductive role [216]. However, the results in Paper III were stable regardless of the inclusion or exclusion of hormonal contraceptives among 30-49-year-olds. Other explanations include an acquired risks of illness and injury, psychosocial factors, prior health care, biological factors, and health-reporting behaviour [217].
The result in Paper III suggests that these factors are less important among the oldest, possibly because the factors are related to condition severity.

As in prior studies, being an ex-smoker was associated with multiple medicine use among 50-64-year-olds [27]. One explanation is that people who fall ill and are prescribed regular medicine, quit smoking, while those who remain healthy despite current smoking, are more likely to continue the habit. As educational level did not remain associated with multiple medicine use among 50-64-year-olds after adding lifestyle factors, it could be assumed that health-related behaviours are more important for the use of multiple medicines than education. Middle-aged people in Sweden with high education are reported to smoke less, eat better, and exercise more than those with low education [218].

Obesity is a major public health issue contributing to cardiovascular diseases and diabetes, as well as to work disability and decreased quality of life [219]. However, it is proposed that the higher mortality risk associated with larger BMI is reduced or even disappears altogether among older people [220]. To some degree obesity seems to protect the 65-75-year-old users of multiple medicines in Paper III. This is presumed to operate through increased available body mass stores in case of illness [221].

In summary, until age 65 being female and ex-smokers are important markers for multiple medicine use. Obesity, however, should not only be treated as a problem related to risks of multiple medicine use among the oldest. Given its strong association with morbidity and poor SRH regardless of age, healthcare providers should view multiple medicine use both as necessary and as a red flag, remembering that establishing concordance is as important as identifying IDU.
CONCLUSIONS

It is not simply a question of measuring quantity or quality. Moen, 2009

• The patients displayed co-existing accounts of positive and negative perspectives of being users of multiple medicines. This illustrates the complexity of being grateful that medicines provide relief of symptoms and extend life while also being afraid of adverse outcomes and insecure about total net benefit. The insecurity arose largely from the fact that the patients perceived a general lack of knowledge concerning treatment of older patients with multiple diseases. Adding to the complexity, the patients’ views of their medicine regimes also depended on their encounters with doctors, stating more faith in medicines provided by ‘good’ doctors.

• The GPs regarded polypharmacy as a term not properly defined or anchored in clinical reality. Although surrounded by treatment guidelines, the GPs sometimes felt insecure when prescribing for patients with multiple diseases. There was an inherent tension between prescribing for a single disease and prescribing for a patient with multiple diseases. Consequently, their patients’ total medicine regime was not perceived as evidence-based medicine. ‘Inheriting’ medicines from hospital specialists as well as negative patient pressure were recognised as contributing factors to multiple medicine use.

• Multiple medicine use defined by the upper quartile gave the cut-offs as ≥ 2 Rx medicines among 30-49-year-olds, ≥ 3 Rx medicines among 50-64-year-olds, and ≥ 5 Rx medicines among 65-75-year-olds.

• Users of multiple medicines did not use OTC or herbal medicines differently than non-users of multiple medicines.

• Most of the users of multiple medicines had their own unique multiple medicine regimes – different from those of all other individuals.
Multiple medicine use was associated with female sex, diabetes, hypertension, and poor self-rated health among 30-49-year-olds. Among 50-64-year-olds, it was associated with female sex, being an ex-smoker, diabetes, hypertension, and poor self-rated health. Obesity, diabetes, and poor self-rated health were associated with multiple medicine use among 65-75-year-olds. Multiple medicine use is associated with morbidity across all age groups, which suggests that it is not a result of medicine over-consumption.

Analysing the interaction in focus groups increased the confidence in the validity of the results of the content analysis. An interaction analysis should therefore always be performed. The Lehoux, Poland, & Daudelin template was easy to understand and apply to both patient and professional groups. One exception was the difficulty experienced when trying to identify the participants’ explicit and implicit purposes for participating. However, further discussion is needed on how to best report the results.
FUTURE DIRECTIONS

The term ‘polypharmacy’ should be abandoned and future studies should clearly define whether they are about ‘multiple medicine use’ or ‘inappropriate drug use’. Only in this way can we start to build up a knowledge base that is consistent and comparable.

In this thesis, it was not possible to use clinical information for assessing the appropriateness of the multiple medicine use among patients, nor was it an aim to do so. However, future research is warranted for assessing the appropriateness of multiple medicine use in different age groups. Further qualitative studies are needed to study multiple medicine use from the hospital specialist’s and pharmacist’s perspectives, and how the perspectives of patients, GPs, specialists and pharmacists interact.

To be able to manage the increasing proportion of uses of multiple medicines, future research needs to move past promoting randomised control trials as the only scientifically valid documentation in treatment guidelines. If not, research will continue to exclude the majority of true participants with multiple conditions and fail to address key issues of prescribing for such patients. One alternative approach is prospective cohort studies with nested clinical trials embedded [222]. The scarcity of relevant evidence, the high medicine utilisation, and the demonstrated quality issues regarding multiple medicine use emphasise the need for continuous monitoring of medicine use. Population-based and healthcare system-based observational studies are important tools for this purpose.

The introduction of the Swedish prescribed drug register, together with register-linkage opportunities with other Swedish sociodemographic and health registers, will allow population-based research on multiple medicine use and health outcomes with more accurate medicine exposure data than in previous studies. It is crucial that such studies focus on multiple medicine-users of all ages, not only the elderly.

The need for improving the doctor-patient communication in order to improve the well-being of users of multiple medicines is another important field for a clinical intervention.
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Nog finns det mål och mening i vår färd men det är vägen som är mödan värd.

[Of course there is a goal and a meaning to our journey, but it is the road that makes it worth our while.]

– Karin Boye

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APPENDIX

Appendix 1 – Debriefing – Papers I-II and IV

The debriefing was based on the 12 questions by Stevens [45].

- How closely did the group adhere to the issues presented for discussion?
- Why, how and when were related issues brought up?
- What statements seemed to evoke conflict?
- What were the contradictions in the discussion?
- What common experiences were expressed?
- Were alliances formed among group members?
- Was a particular member or viewpoint silenced?
- Was a particular view dominant?
- How did the group resolve disagreements?
- What topics produced consensus?
- Whose interests were being represented in the group?
- How were emotions handled?
Appendix 2 – Interview guide – Paper I

(Originally available in Swedish, the interview guide was translated to English for inclusion in Paper I by J. Moen)

- What is your perception of the use of multiple medicines?
- Are there any differences between using one or two medicines and five or more medicines?
- What are the benefits from using your medicines?
- What risks do you associate with using many medicines simultaneously (interactions, adverse reactions)? Is this risk different for prescription, OTC and herbal medicines?
- What helps you remember to take your medicines?
- How difficult is it to comply completely with the recommended dosage your doctor has prescribed?
- How can the current situation be improved for elderly using many medicines?
- Have we missed anything? Or is there anything you would like to add?
Appendix 3 – Interview guide – Paper II

(Originally available in Swedish, the interview guide was translated to English for inclusion in the thesis by J. Moen)

- What is your perception of treating older people who use multiple medicines?
- Are there any differences between prescribing one or two medicines and five or more medicines?
- How common is multiple medicine use (defined as $\geq 5$ medicines)?
- Are there certain groups of older people that are more likely to become users of multiple medicines?
- Can you discuss the risk-benefit ratio for the use of multiple medicines among older people?
- Can you define a number of medicines (cut-off) that equals multiple medicine use?
- How do you think your patients perceive being users of multiple medicines (risk-benefit)?
- Do you think that your patients ask you beforehand about which OTC and/or herbal drugs they can use in addition to the prescribed medicines?
- How does patient adherence affect the treatment outcome?
- How can the situation for older users of multiple medicines be improved?
- What is most important to think about when you prescribe for older users of multiple medicines?
- Have we missed anything? Or is there anything you would like to add?
Appendix 4 – The Lehoux, Poland, & Daudelin template – Paper III

_The Lehoux, Poland, & Daudelin analytical template for focus group research (2006)_ [48]

<table>
<thead>
<tr>
<th>Group processes</th>
<th>Epistemological content</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Research design: Contrasting the researcher’s purposes with those of participants</strong></td>
<td></td>
</tr>
<tr>
<td>Who do participants represent when they speak? (e.g., member of a larger group, an individual sharing his/her own experience)</td>
<td>To what extent do participants comply with the moderator’s cues and/or seek to foster discussion on other issues?</td>
</tr>
<tr>
<td>What are the explicit purposes of participants? What could be their implicit purposes?</td>
<td>Why do these issues matter? And to which participants?</td>
</tr>
<tr>
<td></td>
<td>What do participants’ purposes tell about the research topic?</td>
</tr>
<tr>
<td><strong>Interactive social space: Understanding interactions and what is shared as a result of the relational positioning of participants</strong></td>
<td></td>
</tr>
<tr>
<td>What types of interactions occur among participants? (e.g., limited/significant, empathic/challenging, educational/personal, negative/constructive)</td>
<td>What do dominant and passive positions reveal about the topic at hand?</td>
</tr>
<tr>
<td>To what extent do these interactions reflect the broader social contexts? (e.g., age, gender, status, authority)</td>
<td>What types of knowledge claims (e.g., clinical/experiential knowledge, self-care skills, strategies and resources mobilised) are endorsed and/or challenged by participants? On what basis?</td>
</tr>
<tr>
<td>Which participants dominate the discussion? How does this affect the contribution of other participants?</td>
<td>What types of knowledge claims receive less support? Why?</td>
</tr>
<tr>
<td>Which participants adopt a passive role? How do other participants respond to this position?</td>
<td></td>
</tr>
<tr>
<td><strong>Moderator’s role: Considering the extent to which the moderator participates in the construction of the patients’ views</strong></td>
<td></td>
</tr>
<tr>
<td>How does the moderator set the tone at the beginning?</td>
<td>How does the moderator respond to the validation and/or disputing of knowledge claims?</td>
</tr>
</tbody>
</table>
How does the moderator succeed in making room for each participant to contribute to the common ground?

Do participants accept and/or challenge the leadership of the moderator? How and when is acceptance or defiance manifested? How does the moderator respond?

What is the overall impact on the ‘‘common ground’’?

Does the common ground remain stable over time?
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