Drug therapy - a challenge in primary care.

Milos, Veronica

2014

Drug therapy - a challenge in primary care

Assessment of different methods that influence GPs' adherence to guidelines

LUND
UNIVERSITY

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DOCTORAL DISSERTATION
by due permission of the Faculty of Medicine, Lund University, Sweden.

To be defended at November 21 2014, 9.00 am

Faculty opponent

Professor Per Wändell

Organization	Document name
LUND UNIVERSITY	
	Date of issue
Author(s); Veronica Milos Nymberg	Sponsoring organization

Title and subtitle Drug therapy-a challenge in primary care. Assessment of different methods that influence GP's adherence to guidelines

Introduction: Drug therapy in primary care is a broad field, with two areas previously identified as particularly challenging: treatment of the elderly and prescription of antibiotics against uncomplicated upper respiratory tract infections (URTIs). General practitioners' (GPs') attitudes and adherence to evidence-based treatment guidelines might be influenced by different interventions and need to be studied. *Objectives:* 1. To study different intervention models that might influence GPs' adherence to treatment guidelines. 2. To describe GPs' attitudes towards locally developed treatment guidelines. *Methods:* (Paper I) Systematic medication reviews by pharmacists were performed in a randomised controlled study of 369 elderly patients living in the community or nursing homes, who were using the multi-dose drug dispensing (MDD) system. Drug lists were assessed before and after the intervention with a focus on potentially inappropriate medications (PIMs). (Paper II) A retrospective analysis of medication lists was conducted in the same patient sample, with a focus on fall risk-increasing drugs (FRIDs), orthostatic drugs (ODs) and falls. (Paper III) A randomised controlled study was performed using two questionnaire-based behaviour change interventions aimed at reducing prescription of antibiotics against URTIs in primary care. (Paper IV) A qualitative study was performed using focus group interviews to assess GPs' attitudes towards evidence-based local treatment guidelines. *Results:* Papers I and II: Systematic medication reviews by pharmacists reduced the number of patients taking PIMs and the total number of drugs these patients were taking, but not the number of patients taking more than three psychotropic drugs. A significant proportion (87%) of the study sample was taking FRIDs and ODs. Numbers of FRIDs were associated with the total number of drugs and with severe falls. There was no association between numbers of ODs and occurrence of severe falls. Paper III: There was a significant decrease in the antibiotic prescribing rate in one of the two intervention groups compared to the control group in patients 0-6 years but no differences between the groups in patients of all ages. Paper IV: Trust in evidence-based recommendations and patient safety were found to be key factors in prescribing, as was the patient-doctor encounter, with emphasis on informing the patient. The GPs all experienced a lack of time to self-inform, difficulties managing patients with multiple prescribers and direct-to-consumer drug industry information. Cost containment was perceived as both a barrier and a motivator for adherence to guidelines. *Conclusion*: Multi-professional assessment of patient's drug list and questionnaire-based behaviour change interventions might be feasible methods to improve quality of drug treatment in primary care and need to be studied further. GPs found trust in evidence-based guidelines and patient safety to be essential in drug prescribing.

Key words Drug therapy, elderly, guidelines, primary care, potentially inappropriate medications, fall risk increasing drugs, antibiotics, upper respiratory tract infections, attitudes, adherence, general practitioners, Sweden

Classification system and/or index terms (if any)

Supplementary bibliographical information	Language English
ISSN and key title 1652-8220	ISBN 978-91-7619-016-6
Recipient's notes	Number of pages 143 / Price
	Security classification

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ISBN 978-91-7619-016-6
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2014

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Abstract

Introduction: Drug therapy in primary care is a broad field, with two areas previously identified as particularly challenging: treatment of the elderly and prescription of antibiotics against uncomplicated upper respiratory tract infections (URTIs). General practitioners' (GPs') attitudes and adherence to evidence-based treatment guidelines might be influenced by different interventions and need to be studied.

Objectives: 1. To study different intervention models that might influence GPs' adherence to treatment guidelines. 2. To describe GPs' attitudes towards locally developed treatment guidelines.

Methods: (Paper I) Systematic medication reviews by pharmacists were performed in a randomised controlled study of 369 elderly patients living in the community or nursing homes, who were using the multi-dose drug dispensing (MDD) system. Drug lists were assessed before and after the intervention with a focus on potentially inappropriate medications (PIMs). (Paper II) A retrospective analysis of medication lists was conducted in the same patient sample, with a focus on fall risk-increasing drugs (FRIDs), orthostatic drugs (ODs) and falls. (Paper III) A randomised controlled study was performed using two questionnaire-based behaviour change interventions aimed at reducing prescription of antibiotics against URTIs in primary care. (Paper IV) A qualitative study was performed using focus group interviews to assess GPs' attitudes towards evidence-based local treatment guidelines.

Results: Papers I and II: Systematic medication reviews by pharmacists reduced the number of patients taking PIMs and the total number of drugs these patients were taking, but not the number of patients taking more than three psychotropic drugs. A significant proportion (87%) of the study sample was taking FRIDs and ODs. Numbers of FRIDs were associated with the total number of drugs and with severe falls. There was no association between numbers of ODs and occurrence of severe falls. Paper III: There was a significant decrease in the antibiotic prescribing rate in one of the two intervention groups compared to the control group in patients 0-6 years, but no differences between the groups in patients of all ages. Paper IV: Trust in evidence-based recommendations and patient safety were found to be key factors in prescribing, as was the patient-doctor encounter, with emphasis on informing the patient. The GPs all experienced a lack of time to self-inform, difficulties managing patients with

multiple prescribers and direct-to-consumer drug industry information. Cost containment was perceived as both a barrier and a motivator for adherence to guidelines.

Conclusion: Multi-professional assessment of patient's drug list and questionnaire-based behaviour change interventions might be feasible methods to improve quality of drug treatment in primary care and need to be studied further. GPs found trust in evidence-based guidelines and patient safety to be essential in drug prescribing.

Abbreviations

ATC	Anatomical Therapeutic Chemical classification system
CME	Continuing medical education
DRP	Drug-related problem
DTC	Drug and therapeutic committee
EMR	Electronic medical record
FRID	Fall-risk increasing drug
GP	General Practitioner
GTI	Graded task intervention
MDD	Multi-dose drug dispensing system
NBHW	Swedish National Board of Health and Welfare
OD	Orthostatic drug
OLT	Operant learning theory
PCI	Persuasive communication intervention
PHCC	Primary health care centre
PIMs	Potentially inappropriate medications
RCT	Randomised controlled trial
SCT	Social cognitive theory
STRAMA	Swedish Strategic Programme against Antibiotic Resistance
URTIs	Upper respiratory tract infections
TPB	Theory of planned behaviour

Original papers

This thesis is based on the following papers referred to in the text by their Roman numerals:

I. Milos V, Rekman E, Bondesson A, Eriksson T, Jakobsson U, Westerlund T, Midlöv P: Improving the quality of pharmacotherapy in elderly primary care patients through medication reviews: a randomised controlled study. *Drugs Aging* 2013, 30(4):235-246.

II. Milos V, Bondesson A, Magnusson M, Jakobsson U, Westerlund T, Midlöv P: Fall risk-increasing drugs and falls: a cross-sectional study among elderly patients in primary care. *BMC Geriatr* 2014, 14:40.

III. Milos V, Jakobsson U, Westerlund T, Melander E, Mölstad S, Midlöv P: Theory-based interventions to reduce prescription of antibiotics-a randomized controlled trial in Sweden. *Fam Pract* 2013, 30(6):634-640.

IV. Milos V, Westerlund T, Midlöv P, Strandberg E L: Swedish general practitioners' attitudes towards treatment guidelines - a qualitative study. *Submitted*

Introduction

This thesis addresses aspects of drug prescribing in primary care, with a focus on drug use in the elderly and prescribing of antibiotics against upper respiratory tract infections (URTIs), with an emphasis on optimizing adherence to guidelines and exploring general practitioners' (GPs') attitudes towards them.

Drug prescribing is the most common medical procedure. It is also the leading cause of patient injury and patient safety problems in Sweden [1]. Reports delivered during the recent years by the Swedish authorities have highlighted that different challenging areas need special attention, such as drug-related problems in the elderly and increases in resistant bacteria due to high antibiotic prescription rates [2]. These insights have resulted in a National Pharmaceutical Strategy with a focus on patient safety and quality of care [3]. That particular interest should be paid to these areas is stressed in the yearly initiative from the Swedish government since 2011 [4]. Treatment of elderly patients with multiple illnesses and prescription of antibiotics are two of the most common tasks in every-day praxis in Swedish primary care. Interventions to optimize drug therapy should therefore target these areas, taking GPs' attitudes into consideration to successfully implement prescribing behaviour changes.

Drug therapy in primary care

Drug treatment in primary care is a complex matter, requiring broad knowledge about the effects of medication on human beings. Every decision about drug therapy involves individual consideration of the patient's condition, withdrawal of drug therapy in some patients being a better alternative than prescribing a new drug. The decision has to be a result of careful consideration involving knowledge about medication and the patient's unique characteristics and expectations.

GPs are responsible for most of the drug prescriptions in southern Sweden [5]. Unlike GPs in other European countries such as the Netherlands, Denmark and Norway, Swedish GPs work in public or tax-financed private multidisciplinary surgeries with several physicians, registered nurses and physiotherapists. Each surgery is given economic responsibility by the county council. While the structure of primary care demands financial responsibility on the part of physicians, there are efforts to meet

patients' needs and wishes and also to increase confidence in GPs. The broad skills of Swedish GPs allow them to manage a vast spectrum of diseases and problems, with care accounting for patients' complex needs. Following evidence-based medicine principles while maintaining the holistic view of the individual without risking patient safety are aspects a GP needs to consider in every prescribing decision. Due to the patient-centred approach [6] used in Swedish primary care during recent decades, non-medical factors can influence the prescribing decision, such as organisation structure or patient age and gender. A recent Swedish study showed that drug prescriptions are not dependent on level of multi-morbidity and may vary with different factors such as patients' age, gender and socioeconomic status [7], indicating that the issue is multifaceted.

Today, there is no clear definition regarding "quality of drug treatment". A well-known definition often referred to is the WHO's definition from 1985: *"Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community"*[8]. Given the complexity of primary health care due to an ageing population, co-morbidity and potential inequality of care, drug therapy might be one of the biggest challenges in GPs' every day praxis.

Drug use in the elderly

According to the Swedish Central Bureau of Statistics, the proportion of the population aged 65 years or older in Sweden increased from 13.4 % in 1968 to 19.4 % in 2013. Aging is known to be associated with an increased prevalence of multiple chronic diseases and therefore the use of complex therapeutic regimes. Age-related changes in pharmacokinetics and pharmacodynamics [9], together with co-morbidity and polypharmacy, make the elderly a special group of patients who need to be treated with increased attention [10].

Polypharmacy is a controversial issue and has been found to be related to an increased risk of drug-drug interactions, higher morbidity in the older population, higher numbers of hospital admissions, lower compliance to prescribed treatment and increased institutionalisation [11]. A comprehensive literature review on the topic shows that polypharmacy is increasing in the elderly and is a major cause of morbidity and mortality in the elderly population worldwide [12]. Lack of continuity in physician contacts, lack of a consistent drug list, and inadequate prescribing and monitoring of drug therapy are some of the reasons for drug-related problems (DRPs) and the need for emergency hospital contacts [12]. A DRP has previously been described as "an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome" [13].

A meta-analysis of prospective studies indicated that approximately 15 % of hospital admissions every year between 1966 and 1996 in the USA were caused by adverse drug reactions [14]. Meanwhile, both Swedish and international studies have shown that a majority of hospital admissions related to inappropriate drug use could be prevented [15]. Falls are the most common cause of injuries among patients over 65 years old, a recent report showing that a majority of hospital admissions of patients aged ≥65 years in 2012 in Canada were due to falls [16]. Upper extremity fractures and hip fractures are also the most common fall-related injuries that lead to emergency department visits in the USA [17]. A Swedish study showed that treatment with fall-risk-increasing drugs (FRIDs) was extensive (prevalence 93%) among older hip fracture patients both before and after the fracture [18]. Although the causes of falls are multi-factorial, medications are a significant risk factor.

On the other hand, suboptimal treatment with recommended drugs has been described in the elderly, as secondary prevention of coronary heart disease [19], secondary stroke prevention [20] or therapy of osteoporosis [21]. Even if GPs have access to evidence-based guidelines, they might have mixed feelings about adherence to treatment recommendations. A Swedish study showed that despite their trust in guidelines, GPs thought they were difficult to apply, defining them as "medicine generators" that increase the number of drugs the patients were using [22]. During the patient-doctor encounter, the GP also needs to consider other aspects that impact on the prescribing decision. Patient-related factors such as patients' needs, preferences and abilities have been described as common barriers to adherence to guidelines [23].

Prescribing of antibiotics in primary care

Another area of drug prescribing that should get particular attention is antibiotic treatment of common infections in primary care. Irrational use of antibiotics leads to both the emergence and spread of resistant bacteria [24]. Data from 26 European countries demonstrated a correlation between the use of antibiotics and the level of antibiotic resistance and a high variation in outpatient antibiotic use, countries in northern Europe having the lowest prescribing rates and southern Europe having the highest [25]. A Cochrane analysis from 2005 showed that there is no evidence for any benefits of antibiotic treatment against unspecific URTIs, and that the risk of side effects outweighs the benefits [26]. The danger of increasing antibiotic resistance has been recognised globally, resulting in extensive campaigns aimed at both prescribers and the public, and in the development of treatment guidelines [27].

URTIs are the most common reason to visit a doctor and to receive antibiotic prescriptions in Swedish primary care [28]. Register data collected from 66 primary

health care centres (PHCCs) with 550000 listed inhabitants showed that in 2011 sore throats caused 39 visits per 1000 inhabitants and year and resulted in 27 antibiotic prescriptions per 1000 inhabitants and year [29]. On a national level, it is estimated that sore throats result in 310000 antibiotic prescriptions every year [30].

During the last ten years, Skåne, the county in which the studies in this thesis were conducted, has been the Swedish county with the second highest number of antibiotic prescriptions with approximately 400 antibiotic prescriptions per 1000 patients every year. In 2010, approximately 60 % of these 400 antibiotic prescriptions were for URTIs [31].

Although antibiotic prescribing has decreased during the last years in Sweden and knowledge and awareness of resistance has increased among prescribers and the public, there is a further need for strong actions both nationally and internationally to reduce the spread of antibiotic resistance [31].

Treatment guidelines

There are two sides of the coin regarding drug treatment. Patient safety and clinical effectiveness are two important aspects. On the other hand, increasing costs because of the accelerating prescription and influences from both patients [32] and the pharmaceutical industry put pressure on both GPs [33] and policy makers. Meanwhile, access to and need of good drugs is increasing at the same time as the focus on evidence-based medicine.

Well defined criteria (Beers Criteria) for ***potentially inappropriate medications (PIMs)*** in the elderly that use toxicological aspects and risk of adverse drug reactions were updated in 2012 [34].The lack of good nationally adapted alternatives has led to the wide use in studies of the internationally accepted criteria in order to create tools for identifying PIMs. About half of the drugs listed as PIMs in the Beers Criteria are, however, unavailable in Europe. Therefore, several European countries have developed their own lists using criteria corresponding to European drug formularies. In Germany, a list containing PIMs was developed by a panel of experts [35]. Similar lists have been created in France [36] and Norway [37]. In Sweden, quality indicators were developed by the Swedish National Board of Health and Welfare (NBHW) [38]. These quality indicators support the prescriber in choosing appropriate medications but can even be used by drug and therapeutic committees (DTCs) to follow up doctors' prescribing habits or to assess the quality of prescribing at the local or national level.

Fall risk-increasing drugs (FRIDs) are drugs considered to increase the risk of falling. The most common FRIDs are different types of psychotropic drugs, such as sedatives,

hypnotics, antidepressants and antipsychotic medications, which cause sedation and impair balance and coordination. The use of selective serotonin reuptake inhibitors (SSRI) has been associated with falls, regardless of the presence of depressive symptoms [39]. Due to physiological changes in blood pressure-regulating systems and cardiovascular co-morbidity, cardiovascular drugs might cause orthostatic hypotension and falls [34, 36, 40]. Anti-Parkinson's disease and dopaminergic drugs might also increase the fall risk by causing orthostatic hypotension, dyskinesia or hallucinations. Anticholinergic drugs, such as antihistamines and urological spasmolytics, affect elderly patients' cognitive skills and cause blurred vision, thereby increasing the fall risk [41]. A nationwide register-based study in Sweden showed a strong correlation between the number of prescribed drugs and the number of PIMs, such as anticholinergic drugs and long-acting benzodiazepines [42]. The use of three or more psychotropic drugs was also found to be strongly connected to the number of drugs the patients were using [42]. Use of multiple psychoactive drugs has been identified as particularly problematic in nursing home patients [43], due to adverse drug reactions, inappropriate drug choice for the indication or underuse of beneficial treatment.

There is clear evidence that polypharmacy in general and the use of psychotropic drugs in particular increase the fall risk [41, 44, 45]. The fall risk is especially high in patients using a combination of drugs from the same therapeutic class and when psychotropic and cardiovascular medications are combined [46]. A meta-analysis of interventions aiming to prevent falls in the elderly showed that slow withdrawal of psychotropics decreased the fall incidence and that prescribing modification programs for primary care physicians significantly reduced risk of falling [47].

Authorities in different countries have produced their own lists of drugs considered to increase the risk of falling, in order to alert caution in the health care. The NBHW in Sweden has produced a FRID list, and also a list of drugs causing or worsening orthostatic blood pressure, which is relevant for assessing the fall risk [40].

Rational antibiotic prescribing is promoted on a national level by the Swedish Strategic Programme against Antibiotic Resistance (STRAMA). Even if Sweden, in common with the other Nordic countries, has a more favourable pattern of resistant bacteria compared with Southern Europe [48], a national plan including improved antibiotic use and building a knowledge base was presented in 2000 by the NBHW [48]. STRAMA has a key role in this work, developing and implementing guidelines and organizing academic detailing meetings in both primary and secondary care with information about current local, regional and national antibiotic prescribing rates and treatment recommendations.

In 2012, the Swedish Medical Products Agency (Läkemedelsverket) and the Swedish Institute for Communicable Disease Control (Smittskyddsinstitutet) provided treatment guidelines for sore throats [30]. These and other guidelines are spread through academic detailing using educational outreach visits, interactive lectures and printed folders addressed to both prescribers and patients by STRAMA, which also continuously monitors prescription data and gives feed-back to the prescribers. The effect of these interventions is assessed by following the rate of prescribing, defined as number of antibiotic prescriptions per 1000 listed inhabitants, at local and national levels.

GPs' attitudes towards treatment guidelines

GPs often believe that treatment recommendations (guidelines) are useful in practice and there is generally a positive attitude among Swedish primary care physicians [49] who see prompt benefit as a strong motivating factor [50]. GPs' uptake of clinical practice guidelines and behaviour change have been attributed to their awareness of policies for evidence-based medicine [51].

Adherence to guidelines in primary care might vary and clinical inertia has been described as a possible cause [52]. Drug lists containing drugs from multiple prescribers, especially in patients with multiple illnesses might also be a problem. A Swedish qualitative study with interviews of 20 GPs showed that GPs' understanding of responsibility for patients' medication lists varied [53], with GPs feeling either responsible for their own prescriptions or all prescriptions, or even considering the patients responsible for transferring drug information. GPs might also resist implementing guidelines due to psychological reactance [54], and lower adherence to medication guidelines could thus potentially arise.

However, a meta-analysis of qualitative research shows that GPs attitudes towards treatment guidelines may be influenced by the purpose of the guidelines and that creating trust in guidelines might be more important than increased efforts to improve guideline format or accessibility when implementing them [55]. Transparency and involvement of GPs in the development and implementation of guidelines might thus increase adherence [56].

Methods influencing prescribing behaviour

Interventions to improve adherence to guidelines in primary care in certain problematic areas have been widely tested. A systematic meta-review shows that various factors might influence prescribing patterns, such as lack of support from superiors, or insufficient staff and time [57]. Evidence shows that effective interventions to increase compliance with guidelines in primary care should use a combination of methods instead of one single strategy [58]. A Cochrane report [59] shows that educational visits alone are not likely to change complex behaviours. The same report suggests that strategies to increase attendance at educational meetings, using mixed interactive and didactic formats and focusing on outcomes perceived as serious might increase the effectiveness of such interventions.

Optimisation of drug therapy in the elderly can be challenging and different tools have been implemented, such as educational outreach visits [60], medication reports at hospital discharge [61] and pharmaceutical care programmes using community pharmacists and medication reviews [62].

Multidisciplinary approaches such as **medication reviews** have been shown to be a feasible method to improve drug therapy in elderly patients with a focus on polypharmacy, DRPs and inappropriate medications [60, 63-65]. Currently, there is no well-established definition of the term "medication review" but Pharmaceutical Care Network Europe has suggested the following definition: "*Medication review is an evaluation of patients' medicines with the aim of managing the risk and optimising the outcome of medicine therapy by detecting, solving and preventing drug-related problems*" [66].

Collaboration between physicians and pharmacists to identify DRPs has proven to be useful and led to better patient safety, as well as cost savings [67, 68]. Multidisciplinary approaches have proved to be very satisfactory in elderly patients, being appreciated by physicians and nurses and having long-term effects on the drug therapy [63]. However, a recent systematic review showed that medication reviews with or without pharmacists did not reduce mortality or hospitalisation of nursing home residents [69]. Other models for review of the drug list by a physician have been shown to reduce polypharmacy and inappropriate medication [70, 71], but did not significantly decrease treatment with fall risk-increasing drugs [18]. Fall prevention programs using medication reviews performed by pharmacists have also been tested. However, there is a need for better coordination of care between pharmacists and physicians in order to get the potential beneficial effects of medication management on fall prevention [72].

In primary health care in Skåne County, medication reviews have been conducted during the past ten years in different projects, both in nursing homes and community-dwelling elderly patients with multiple illnesses, and several models and approaches have been tried [73]. The instruments used in hospitals were subsequently adapted for use in primary care. The main aim of adapting the instruments for primary care was to implement a new model of care with medication reviews before the patient's annual assessment by a GP in order to improve the quality of pharmacotherapy in elderly community-dwelling and nursing home patients. However, no previous studies have assessed this structured model in primary care with a focus on PIMs.

Another target area for optimising drug therapy is reducing the prescriptions of antibiotics against URTIs in primary care. Different interventions have been tested, including educational programs for caregivers [74], web-based decision support tools [75] and even multifaceted strategies with audits, clinical guidelines, patient education and point-of-care tests [76]. These interventions have had varying results. A comprehensive 2005 Cochrane review of different interventions in primary care showed that efficient methods must be targeted to physicians, patients and the public and must also aim to influence barriers in the form of prescribers' behaviour and local therapy traditions [77].

A recently published study from Sweden on GPs' perceptions of the treatment of infections in primary care showed a strong conviction of the importance of strict indications for the prescription of an antibiotic to maintain its effectiveness and for the benefit of the patient in the long run. The study also showed that doctors may have different views and may need different types of support [78].

Application of psychological theories of behaviour [79, 80] in order to understand and influence GPs' attitudes and behaviour in the prescribing situation is an exciting new approach that has not been sufficiently explored. Three theories have come into focus: the theory of planned behaviour (TPB), social cognitive theory (SCT) and operant learning theory (OLT) [79-81]. TPB is a cognitive theory that has been widely used to predict and explore determinants of professional behaviour [82]. According to TPB, behavioural intention predicts behaviour. Behavioural intention is itself determined by an individual's attitudes, subjective norms and perceived behavioural control. Other important determinants of learning and behaviour change include self-efficacy (SCT) and perception of anticipated consequences (OLT).

Assessing behaviour with a theory-based approach has been used, for example, to increase knowledge of British GPs' attitudes towards specific laboratory blood tests and target the factors that influence behaviour [83] in order to reduce unnecessary requests for blood testing. Experimental studies have designed and validated survey instruments

based on the three aforementioned theories of human behaviour [84]. In one experimental study, examining physicians' knowledge, attitudes and self-efficacy, and reinforcing these determinants through targeted interventions, improved behaviour in prescribing antibiotics for URTIs [85].

Such knowledge of the mechanisms underlying behaviour can be used to develop useful tools that can lead to a change of attitude and thus a change in behaviour.

Aims of the thesis

The general aim of this thesis was to study drug therapy of the elderly and prescribing of antibiotics against URTIs in primary care, assess different methods that influence GPs' prescribing behaviour and describe their attitudes towards evidence-based guidelines.

The specific aims were:

- To assess a structured model of care by studying the impact of pharmacist-led medication reviews on the number of elderly patients using PIMs. (Paper I)
- To assess FRIDs and ODs and their correlation with reported falls in a population of elderly community-dwelling and nursing home patients on multi-dose drug dispensing. (Paper II)
- To determine whether interventions based on behavioural theories can reduce the antibiotic prescription rate for URTIs in primary care in southern Sweden. (Paper III)
- To describe Swedish GPs' attitudes towards locally developed evidence-based treatment guidelines. (Paper IV)

Methods

The dissertation comprises three quantitative studies and one qualitative study. An overview of the studies is presented in Table I.

Table I. Overview of the four studies

Study	I	II	III	IV
Design	RCT*	Cross-sectional	RCT*	Qualitative
Participants	Patients ≥ 75 years (N=369)	Patients ≥ 75 years (N=369)	GPs from 22 PHCCs in Southern Sweden (N=162)	GPs in Southern Sweden (N=17)
Outcomes	Change in proportion of patients taking PIMs Change in proportion of patients using ≥ 10 drugs and ≥ 3 psychotropics Description of identified potential DRPs	Number of FRIDs and ODs in fallers and non-fallers Proportion of the study sample using FRIDs and ODs Distribution of drug types among FRIDs and ODs	Change in rate of prescription of antibiotics against URTIs	Attitudes towards guidelines Impact of using guidelines on the doctor-patient relationship
Data collection method	Data from patients' MDD lists** and EMRs***	Data from patients' MDD lists** and EMRs***	Prescribing data from the Swedish National Pharmacy Register	Focus group interviews
Data analysis	Student's t-test McNemar's test	Student's t-test Fisher's exact test Multiple linear regression	ANOVA Chi-square test Student's t-test	Thematic content analysis

*Randomised controlled trial

** Multi-dose drug dispensing lists

***Electronic medical records

Study settings and participants

Skåne County is situated in the southern part of Sweden and has approximately 1,150,000 inhabitants. Primary care is provided by tax-financed private or public PHCCs. At the time of the first study, there were 90 public and approximately 40 private PHCCs in Skåne.

Papers I and II

The first two studies in this thesis (Papers I and II) were carried out as parts of a bigger project in Skåne with the goal of implementing and assessing multidisciplinary medication reviews in nursing homes and community-dwelling elderly people. For practical reasons, such as to minimise the number of different EMRs, we only invited public PHCCs to participate.

Between September 1 and December 16 2011, 374 patients were included. Patients eligible for inclusion were users of the MDD system aged 75 years or older, living in nursing homes or their own homes with municipally provided home care, in order to ensure that drug lists were accurate and that the patients were compliant to the prescribed treatment. Prior to each patient's annual visit and medication renewal by the GP, nurses collected the patient's written consent for participation in the study and conducted a specific symptom evaluation and health status check including blood pressure, pulse, weight, tendency to fall and confusion, using a validated symptom assessment form (PHASE-20) [86]. The patients were randomised to control and intervention groups. (Figure I) The randomisation was performed using a random number generator and was stratified only for geographic area.

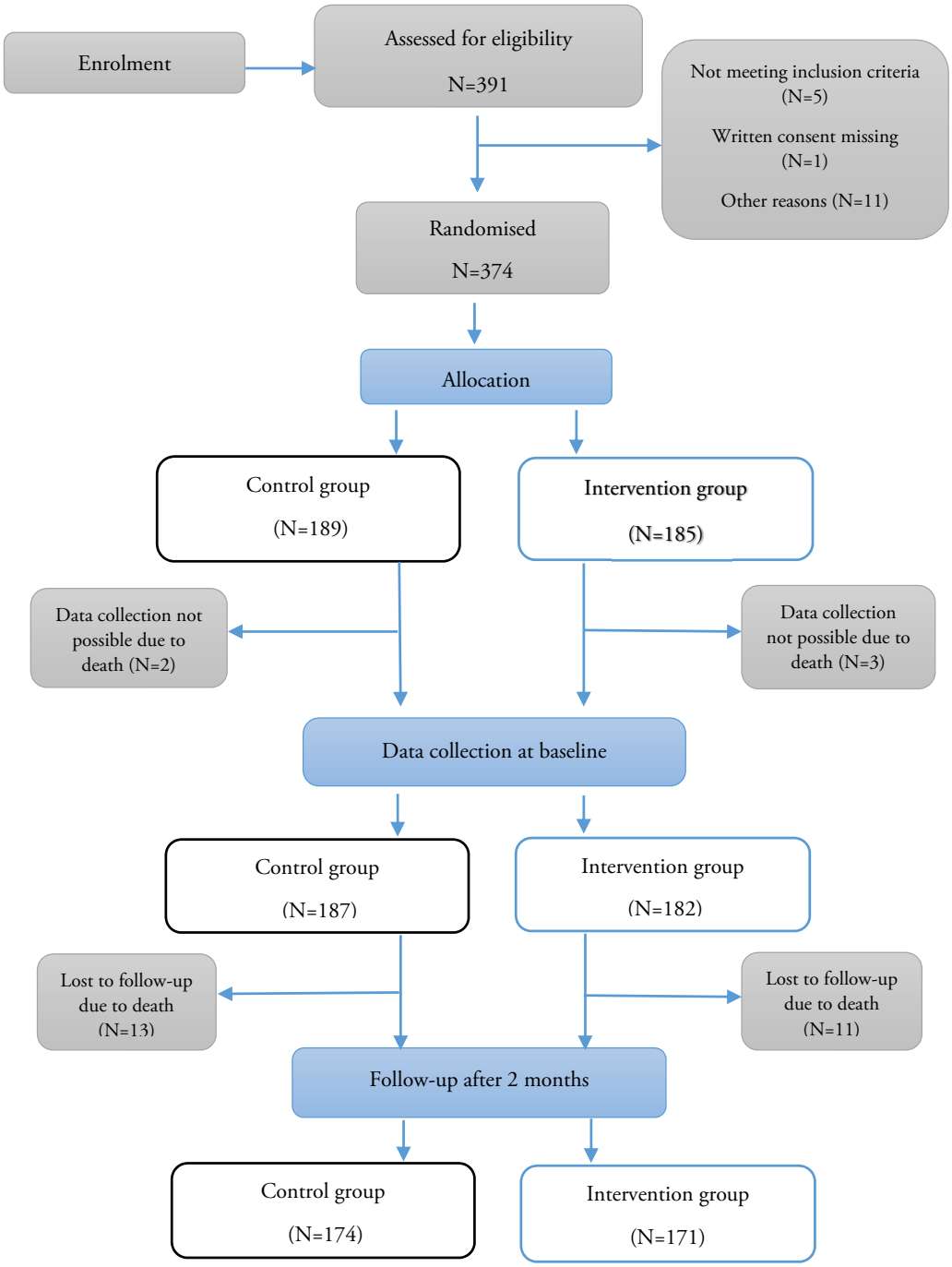

Figure I. Flow chart of randomisation and data collection for patients included in Papers I and II

Paper III

At the time of the study, primary care was divided into four geographical areas, with one manager for each area. For practical reasons, such as to facilitate inclusion, we invited all public PHCCs in Skåne to participate in this study by informing the four area managers by e-mail. Three of the four area managers responded by e-mail and received information about the study, together with PHCC chiefs from each area, at three meetings, one per area. 22 PHCCs agreed to participate and were randomised to one control group and two intervention groups, receiving Persuasive Communication Intervention (PCI) or Graded Task Intervention (GTI) (Figure II). The randomisation was performed at the PHCC level to ensure that the participants in each practice received the same intervention and was stratified by the number of listed inhabitants for each PHCC in order to ensure equivalence of groups. Each PHCC was blindly allocated to one of the three groups consecutively starting with the largest one. The smallest PHCC was allocated to the group with fewest listed inhabitants to ensure equivalence of groups.

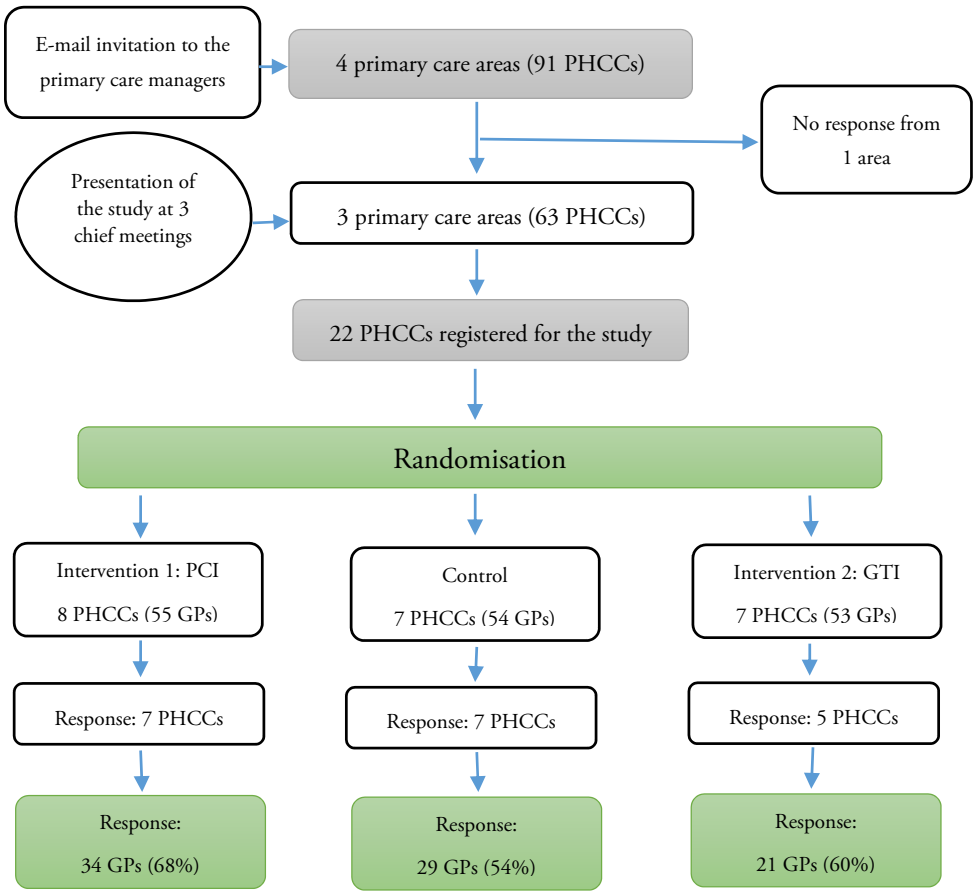

Figure II. Flow chart of the randomisation and data collection in Paper III for the two intervention groups and one control group

Paper IV

The GPs in the focus groups were recruited to the study through an invitation letter. In Skåne, GPs from both public and private health care centres have the possibility to meet regularly in previously established continuing medical education (CME) groups to discuss patient cases or different medical, practical or scientific issues [87]. We invited pre-existing CME groups of GPs working at different public and private PHCCs to participate in the study. The GPs didn't interact with each other on a daily basis but had regular meetings every month. Because of the assumed difficulty in creating new groups, we strategically invited all the pre-established CME groups in Skåne to participate in the study. The groups usually contain 6-12 GPs of different age, gender and experience, from different public and private health care centres. The

groups are used to interacting and debating, and feel comfortable expressing and sharing opinions. The invitation letter, sent by e-mail, contained information about the aim of the study and an informed consent form, and offered the possibility to perform the interviews at the CME group's regular time and place of meeting.

Three CME groups with a total of 17 GPs (5, 5 and 7, respectively) participated in the study. Baseline characteristics of the participants are shown in Table II.

Table II. Characteristics of the participants (Paper IV)

Focus group	Participant	Sex	Age (years)	Median age (years)	Years of primary care practice	Median years of primary care practice	PHCC
	A	F	57		20		Public
	B	F	54		25		Public
1	C	F	50	54	15	20	Public
	D	F	45		16		Public
	E	F	58		30		*Private*
	A	M	53		10		Public
	B	F	61		33		Public
2	C	F	64	53	35	10	Public
	D	F	34		4		Public
	E	F	38		3		Public
	A	F	35		7		Public
	B	F	48		5		Public
	C	M	41		10		Public
3	D	F	48	40	5	5	*Private*
	E	M	35		5		Public
	F	F	40		8		Public
	G	M	33		2		Public

Procedure

Papers I and II

For the first RCT, four pharmacists with previous experience in performing medication reviews using a structured model were selected and assigned to one area each. The pharmacists collected the symptom evaluation formulary from the nurses, randomised eligible patients to control and intervention groups and printed medication lists (MDD cards), with previously received permission to access patients' EMR as well as the

electronic MDD record. The patients in the control group were not further assessed but were treated according to the PHCC's usual care routine, for example through planned or as-needed contact with their GP. For patients in the intervention group the pharmacists performed a systematic medication review without personal patient contact according to a structured model [73] in order to identify potential DRPs. PIMs were identified according to the national guidelines of the NBHW regarding drug therapy in the elderly [38].The DRPs were classified into the seven categories, used by Cipolle, Strand and Morley [88]: need for additional therapy, unnecessary drug therapy, wrong drug, dosage too low, adverse drug reaction, dosage too high and compliance problems.

The pharmacists' recommendations were documented in patients' EMRs. The feedback to the physician varied depending on the PHCC's routines and organisation and consisted of team rounds, written contact, personal contact and telephone contact.

The outcome measures for Paper I were:

- Change in proportion of patients using PIMs
- Change in proportion of patients using ≥ 10 drugs and ≥ 3 psychotropics
- Description of identified potential DRPs.

Paper II describes a cross-sectional retrospective study of the same patient sample included in Paper I. Data collection for Paper II was conducted between September 1 2012 and February 15 2013. Baseline drug lists were screened for FRIDs and ODs according to the NBHW list (Table III).

Data on FRIDs and ODs were collected and analysed separately due to the distinction made by the NBHW and the fact that drugs from certain ATC groups (e.g. antipsychotics) appear on both the FRID and OD lists. Data for reported falls and severe falls were collected. Reported falls were defined as falls during the past three months reported by the nurse in the patient's PHASE-20 checklist evaluation. Severe falls were defined as falls during the previous year leading to emergency visits at hospitals or hospital admission as a consequence of syncope, contusion or bone fracture year as documented in the patient's EMR. Data on hospital admissions and hospital emergency visits relating to falls during the year prior to inclusion in the study were collected from the patient's hospital EMRs.

The outcome measures for Paper II were:

- Number of FRIDs and ODs in fallers and non-fallers
- Proportion of the study sample using FRIDs and ODs
- Distribution of drug types among FRIDs and ODs

Table III. FRIDs and ODs according to the lists from the Swedish NBHW

ATC* code	Drugs/group of drugs
Increase the fall risk (FRIDs)	
NO2A	Opioids
N05A (NO5AN excluded)	Antipsychotics (lithium excluded)
N05B	Anxiolytics
N05C	Hypnotics and sedatives
N06A	Antidepressants
May cause or worsen orthostatism (ODs)	
C01D	Vasodilators used in cardiac diseases
C02	Antihypertensives
C03	Diuretics
C07	Beta blocking agents
C08	Calcium channel blockers
C09	Renin-angiotensin system inhibitors
G04CA	Alpha-adrenoreceptor antagonists
N04B	Dopaminergic agents
N05A (NO5AN excluded)	Antipsychotics (lithium excluded)
N06A	Antidepressants

*Anatomical Therapeutic Chemical classification system

Paper III

Questionnaire-based behaviour change interventions that had been validated in a previous experimental study were translated into Swedish, back-translated into English for verification and sent to the GPs by mail. All groups received a questionnaire assessing attitudes, beliefs and subjective norms (Appendix A). The first intervention group received a graded task intervention (GTI) (Appendix B) with a first part including a set of questions and a second part asking the GP to describe a difficult situation of managing a patient with a URTI without prescribing antibiotics and how to handle it. GTI used graded task behaviour change techniques: rehearsal and action planning (SCT) and addressed the GP's belief in his/her ability to manage URTIs without prescribing an antibiotic. The second intervention group received a persuasive communication intervention (PCI) (Appendix C) with the aim of influencing the GP's belief about the positive consequences of managing URTIs without prescribing an antibiotic (OLT and SCT).

The survey ran from 1 December 2011 to 15 February 2012. Questionnaire were posted to GPs with a letter of invitation. Anonymous completed questionnaires were collected by the PHCCs' heads and were returned by post to the head researcher in order to maintain the group randomisation. Two reminders were sent by e-mail during the data collection.

URTIs were defined in the questionnaires as common cold, pharyngitis, tonsillitis, acute otitis media, sinusitis and laryngitis.

The outcome measures for Paper III were:

- Change in prescription rate (number of antibiotic prescriptions for URTIs per 1000 inhabitants listed at the PHCC)
- Description of measures predictive of prescribing behaviour (e.g. behavioural intention, self-efficacy, subjective norm)

The following antibiotics were included: tetracycline (J01A), beta-lactamase sensitive penicillins (J01CE), combinations of penicillins (J01CR), macrolides (J01FA), lincosamides (J01FF), broad-spectrum penicillins other than mecillinam (J01CA) and first- to fourth-generation cephalosporins (J01DB-DE).

Paper IV

Three focus group interviews were held. The first interview was performed by a moderator with prior experience of leading focus group interviews. The author of this thesis took notes during the interviews in order to recall impressions of non-verbal

communication between the participants during the analysis. The researchers switched roles in the second and third interviews. All three interviews were performed using a semi-structured interview guide (Appendix D).

Interview questions were created with an emphasis on the following themes:

- Attitudes towards guidelines
- The impact of using guidelines on the doctor-patient relationship

Quantitative analysis

Data in Papers I-III were analysed using a significance level of 0.05 with IBM SPSS version 20.0 UK. Drugs were classified according to the ATC classification system [89].

In Paper I, the focus was on medication changes in the medication lists, with data collection before and after the medication reviews. Data were analysed using a single imputation method according to the "intention-to-treat" principle with the last observation carried forward [90]. Statistical tests were performed for both intention to treat and per-protocol analyses using Student's t-test and McNemar's test.

In Paper II, data were collected from patients' MDD lists and EMRs and analysed using Student's t-test and Fischer's exact test for two-group comparisons, and by multiple linear regression. In the two regression analyses FRIDs and ODs were used as the respective dependent variables while age, sex, place of living, number of drugs and severe falls were entered as independent variables. The analyses were performed using a backward method, with the computer eliminating the least significant independent variables stepwise until significant variables remained as predictors.

In Paper III, prescribing data on dispensed drugs were collected from the Swedish National Pharmacy Register. Antibiotic prescription data for the three groups for January to June 2011 were compared with data for January to June 2012 (after the intervention) in order to eliminate confounding due to seasonal variation in URTI incidence. Data were analysed by analysis of variance (ANOVA) with Bonferroni post-hoc test, chi-square test and Student's t-test. Outcome variables derived from the theoretical construct (behavioural intention, attitudes, subjective norms, perceived behavioural control, risk perception, self-efficacy, anticipated consequences, evidence of habits and prior planning) were measured using sum scores and z-scores. Different items in the questionnaire measured these variables on a 7-point Likert scale from Strongly Disagree to Strongly Agree or from 0 to 10 (Table IV), according to the experimental model [85]. A composite variable was created as a behavioural intention

score from items with different scales by converting the item scores to z-scores and summing them.

Table IV. Examples of the theoretical constructs used as predictive measures in the questionnaires

Variable	Example Item(s)
Theory of planned behaviour (TPB)	
Behavioural intention	I intend to manage patients with URTIs without prescribing an antibiotic. Given 10 patients presenting for the first time with a URTI, how many patients would you intend to manage without prescribing an antibiotic?
Attitudes	In general, the benefits of managing patients with URTIs without prescribing antibiotics outweigh the harm. In general, managing a patient with a URTI without prescribing an antibiotic would reassure them. Reassuring the patient is unimportant/important.
Subjective norm	I feel under pressure, for example from published literature, to manage patients with a URTI without prescribing an antibiotic. How motivated are you to do what the published literature states that you should (from very to not at all)?
Perceived behavioural control	Whether I manage patients with a URTI without prescribing an antibiotic is entirely up to me. I find it difficult to manage patients presenting with a URTI without prescribing an antibiotic if the patient expects me to prescribe an antibiotic.
Social cognitive theory (SCT)	
Risk Perception	It is highly likely that patients with a URTI will be worse off if I manage them without prescribing an antibiotic.
Self-efficacy	Without an antibiotic: How confident are you in your ability to manage patients with URTIs who have tried to self-medicate?
Operant learning theory (OLT)	
Anticipated consequences	If I routinely manage patients with URTIs without prescribing an antibiotic then, on balance, my life as a GP will be easier in the long run.
Evidence of habit	When I see patients with URTIs, I automatically consider managing them without prescribing an antibiotic.

Qualitative analysis

In paper IV, the interviews were studied using thematic content analysis [91, 92]. The interviews were audio-recorded and transcribed verbatim. After the transcribed interviews and additional notes had been read, the text was divided into meaning units and condensed. An example of the text condensation into meaning units is shown in Table V. Units with similar content were compiled into different sub-categories, categories and themes, and the results were discussed until a consensus was reached. The method is conventional inductive content analysis with codes and categories derived from data during analysis [93].

Table V. Example of text condensation and coding

Theme	GP-related influencing factors		
Category	Beliefs about adherence to guidelines		
Final coding	Reported adherence behaviour in everyday practice		
Initial coding	Lower adherence if more frequent changes to guidelines	High adherence if guidelines similar to own experience	High adherence when feeling unsure
Condensed meaning unit	It was decided that the insulin kind would change to another, cheaper one, and soon afterwards it would change back again, but I have learned from previous experience and have not changed anything yet.	In the case of migraine drugs, when I did not have enough experience to say that the more expensive drugs were better, I supported my argument with the guidelines.	When I feel unsure I stick to the guidelines.
Meaning unit	"… we were supposed to change from the usual insulin that we had used for many years to a cheaper one, and it is a lot of work if you are going to change it for all patients. And then after a couple of months they lowered the price of the first one, so there was no difference any more. But I have some previous experience and have not changed anything yet, but will wait and see what happens."	"… and an area where I've benefited from them (the guidelines) … in agreement with the patient or against the patient's will … is when they want migraine drugs, triptans, more expensive ones … and when I didn't have enough experience to say that that the more expensive ones were better, I supported my argument with the guidelines…"	"You feel sometimes that you should be more informed, but if I feel unsure I stick to the guidelines."

Ethical considerations

All four studies conform to the principles outlined in the Declaration of Helsinki. The studies in Papers I and II were approved by the Regional Ethical Review Board in Lund, (case no. 2011/245). The same board decided that studies in Papers III and IV did not need ethical approval (case nos. 2011/431 and 2013/392, respectively).

The patients in Paper I and II provided written consent (directly or through relatives in cases of severe cognitive impairment). The randomization was performed blinded, prior to the printing of MDD lists ensuring that the patients in the control group were not subject to an intervention by the pharmacist. However, the pharmacists printed all the MDD lists and might have observed potentially inappropriate medication in control patients after the randomization. No difference in mortality between the groups was seen at follow-up after 2 months, suggesting no negative consequences of this procedure in the patients in the different groups. The RCT studied outcome variables previously found to be associated with higher morbidity and mortality in the elderly. Differences in quality of life between the groups were not measured.

The GPs in Paper III received written information about the study and participated by returning the questionnaires anonymously. The questionnaires were sent to the GPs through the heads of their PHCCs. This way of invitation was chosen in order to maintain the initial group randomisation. Due to this design, GPs might have felt less or more prone to respond despite the questionnaire being anonymous. Although we studied the effect of the educational intervention on the prescribing rate, no particular ethical issues are believed to have affected the patients.

The GPs in Paper IV received written and oral information about the purpose of the study and provided oral consent by participating in the focus groups discussions. Data were collected using a digital sound recorder and anonymised prior to the transcription. The transcripts were analysed anonymously. The role of the author of this thesis as a researcher was stressed during the interviews in order to address potential response bias from the interviewed GPs due to her membership in the local DTC.

Results

Medication reviews and PIMs

A total of 391 patients were assessed, and 369 were included in the intention-to-treat analysis. A flow chart of the inclusion and assessment steps is presented in Figure I. Baseline characteristics are presented in Table VI.

Table VI. Baseline characteristics of the studied population (Paper I)

Characteristic	Control group	Intervention group	p-value
Female, n (%)	142 (75.9)	138 (75.8)	0.98[a]
Age (years), mean (SD)	87.7 (5.5)	87.0 (5.8)	0.66[b]
Type of residence, n (%)			
Community	47 (25.1)	43 (23.6)	0.74[a]
Nursing home	140 (74.9)	139 (76.4)	
No. of drugs, mean (SD)	12.1 (4.7)	11.4 (4.2)	0.90[b]
No. of continuous-use drugs, mean (SD)	9.7 (3.9)	9.3 (3.7)	0.53[b]
No. of as-needed drugs, mean (SD)	2.2 (1.8)	2.1 (1.7)	0.39[b]
No. of psychotropics[1], mean (SD)	1.93 (1.37)	1.71 (1.37)	0.75[b]

SD = standard deviation

[a] Chi-square test

[b] Student's t-test

[1]N05A, N05B, N05C and N06A according to the ATC System

In the intervention group the pharmacist had a face-to-face encounter with the physician during team sessions in 20% of cases. Remote medication reviews were performed in the other 80% of cases. There were no significant differences in actions taken by the GPs between the group receiving team-based medication reviews and the group receiving remote medication reviews. The control and intervention groups were similar. A majority of patients were females and lived in nursing homes.

The proportion of patients with at least one PIM decreased between randomisation and follow-up in the intervention group (by 18 %; $p<0.01$), but not in the control group ($p=1.00$) (Table VII). Similarly, the number of patients taking 10 or more drugs decreased in the intervention group but not in the control group (Table VII).

Table VII. Changes in number of patients with PIMs, patients with ≥ 10 drugs and patients with ≥ 3 psychotropic drugs

Variable	Group	Base-line	Follow-up	p-value*
No. (%) of patients with ≥ 10 drugs	Control group	123 (65.7)	120 (64.1)	0.55
	Intervention group	120 (65.9)	107 (58.7)	<0.01
No. (%) of patients with ≥ 3 psychotropics	Control group	60 (32.0)	64 (34.2)	0.22
	Intervention group	47 (25.8)	49 (26.9)	0.75
No (%) of patients with at least one PIM	Control group	58 (31.1)	57 (30.5)	1.00
	Intervention group	60 (33.0)	49 (27.0)	<0.01

* McNemar's test

The total number of drugs and number of continuous-use drugs decreased significantly between baseline and follow-up in the intervention group (Table VIII) but not in the control group. No significant decreases after the medication reviews were noted for the medication subgroups (antipsychotics, benzodiazepines, propiomazine and tramadol). Similar results were found in both intention-to-treat and per-protocol analyses.

Table VIII. Changes in medication in the control and intervention groups at follow up

Variable	Group	Number of drugs, mean (range) Baseline	Number of drugs, mean (range) Follow-up	p-value*
No. of drugs	Control	12.1 (3-28)	12.1 (3-29)	0.78
	Intervention	11.4 (2-21)	10.8 (0-22)	<0.01
No. of continuous-use drugs	Control	9.7 (1-27)	9.6 (1-25)	0.33
	Intervention	9. 3 (1-20)	8.8 (1-18)	<0.01
No. of as-needed drugs	Control	2.2 (0-12)	2.5 (0-12)	0.06
	Intervention	2.1 (0-10)	2.0 (0-8)	0.17
No. of psychotropics[1]	Control	1.93 (0-6)	1.96 (0-6)	0.22
	Intervention	1.71 (0-6)	1.69 (0-6)	0.08

*Student's t-test

[1]N05A, N05B, N05C and N06A according to the ATC System

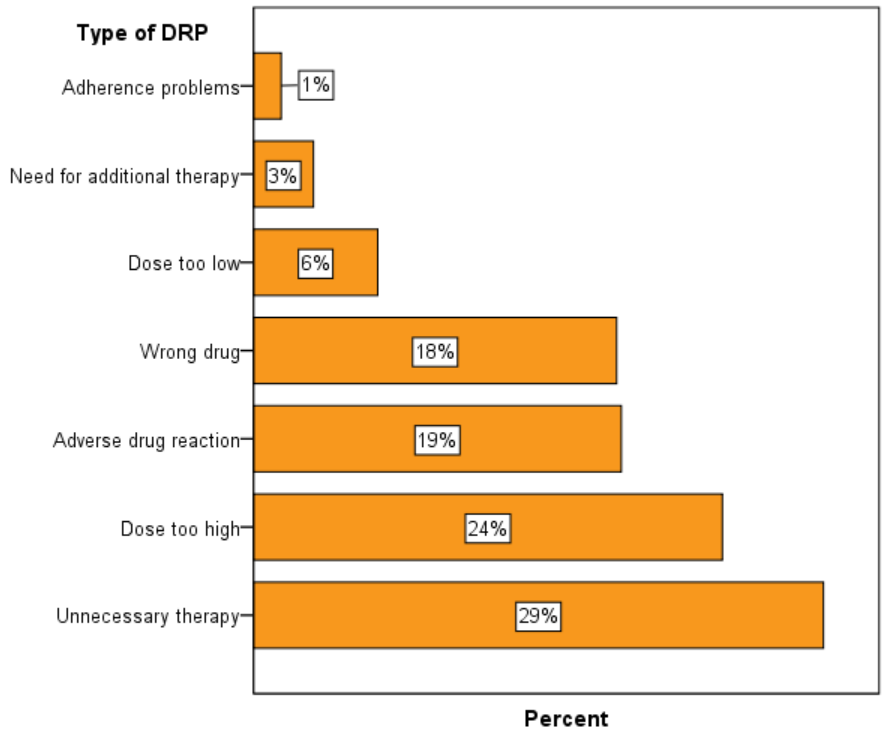

Figure III. Distribution of DRPs

DRPs were identified in 93% of the 182 patients in the intervention group with a mean of 2.5 DRPs per patient. There was no difference between in number of DRPs between community-dwelling patients and nursing home patients (p-value 0.767). The distribution of DRPs is shown in Figure III.

Drugs acting on the nervous system (26%), cardiovascular system (25%) and blood and blood-forming organs (15%) were the most common ATC classes involved in DRPs.

The two most common intervention recommendations the pharmacist presented to the physician were to withdraw drug therapy (30%) and to reduce drug dose (28%) (Figure IV).

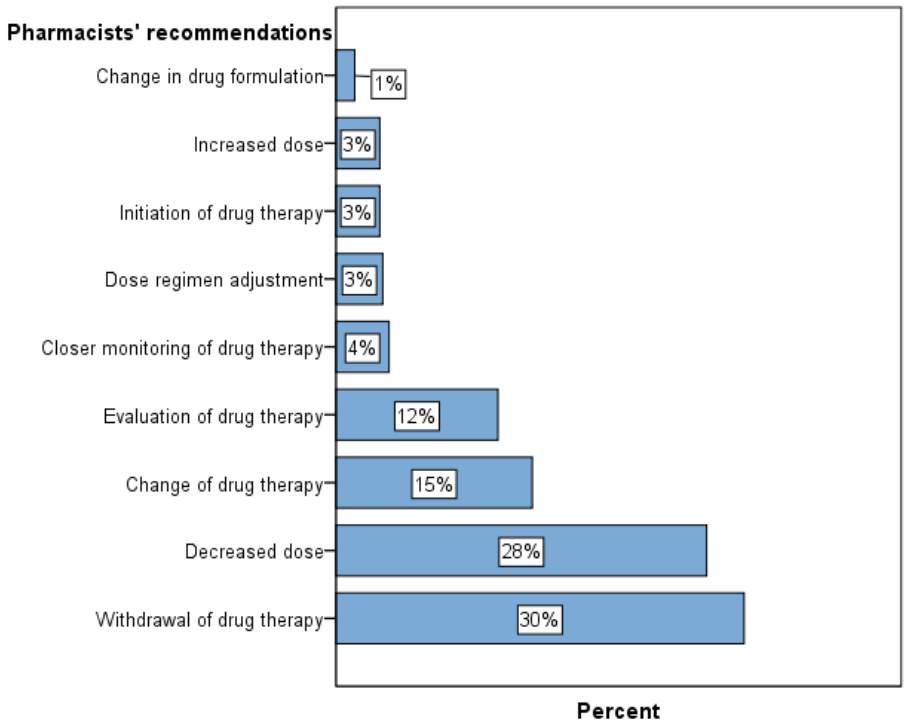

Figure IV. Distribution of pharmacists' recommendations

Fifty-six percent (241) of the presented DRPs resulted in actions being taken by the physician and their frequencies is shown in Table IX. There were no significant differences in actions taken on PIMs between the community-dwelling patients and the nursing home patients.

Table IX. Frequency of changes in PIMs in the control group versus the intervention group

Action taken by the physician regarding drug therapy	No. of cases (%)	No. of cases (%)	p-value*
	Control group	Intervention group	
No change	56 (76.8)	45 (64.8)	0.35
PIM out	8 (11.5)	13 (17.5)	0.24
New PIM in	7 (10.1)	2 (2.7)	0.09
Lowered dose	0 (0.0)	10 (13.5)	<0.01
Increased dose	1 (1.4)	1 (1.3)	0.99

*McNemar's test

Fall risk-increasing drugs and falls

There were no significant differences between total number of drugs, number of FRIDs, number of ODs or blood pressure between community-dwelling and nursing home patients. (Table X).

The patients were prescribed a mean of 2.2 (SD 1.5) FRIDs according to the FRID list of the NBHW and 2.0 (SD 1.6) drugs from the OD list of the NBHW. Only 13% of the study sample had no prescribed drugs from the FRID or OD lists. A higher proportion of men reported falls during the past three months, but more women experienced severe falls (Table X). Seventeen percent of the patients had had at least one severe fall during the previous year. Severe falls were more common in nursing home patients compared to community-dwelling patients.

Two multiple linear analyses with numbers of FRIDs and ODs as the dependent variables showed positive associations between number of FRIDs and total number of prescribed drugs ($p<0.01$) and occurrence of severe falls ($p<0.01$). Being female was associated with a higher number of FRIDs ($p=0.03$). Associations were found between number of ODs and both total number of prescribed drugs ($p<0.01$) and community dwelling ($p=0.02$). No association was found between number of ODs and occurrence of severe falls.

Table X. Comparisons between fallers and non-fallers regarding age, sex, type of residence, number of drugs, FRIDs and ODs

Outcome variable	Falls during the last 3 months before the symptom evaluation			Falls leading to emergency visits or hospital admissions during the last 12 months		
	Falls	No falls	p-value	Falls	No falls	p-value
Sex, N (%)						
Male	31 (44)	39 (56)	<0.01*	4 (4)	85 (96)	<0.01*
Female	50 (24)	155 (76)		58 (21)	222 (79)	
Age (years), mean (SD)	87.2 (5.7)	87.2 (5.4)	0.97**	87.8 (5.6)	87.3 (5.7)	0.53**
Type of residence, N (%)						
Nursing home	53 (26)	149 (74)	0.07*	56 (20)	223 (80)	<0.01*
Community	28 (38)	45 (62)		6 (7)	84 (93)	
No. of drugs, mean (SD)						
Total	11.5 (3.8)	11.8 (4.8)	0.58**	12.6 (4.4)	11.6(4.5)	0.12**
Continuous-use	9.5 (3.6)	9.2 (4.0)	0.64**	9.8 (3.5)	9.4 (3.9)	0.39**
As-needed	2.0 (1.4)	2.5 (2.0)	0.01**	2.7 (2.1)	2.2 (1.6)	0.08**
No. of FRIDs, mean (SD)						
Total	2.4 (1.5)	2.0 (1.4)	0.06**	2.7 (0.7)	2.0 (0.6)	<0.01**
Continuous-use	2.0 (1.4)	1.6 (1.2)	0.02**	2.1 (1.4)	1.6 (1.3)	<0.01**
As-needed	0.4 (0.6)	0.5 (0.7)	0.41**	0.5 (0.7)	0.4 (0.6)	0.13**
No. of ODs, mean (SD)						
Total	1.8 (1.4)	2.0 (1.6)	0.26**	1.7 (1.5)	2.0 (1.5)	0.15**
Continuous-use	1.6 (1.3)	1.7 (1.4)	0.38**	1.4 (1.2)	1.7 (1.3)	0.05**
As-needed	0.2 (0.4)	0.2 (0.4)	0.28**	0.2 (0.4)	0.2 (0.4)	0.36**

*Fishers exact test

**Student's t-test

The ten most frequently prescribed drugs among the FRIDs and ODs in the NBHW lists had the ATC codes N (Nervous System) (54.1%) or C (Cardiovascular System) (45.6%). The frequency of the ten most prescribed FRIDs and ODs is shown in Figure V.

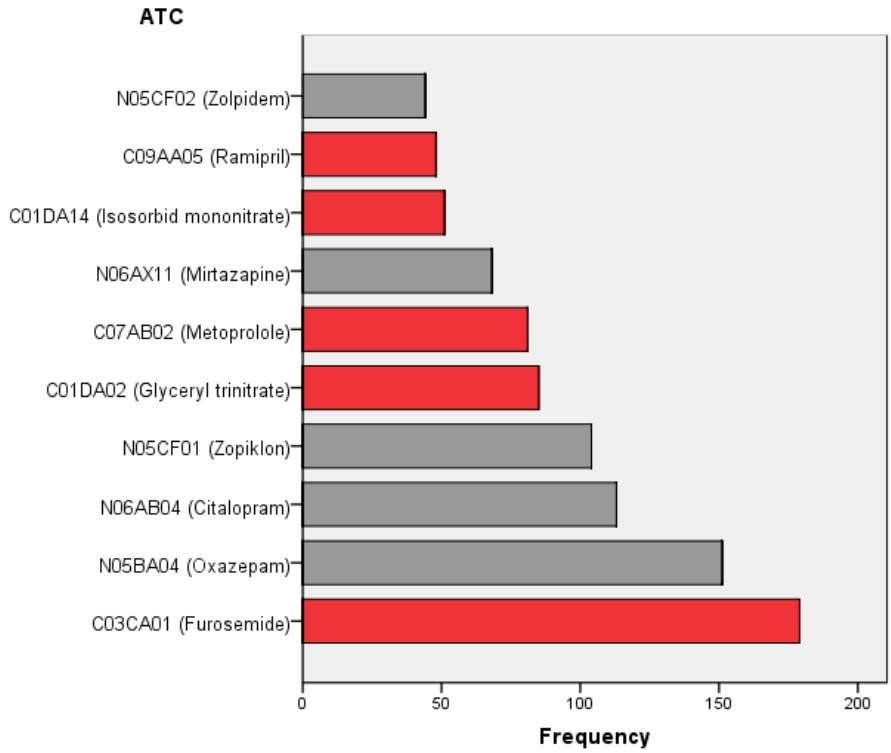

Figure V. Frequency of the ten most prescribed FRIDs and ODs

Theory-based interventions and prescribing of antibiotics in primary care

Of the 63 PHCCs that received information about the study, 22 (35%) agreed to participate and were included and randomised (Figure II). All practices were multi-practitioner surgeries. 19 PHCCs (86%) responded (Figure II) with a total 60365 (PCI group), 51077 (GTI group) and 69887 (control group) inhabitants respectively. Completed questionnaires were returned by 84 (60%) of the 139 GPs working at these PHCCs. The response rate was 68% in the PCI group, 60% in the GTI group and 54% in the control group.

The PCI intervention was completed by 71% of the GPs in the PCI group. The first part of the GTI intervention was completed by 100% of the respondents; however, only 33% completed the second part.

The randomised groups did not differ significantly in terms of measures derived from the theoretical behaviour construct or demographic measures (Table XI) measured at baseline. There were no significant differences in the rates of prescription of antibiotics in patients of all ages or in patients aged 0-6 years before and after the intervention in any of the three studied groups (Student's t-test). However, the rate of prescription tended to be higher in the control group and the GTI group post-intervention, and unchanged or lower in the PCI intervention group (Figure VI).

ANOVA showed no effect of the interventions on prescription rates in patients of all ages. However, in patients aged 0-6 years there was a significant lower prescription rate in the PCI group ($p=0.037$) compared to the control group after the intervention.

Table XI. Baseline characteristics of the participants (Paper III)

Outcome measure	Control group	GTI	PCI	p-value
Demographic measure				
Age (years), %				0.31*
<35	34.5	33.3	20.6	
36-45	27.6	23.8	23.5	
46-55	17.2	9.5	20.6	
>56	20.7	33.3	35.3	
Female (%)	72	47	55	0.19**
No of physicians at the PHCC, mean (range; SD)	8 (4-11; 2.3)	7 (4-10; 2.1)	7 (1-12; 2.5)	0.27**
No of GPs, mean (range; SD)	5 (1-8; 2.6)	5 (2-8; 2.1)	5 (3-7; 1.4)	0.96**
Years of experience, %				0.31**
<10	41.4	52.4	35.3	
10-20	34.5	23.8	23.5	
>20	24.1	23.8	41.2	
Measures derived from the theoretical constructs, mean (range; SD)				
Behavioural intention	0.15 (-4.2-1.1; 1.5)	0.1 (-5.6-19.4; 4.8)	-0.18 (-4.9-1.1; 1.5)	0.88**
Attitudes, Direct	10 (3-16; 2.5)	10.5 (9-14; 1.7)	10.1 (7-16; 2.4)	0.73**
Attitudes, Indirect	188 (109-251; 34)	189 (90-281; 45)	184 (103-261; 43.6)	0.89**
Subjective norms	87.7 (18-180; 51.1)	69.2 (12-169; 44.7)	87.1 (22-158; 38.6)	0.28**
Perceived behavioural control-direct	16.7 (7-27; 5.6)	16.1 (6-26; 6)	16.4 (7-26; 4.5)	0.94**
Perceived behavioural control-indirect	15.2 (4-21; 4.2)	15.9 (1-20; 4)	16.5 (9-22; 3.8)	0.44**
Risk perception	3.3 (2-14; 2.6)	3.5 (2-10; 2.2)	3.8 (2-14; 2.6)	0.68**
Self-efficacy	31.1 (16-39; 5.6)	31.5 (23-41; 4.9)	30.8 (23-41; 4.6)	0.87**
Anticipated consequences	7.7 (2-10; 1.6)	6.9 (2-9; 1.9)	7.9 (4-14; 1.8)	0.11**
Evidence of habit	10.6 (2-14; 3.2)	9.5 (2-14; 3.1)	10.9 (7-14; 2.2)	0.21**
Prior planning	6.1 (3-7; 1.2)	5.7 (1-7; 1.5)	6 (2-7; 1.1)	0.64**

*Chi-square test

**ANOVA

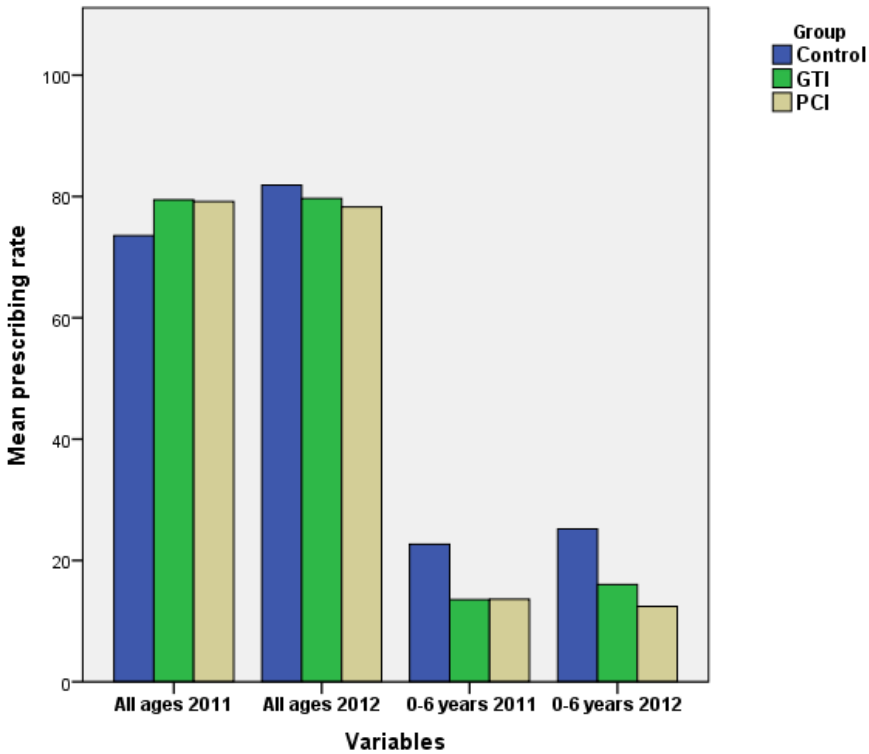

Figure VI. Changes in antibiotic prescribing rate (number of prescriptions per 1000 inhabitants and 6 months prescribed by the PHCCs) in the groups

GPs' attitudes towards treatment guidelines

We found two main themes describing GPs' attitudes towards local treatment guidelines: **GP-related influencing factors** and **External influencing factors**. The attitudes were grouped into seven main categories (Table XII).

Trust in evidence-based guidelines was described as a key motivating factor for adherence. Patient safety was reported to be more important than adherence to guidelines or maintaining a good patient-doctor relationship. GPs expressed concerns about difficulties with adherence to guidelines when managing drugs from other prescribers. Some GPs described strong beliefs that guidelines were directed towards primary care and were not compulsory for hospital doctors or private secondary care specialists. GPs described both positive and negative attitudes to cost containment, which was perceived both as a motivating factor and a barrier for adherence to

guidelines. They expressed a feeling of economic responsibility for both patients and society, revealing a dilemma faced in the prescribing situation.

Table XII. Categories and themes (Paper IV)

Categories	Themes
Expectations and perceptions about existing local guidelines	GP-related influencing factors
Knowledge about evidence-based prescribing	
Trust in development of guidelines	
Beliefs about adherence to guidelines	
Patient-related aspects	External influencing factors
Drug industry-related aspects	
Health economic aspects	

The first focus group had longer experience in primary care practice (Table II). This group described a historical change in GPs' attitudes towards the guideline implementation process. The second group included physicians with a great range of experience and the debate within the group was dominated by the more experienced GPs; the younger GPs hade a more passive and confirmatory role. The third group, which included younger physicians with shorter experience, expressed a greater concordance of opinions regarding the acceptance of guidelines as a prescribing tool. The group explained it as being the result of early training in following evidence-based practice.

All the GPs welcomed the detailed background information accompanying the guidelines. They reported that they felt more prone to adhere to guidelines after reading the evidence-based background information behind the decision process presented by the DTC about the recommended drugs. The frequency of guideline updates was discussed and some GPs requested more frequent updates than the current annual ones, with faster introduction of new drugs. However, a majority of GPs reported lower adherence if recommendations changed often.

A recurrent subject, spontaneously discussed by all three groups, was the existence of local guidelines, with emphasis on the risk for unequal care in Sweden. Although most GPs agreed about the importance of local experience and increased adherence if guidelines were local, some GPs were concerned about different prescribing habits in different regions and the consequences for patients, such as differences in access to expensive drugs.

Discussion

Summary of main findings

Drug therapy in the elderly

The results in Paper I demonstrate that the assessed care model with medication reviews involving pharmacists in primary health care led to reductions in the number of patients taking PIMs and the total number of drugs these patients were taking, results consistent with findings in other studies of multidisciplinary interventions in nursing home patients [64,68]. Potential DRPs were identified in 93% of the patients in the intervention group, results similar to findings in a previous study [94]. This suggests that the method should be a standard component of geriatric assessment of frail elderly people. A significant proportion (87%) of the study sample used FRIDs and ODs. Numbers of FRIDs were associated with the total number of drugs and with severe falls. This is in agreement with previous studies showing strong evidence of an association between the use of psychoactive drugs and falls in the elderly [45] and between polypharmacy and falls [95-97]. Number of ODs was associated with total number of drugs but not with occurrence of severe falls. The results are similar to those in recent studies showing that treatment with ODs such as alpha-blockers [98] or anti-hypertensive drugs [99] does not increase the fracture rate and may even decrease it.

Similar to another study with a multidisciplinary approach [100], the first study did not show a decrease in the number of patients taking three or more psychotropics two months after the intervention, possibly due to multiple illnesses and the continuing need for psychotropics due to cognitive or other psychiatric impairments in this group of patients. Future research may however be required to confirm a possible association between elderly patients' use of multiple drugs affecting the nervous system and psychiatric morbidity.

Prescribing of antibiotics against URTIs

The theory-based interventions for GPs had limited impact on the rate of antibiotics prescribing against URTIs for the patients listed at the included PHCCs. The antibiotic prescription rate tended to be lower in the PCI intervention group compared to the

control group when patients of all ages were analysed, and significantly lower compared to the control group in individuals aged 0-6 years. This result might be due to a higher incidence of viral URTIs in this age group and, thus, a higher proportion of unnecessary antibiotic prescriptions. No previous studies of these intervention methods exist for comparison. However, in the experimental study in which the instruments were developed, the GPs receiving the PCI intervention responded with significantly stronger intentions not to prescribe antibiotics for URTIs and the rates of antibiotic prescribing in patient scenarios were lower compared to a control group [85].

GPs' attitudes towards local treatment guidelines

The core motivators for adherence to guidelines were found to be the time-saving aspect, trust in evidence-based market-neutral guidelines, patient safety and the feeling of economic responsibility for both patients and society. Main barriers to adherence were cost containment as a decision factor in developing guidelines, multiple prescribers with unclear responsibility for patients' medication lists and drug industry information addressed directly to the public. Patient safety was ranked as more important than maintaining a good patient-doctor relationship, e.g. prescription of antibiotics. An important factor described was the patient-doctor encounter, with an emphasis on informing the patient. This is consistent with findings in a Swedish study showing that mutual trust and continuity in the patient-doctor encounter increased adherence to guidelines, such as recommendations for prudent antibiotic prescribing [101]. The GPs all experienced a lack of time to self-inform. Time was previously found to be a crucial factor in GPs' handling of knowledge and prescribing, suggesting that simple, easily accessed guidelines facilitate the prescribing situation and are therefore appreciated [50]. The GPs in this study stated unanimously that they perceive guidelines as a form of support, that they do not feel bound by them and feel safe when using them. They also stated that they feel free to deliberately deviate from guidelines if necessary. This attitude might be related to the holistic view of individuals in primary care, an important principle of patient assessment given the diversity of patients.

The GPs described a paradigm shift in the attitudes towards drug information sources during recent decades, with an increasingly positive attitude towards academic detailing provided by the local DTC instead of drug industry-supplied information, results consistent with findings from a recent Swedish study [102].

Methodological considerations

Strengths

This thesis comprises two randomised controlled interventions, one cross-sectional study and a qualitative paper examining aspects of drug prescribing in primary care from different angles and using various designs. The studied samples were from several different geographic areas in Skåne, Sweden, which increases the generalizability of the results for this region.

The randomisation process used in the design of the two intervention studies was a strength. The blinded randomisation of the elderly patients was performed by the pharmacists before they accessed patients' EMRs and MDD lists, which reduced the risk of selection bias. Moreover, the randomisation was only stratified for geographic area. The randomisation in the theory-based intervention was performed at the PHCC level to ensure that the participants within each PHCC received the same intervention and was stratified by number of listed inhabitants for each PHCC to ensure equivalence of groups in terms of size. The PHCCs were blindly allocated to one of the three groups consecutively starting with the largest one in terms of listed inhabitants.

The MDD cards and EMRs were the central instruments for assessing drug therapy in the studied elderly population, ensuring high validity of the examined outcome variables. The drug lists were accurate and compliance with prescribed drug therapy was high due to use of the MDD system, which gave current information to the pharmacist and responsible physician and thereby increased the ability of pharmacists to make an accurate decision in recommending changes in medication.

Nurses who used the symptom checklist (PHASE-20) had direct contact with the patients, which ensured more accurate description of their symptoms. Almost a third of the patients who complained of moderate to severe dizziness or unsteadiness reported falling in the three months prior to the data collection, compared to less than 10% of those who had no complaints (Paper II). This suggests that the PHASE-20 symptom checklist might be a useful tool to predict falls in elderly patients. The reliability of the data in Papers I and II was high since it was collected in a standardized manner by a single individual.

Physicians' decision making in medication changes was not influenced by patients' type of residence, implying that the present model of medication review could be applied to both community-dwelling and nursing home patients with similar results. The results in Paper I also show that the physicians responded in similar ways after the remote medication reviews and the team-based medication reviews. Inter-professional

medication reviews with pharmacists are often studied when performed in face-to face team discussions [63, 103]. Despite this, remote medication reviews can have benefits such as ability to cover large geographic patient distributions and have been performed in southern Sweden as an alternative to team-based medication reviews with positive results for quality and quantity of medication and drug costs [104]. The results in the first study suggest that both team-based and remote medication reviews should be taken into account in order to improve physicians' adherence to drug therapy guidelines and inter-professional collaboration. It is however important that the chosen method for medication review fits into the PHCCs every day work routine and contributes to quality improvement of drug therapy rather than to work overload.

The possibility to study the effect on everyday clinical work and to reach a large number of GPs in a large geographical area by means of e-mail questionnaires was a strength of the intervention using theory-based questionnaires. An Irish study showed that postal prescribing feedback had the same effect on antibiotic prescription rate and same cost-effectiveness as academic detailing [105] indicating that this kind of intervention might have a large impact on the prescribing behaviour.

A strength of the qualitative study was the strategic use of pre-existing groups of GPs with differences in experience level and gender. The GPs worked at both private and public health care centres, had had previous contact and were familiar with the debate within the group. Five to seven participants are recommended for focus groups and we included at least five GPs in each group. There was a general concordance of opinions within the groups; however, the interviews created a debate allowing the participants to express a great variety of attitudes towards particular issues, such as the frequency of updates and economic aspects, which increased the credibility of the results. Including GPs with different levels of experience might have increased the transferability of the results of this study.

Previous research has focused on GPs' adherence to nationally developed guidelines [49, 56], using a questionnaire-based approach. We found no previous qualitative research with focus groups studying GPs' attitudes towards adherence to local guidelines, which is a novel aspect of the qualitative study.

The second researcher present during the interviews had a background as a social worker and had no previous contact with the participants or pre-understanding of the studied topic. Due to the researchers' different levels of pre-understanding, they switched roles during the interviews. This might have served as a strength by increasing the dependability of the results.

Limitations

The results in this thesis have to be interpreted with acknowledgement of its limitations. In the first intervention study, the pharmacists did not have any direct contact with the assessed patients. Therefore, the identified DRPs are only potential DRPs. Medication reviews as interventions performed by pharmacists not primarily responsible for the prescribing decision have previously been criticised for not delivering clear positive outcomes or even potentially worsening health outcomes [106]. Outcomes such as quality of life or care need after the medication reviews were not studied in our study and need to be explored further in order to draw firm conclusions about the effect of this kind of intervention. Pharmacist-led medication reviews have recently received attention for not showing effect on outcomes such as mortality and hospital admissions [69, 107]. We did not assess these potential effects of the intervention and this is a major limitation.

Feedback between the pharmacists and the physicians varied from team discussions to remote reviews, which may partly explain the low rate of physician response in performing medication changes. Fifty-six percent of the presented suggestions led to medication changes. This figure is low compared to those for team-based interventions including a responsible physician in secondary care (65-90%) [108, 109]. The medical literature supports the theory that valid clinical care recommendations do not always have the desired impact on physicians' behaviour due to cultural barriers [54, 110] or contextual factors (e.g. staffing and resources) [111]. We estimated that physicians might be most prone to take action within 2 months after the medication review. A longer follow-up period might have risked a higher drop-out rate because of death in this group of frail patients. However, the 2-month follow-up period after the intervention may have been too short to measure withdrawal of psychotropic drugs that need a slow reduction in dosage. Analysis of the actions taken by physicians showed a significantly higher frequency of PIM dosage reduction in the intervention group compared to the control group. Dosage reduction is a preferable and recommended step when withdrawal of psychotropics such as long-acting benzodiazepines or antipsychotics is planned, suggesting that the intervention had a positive impact on GPs' behaviour.

The cross-sectional design with collection of retrospective data about falls is a major limitation in Paper II. Since no risk assessment tool was used, we were unable to stratify patients into those at low and high risk of falls. Another major limitation of Paper I and II is also the lack of geriatric assessment. The identification of cognitive impairment, comorbidity and functional disability would clarify the contribution of other potential factors to increased fall risk or therapy with several psychotropic drugs.

Another limitation is that we assessed data for number of drugs regardless of the defined daily dose of each drug. More detailed drug information might have provided better understanding of whether drug dosage affects fall risk.

All patients were included in the fall evaluation, even though some of them were not ambulatory. This may have caused some bias, since the chair-bound and bed-bound patients were not able to walk freely and were possibly less prone to falling.

In Paper III, only 60% of the GPs returned their questionnaires, a similar response rate to that in an experimental study evaluating the intervention instruments [85]. It is important to mention that the instruments were developed for and tested on British GPs using simulated patient cases. The lack of similar studies on the effect of these interventions on GPs' every-day work makes it difficult to compare the results. Furthermore, we cannot draw conclusions about whether our theory-based interventions are better than non-theory-based interventions.

The first part of the GTI questionnaire was completed by all participants, while the second part, which included written reflection on and description of the strategies, showed a much lower rate of completion (33%). This is not surprising in a busy primary care setting, where time-consuming paperwork is not highly prioritised. It is difficult to know whether the low rate of completion of the questionnaire may explain the lack of effect on the prescription rate.

A major limitation in Paper III is that the outcome measure was rate of prescription of antibiotics used for respiratory tract infections, which included prescriptions for lower respiratory tract infections. This may have affected the results for individuals of all ages, in which there were minor differences after the interventions. A better effect was noted in individuals aged 0-6 years, in whom the majority of respiratory infections are URTIs and in whom we assume antibiotics are overprescribed. Another limitation of the study is that the outcome measure (antibiotic prescribing rate) was for the whole PHCC populations, regardless of the number of GPs who participated in the intervention.

In Paper IV, the interesting aspects of different group dynamics suggest that even if group heterogeneity might facilitate debate, great variation in professional experience is a possible limiting factor, less experienced doctors being more hesitant in expressing their opinions. One of the researchers, the author of this thesis, knew 12 of the 17 participants as colleagues, which could be viewed as both an advantage and an obstacle. Her role as a GP might have encouraged free debate due to an assumed mutual understanding of the professional context the participants worked in. However, no specific reactions on this matter were discussed or observed. The author is also a member of the local DTC and her role as an objective researcher in the study with no links of an economic or employment nature was stressed prior to the interviews. She

also explained her role as a researcher in order to avoid addressing debate questions relating to her pre-understanding of the discussed topic. However, even if the data collection and analysis were performed with objective reflexivity and with awareness of her pre-understanding of the topic being taken into account, her membership in the local DTC might have been a limitation of the study.

Clinical implications and future research

The aim of this thesis was to approach different challenging fields of drug therapy in primary care, assess the effects of several methods to optimize prescribing and investigate GPs' attitudes towards treatment guidelines.

The structure of primary care in Sweden, in which individuals of all ages and with a large variety of diseases are managed, is both satisfactory and difficult for the physicians who choose to specialize in this area. Working as a GP demands good professional and empathic skills and a holistic view of the patients, but also broad knowledge about prescribing drugs. In the prescribing decision, there is a delicate balance between choosing drug therapy according to evidence-based principles and patient safety, individual needs and expectations.

The assessed method with medication reviews addressed the complexity of prescribing in the elderly, where the professionals were able to collaborate and where use of information technology tools improved drug therapy. It is important to mention that the pharmacist's role in reviewing the medication list must be weighed against the clinical reasoning in the final patient assessment, and that the path from medication review to actual implementation of the proposed changes is complex. It starts with a nurse's observation and ends up with the physician's decision. Health outcomes such as quality of life and effect on hospital admissions were not investigated in this study but should be considered in future studies in order to demonstrate the effectiveness of this kind of intervention.

Interventions to optimize drug therapy in elderly patients with an emphasis on preventing falls would need to use a fall risk assessment tool including FRIDs to be able to stratify the patients into those at low and high risk of falling. A prospective study design would also confirm the strength of the association between exposure to FRIDs and subsequent falls. Our results didn't show an association between ODs and severe falls. Assessing this result, we need to consider that the NBHW OD list includes both drugs with effects on the cardiovascular system and drugs with effects on the nervous system. Evidence shows that despite the lowering of blood pressure, treatment with anti-hypertensive drugs such as thiazide-like diuretics and ACE inhibitors may decrease

the fracture rate in patients aged ≥ 80 years [99]. International studies have found associations between falls and other drug groups, such as analgesics and urinary antispasmodics [112] and nonsteroidal anti-inflammatory drugs [113], suggesting that it is very difficult to compare results from different studies using different lists of FRIDs and ODs. However, a systematic meta-analysis of studies including relevant drug classes showed that the use of sedatives, hypnotics, antidepressants and benzodiazepines was significantly associated with falls in elderly individuals [114]. Future interventions should therefore focus on FRIDs that affect the nervous system to optimize drug therapy in elderly patients.

The elderly patients studied in this thesis used the MDD system. Although the system was originally developed to improve patient safety and drug compliance in elderly patients with multiple chronic co-morbidities, no studies provide evidence that it has positive effects compared to traditional prescribing. The MDD system facilitates an overview of patients' medication; however, there are several impediments, such as not encouraging withdrawal of drugs. Recent studies indicate that use of the MDD system may be associated with a higher number of drugs, especially psychotropics [115], and poorer drug treatment. However, Swedish nurses appreciate the system for reducing their responsibility for drug handling and making delegation to nursing stuff possible [116], and consider these advantages more important than the risk for polypharmacy and inappropriate medications. Future studies should assess the potential health economic impact of using the MDD system in the care of frail elderly patients.

Our findings suggest that medication reviews might lead to a decreased number of FRIDs, and therefore a reduced number of falls in the elderly. However, this is only an assumption and future intervention studies using the same medication review model, with a focus on FRIDs in elderly patients, are necessary.

The intervention in Paper III had limited impact on the antibiotic prescription rate. Using British intervention materials meant that we assumed that predictors of clinician behaviour are the same in Sweden as they are in the UK. This might be true, but further research with Swedish GPs is needed to develop interventions targeted to them. Audit-based methods to enhance GP learning and behavioural change in antibiotic prescribing have shown effects [117] reducing antibiotic prescribing rates; however, it is important to mention that the high rate of prescription of antibiotics against URTIs is a complex phenomenon, and interventions to change it should be multifaceted and must address health care providers, patients and governmental decision makers. A meta-ethnographic assessment of different interventions concluded that it is important to allow GPs to reflect on their own prescribing, and to educate GPs about appropriate prescribing and the benefit of implementing it in practice, in order to enhance the acceptability of the interventions [118]. This suggests that the development and

implementation of theory-based instruments might be a good complement to other interventions. Future research should focus on further evaluation of theory-based interventions to reduce the prescription of antibiotics against URTIs.

Paper IV shows that Swedish GPs perceive local guidelines as a form of support, reporting high adherence and mixed feelings towards cost containment. However, international data showed that GPs overestimate their adherence to guidelines, suggesting that self-reported adherence might not correlate well to the actual prescribing behaviour and should not be used as the sole measure of guideline adherence [119]. No prescribing data were collected as we did not aim to assess prescribing behaviour. This means that we cannot draw any conclusions from this study about Swedish GPs' adherence to local guidelines.

The GPs reported difficulties managing patients with multiple prescribers. Unlike in other European countries such as Denmark, the Netherlands and the UK, in Sweden GPs do not have a gate-keeper role and the patients are free to consult other physicians without a referral. Though it is not clear whether the involvement of multiple physicians affects the quality of drug treatment, future research should establish whether individual overall responsibility for a patient's medication list reduces errors and enhances adherence to guidelines.

GPs appreciated the market-neutral academic detailing from the local DTC. This confirms that the national and regional reforms implemented in recent years not only moderated the rate of increase in drug expenditures [120] but also fulfilled the need for non-drug-industry information and education [121, 122]. The GPs also reflected on the existence of local versus national guidelines, discussing the importance of equality of care. However, trust in evidence-based guidelines was perceived to be essential to enhance adherence, suggesting that the present model with local DTCs involving GPs all the way from the emergence to the implementation of guidelines is successful [123]. Future studies should explore the importance of transparency in forming and implementing guidelines, which might further increase adherence to evidence-based treatment guidelines in primary care.

Conclusions

This thesis verifies that inappropriate prescribing is a problem in Swedish elderly patients living in the community and in nursing homes, and that medication reviews involving pharmacists might be a feasible method to optimize drug treatment in elderly patients. The thesis also provides evidence that questionnaire-based behaviour change interventions are an interesting new approach with a limited effect on antibiotic

prescribing in primary care and need to be studied further. The GPs studied in this thesis found trust in evidence-based guidelines and patient safety to be essential in drug prescribing.

There are several challenging aspects of drug therapy in primary care. The broad field of practice, aging population, fast development of new drugs and spread of resistant bacteria are only some of the pieces in this complicated puzzle. GPs need support to avoid medicalization, over- and under-treatment, and to maintain the holistic view of the patient. In order to ensure patient safety, we need to cooperate in a multi-professional way, consider behavioural change interventions, continue to develop transparent evidence-based treatment guidelines and implement different intervention methods to successfully optimize drug therapy in primary care.

Svensk sammanfattning

Bakgrund: Förskrivning av läkemedel är en av de vanligaste medicinska åtgärderna men samtidigt den största orsaken till patientskador och patientsäkerhetsproblem i Sverige. Läkemedelsbehandling av multisjuka äldre och förskrivning av antibiotika mot okomplicerade luftvägsinfektioner är två områden där patientsäkerhetsproblem har uppmärksammats. Behandling med potentiellt olämpliga läkemedel av äldre sköra patienter kan leda till problem som läkemedelsinteraktioner, fall, onödiga sjukhusinläggningar, ökad morbiditet och mortalitet i den här patientpopulationen. Felaktig förskrivning av antibiotika kan resultera i ökad förekomst och spridning av resistenta bakterier. Behandlingsrekommendationer på både nationell och lokal nivå utformas årligen för att optimera läkemedelsförskrivningen på dessa två områden. För att förbättra följsamhet till behandlingsrekommendationer är det viktigt att utforska allmänläkares attityder gentemot dessa rekommendationer.

Syfte: Det övergripande syftet med avhandlingen är att studera olika åtgärder som kan optimera läkemedelsbehandlingen av äldre multisjuka patienter och antibiotikaförskrivningen i primärvården samt att beskriva allmänläkarnas attityder gentemot lokala behandlingsrekommendationer.

Metod: (Studie I) Apotekarledda läkemedelsgenomgångar utfördes för 369 multisjuka patienter, 75 år och äldre, boende i egna hem med hjälp av hemsjukvård eller på särskilda boenden och som använde dosdispenserade läkemedel. Data från läkemedelslistor insamlades före och efter läkemedelsgenomgångar med fokus på potentiellt olämpliga läkemedel.

(Studie II) En retrospektiv analys av läkemedelslistorna utfördes på samma patienter som medverkade i studie I. Fokus i studie II var fallriskhöjande läkemedel, ortostatiska läkemedel och fall.

(Studie III) En randomiserad kontrollerad studie genomfördes med två frågeformulär utformade enligt kognitiva beteendeteorier i syfte att minska antibiotikaförskrivningen mot okomplicerade luftvägsinfektioner i primärvården. (Studie IV) En kvalitativ studie med fokusgrupper genomfördes för att studera allmänläkarnas attityder gentemot evidensbaserade lokala behandlingsrekommendationer.

Resultat: Studie I och II: Apotekarledda läkemedelsgenomgångar ledde till en minskning av antalet patienter som använde potentiellt olämpliga läkemedel, en minskning av totalantalet läkemedel som dessa patienter använde, men inte av antalet patienter som använde fler än tre psykofarmaka. En stor andel (87 %) av dessa patienter använde fallriskhöjande läkemedel och ortostatiska läkemedel. Det fanns samband mellan antalet fallriskhöjande läkemedel, totalantalet läkemedel och allvarliga fall. Det fanns inget samband mellan antalet ortostatiska läkemedel och allvarliga fall.

Studie III: Det blev en signifikant minskning i antalet antibiotikarecept per 1000 listade patienter hos patienter mellan 0-6 år, men ingen skillnad mellan interventionsgruppen och kontrollgruppen hos patienter av alla åldrar.

Studie IV: Tillit till evidensbaserade rekommendationer och patientsäkerhet var nyckelfaktorer i läkemedelsförskrivningen, såsom mötet mellan läkare och patient, med fokus på patientinformationen. Alla intervjuade allmänläkare upplevde brist på tid för att informera sig, svårigheter att hantera patienter med läkemedelslistor från flera förskrivare och läkemedelsreklam riktad direkt till allmänheten. Ekonomiska styrmedel upplevdes vara både en barriär och en motiverande faktor vad gäller följsamhet till behandlingsrekommendationer.

Slutsatser: Avhandlingen visar att tvärprofessionella läkemedelsgenomgångar och interventioner baserade på kognitiva beteendeteorier kan vara fungerande metoder för att optimera kvalitén av läkemedelsbehandlingen i primärvården.

Allmänläkare tycker att tillit till evidensbaserade rekommendationer och patientsäkerhet är nyckelfaktorer som påverkar följsamheten till behandlings-rekommendationer i primärvården.

Acknowledgements

I wish to express my sincere gratitude to all that have inspired and supported me during my journey, especially to:

Patrik Midlöv, main supervisor, for always being responsive to my ideas and thoughts, keeping me on the right track, for giving me support and courage in a enthusiastic, professional and structured way and for being keen to maintain the joy and good spirits during the learning process. Your guidance has been a true inspiration!

Tommy Westerlund, co-supervisor, for offering me other perspectives to look at my field of work and research, having the patience to review my manuscripts and for fast and valuable feed-back. Your joyful support has helped me in times of discouragement!

Ulf Jakobsson, co-supervisor, for support, statistical advice and allowing me to early grow independent during my doctoral studies

Åsa Bondesson, Eva Rekman, Tommy Eriksson, Eva Melander, Sigvard Mölstad and Eva Lena Strandberg, co-authors, for support, cooperation, for inspiring me and offering me access to broad fields of knowledge

Kerstin Troein, for practical and administrative support

Stephen Gilliver, for excellent support and patience in proof-reading the manuscripts and this thesis and for positive and fast feed-back

Annika Dobszai, Karin Fält, Martina Haggren, Krister Karlsson, the pharmacists who performed the medication reviews, for data collection and for performing the interventions in an excellent professional manner

Susan Wong and Martina Magnusson, pharmacy students, for help with data collection in two of the studies

The patients and the GP colleagues who participated in the studies. My inspiration comes from my patients and from the daily encounter with my colleagues and I hope this thesis and future research will make their lives easier.

My colleagues at the Centre for Primary Care Research, CPF, for support, interesting discussions and seminars and for excellent company

Sten Tyberg, my former supervisor during the GP residency, for encouraging me to study, for being an inspiration in mentorship and for teaching me how to set limits

My work colleagues at Laröd Health Care Centre, for your support, encouragement and good company with many laughs every day

My parents, Gina and Ion Milos, for encouraging me to study since young age, for your unconditional love and for always having faith in my judgement

My beloved girls, Maria and Paula, and my great bonus children, Emil and Klara, for your love and support, for sharing laughs and tears, for showing me the meaningful things in life, and for often helping me to break from the constant flow of work.

Andreia Balan, my friend, for support and for giving me perspectives from another academic field

Peter, my beloved husband, for your warm love and for being an inspiration. Maybe I will eventually join you on a Marathon.

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Appendices

Appendices

Appendix A

Behandling med antibiotika av övre luftvägsinfektioner i primärvården

Tack för Ditt deltagande i denna studie som handlar om läkarnas attityder kring förskrivning av antibiotika mot övre luftvägsinfektioner. **ÖLI definieras i följande enkätfrågor som snuva, halsont och hosta.** Det kommer att ta ca 10-15 minuter att besvara enkäten.

De flesta av frågorna besvaras genom att ringa in en siffra; några frågor kräver lite mer tid att besvaras.

Vissa frågor är formulerade på ett liknande sätt men de är olika. Det är viktigt för studien att du besvarar alla frågorna.

Fundera inte för länge kring svaret eftersom vi är intresserade av Dina spontana tankar och erfarenheter.

Dina svar behandlas konfidentiellt.

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1 **Från minnet, ungefär hur många av de senaste 10 patienterna Du träffade med en ÖLI lyckades du handlägga utan att skriva ut antibiotika?**

0 1 2 3 4 5 6 7 8 9 10

2 **Jag känner press att handlägga patienter med ÖLI utan att skriva ut antibiotika:**

	Instämmer inte alls						*Instämmer helt*
a) från patienter	1	2	3	4	5	6	7
b) från slutenvårdskollegor	1	2	3	4	5	6	7
c) från öppenvårdskollegor	1	2	3	4	5	6	7
d) från STRAMA feedback	1	2	3	4	5	6	7
e) från publicerad litteratur	1	2	3	4	5	6	7

3 **Generellt, att handlägga patienter med ÖLI utan att skriva ut antibiotika skulle:**

	Instämmer inte alls						*Instämmer helt*
a) Få patienterna att känna sig trygga	1	2	3	4	5	6	7
b) Lindra deras symptom	1	2	3	4	5	6	7
c) Öka deras tillfredställelse med min handläggning	1	2	3	4	5	6	7
d) Göra dem mindre benägna att förvänta sig ett antibiotikum i framtiden	1	2	3	4	5	6	7
e) Innebära att patienten kommer att söka igen för samma ÖLI episod	1	2	3	4	5	6	7

f) Öka tiden för deras ÖLI att läka ut	1	2	3	4	5	6	7
g) Minska tiden för konsultationen	1	2	3	4	5	6	7
h) Minska sannolikheten för antibiotikaresistens i samhället	1	2	3	4	5	6	7
i) Innebära att patienten kommer att söka en annan doktor vid upprepade episoder	1	2	3	4	5	6	7

4. Om jag rutinmässigt handlägger patienter med ÖLI utan att skriva ut antibiotika då:

	Instämmer inte alls						*Instämmer helt*
a) På det hela taget kommer mitt liv som allmänläkare att vara lättare i det långa loppet	1	2	3	4	5	6	7
b) På det hela taget kommer konsekvenserna för mig som läkare (t ex stress, tid, framtida konsultationer mm) bli sämre i det långa loppet	1	2	3	4	5	6	7

		Instämmer inte alls						*Instämmer helt*
5	**Det är högst sannolikt att patienter med ÖLI kommer att bli försämrade om jag handlägger dem utan att skriva ut ett antibiotikum.**	1	2	3	4	5	6	7

6 Hur säker är Du på Din förmåga

	Inte alls säker						*Mycket säker*
a) Att handlägga patienter med ÖLI utan att skriva ut ett antibiotikum?	1	2	3	4	5	6	7
b) Att avsluta ett besök för en patient med ÖLI som du har handlagt utan att skriva ut antibiotika?	1	2	3	4	5	6	7
c) Att handlägga en patient med ÖLI med symptom som är besvärande, utan att skriva ut antibiotika?	1	2	3	4	5	6	7

		Instämmer inte alls						*Instämmer helt*
7	a) När jag ser patienter med ÖLI, jag planerar automatiskt att handlägga dem utan att skriva ut antibiotika	1	2	3	4	5	6	7
	b) Det är min vanliga praxis att handlägga patienter med ÖLI utan att skriva ut antibiotika.	1	2	3	4	5	6	7
	c) Jag strävar efter att handlägga patienter med ÖLI utan att skriva ut antibiotika.	1	2	3	4	5	6	7

8. Av 10 patienter som söker <u>för första gången</u> med en ÖLI, hur många patienter skulle du avse att handlägga utan att skriva ut antibiotika?

0 1 2 3 4 5 6 7 8 9 10

9 Jag har svårt att handlägga patienter med ÖLI utan att skriva ut antibiotika som:

	Instämmer inte alls						*Instämmer helt*
a) Har redan försökt att självbehandla med antibiotika	1	2	3	4	5	6	7
b) Förväntar sig att jag skriver ut antibiotika	1	2	3	4	5	6	7
c)Har KOL i anamnesen	1	2	3	4	5	6	7

10 Generellt har jag svårt:

	Instämmer inte alls						*Instämmer helt*
a) Att handlägga patienter med ÖLI utan att skriva ut antibiotika	1	2	3	4	5	6	7
b) Att avsluta ett besök för en patient med ÖLI som jag handlagt utan att skriva ut antibiotika	1	2	3	4	5	6	7
c) Att handlägga en patient med ÖLI med symptom som är besvärande, utan att skriva ut antibiotika.	1	2	3	4	5	6	7

11

	Instämmer inte alls						*Instämmer helt*
a) Jag skulle vilja handlägga patienter med ÖLI utan att skriva ut antibiotika men jag vet inte om jag kan.	1	2	3	4	5	6	7
b) Om jag handlägger patienter med ÖLI utan att skriva ut antibiotika är det helt upp till mig	1	2	3	4	5	6	7
c) Jag är övertygad om att jag kan handlägga patienter med ÖLI utan att skriva ut antibiotika när jag vill	1	2	3	4	5	6	7
d) Jag kan övervinna alla hinder, oavsett vilka, för att handlägga patienter med ÖLI utan att skriva ut antibiotika.	1	2	3	4	5	6	7

12 Generellt

	Instämmer inte alls						*Instämmer helt*
a) Fördelarna med att handlägga patienter med ÖLI utan att skriva ut antibiotika överväger nackdelarna.	1	2	3	4	5	6	7
b) Handläggning av patienter med ÖLI utan att skriva ut antibiotika är oftare en sämre handläggning	1	2	3	4	5	6	7
c) Handläggning av patienter med ÖLI utan att skriva ut antibiotika är oftare otillfredsställande än tillfredställande.	1	2	3	4	5	6	7

13 Generellt:

	Oviktigt						*Viktigt*
a) Ge patienten trygghet är:	1	2	3	4	5	6	7
b) Lindra patientens symptom är:	1	2	3	4	5	6	7
c) Öka patientens tillfredställelse med min handläggning är:	1	2	3	4	5	6	7

d) Minska patientens förväntningar för antibiotika i framtiden är:	1	2	3	4	5	6	7
e) Minska sannolikheten att patienten söker igen för samma ÖLI-episod är:	1	2	3	4	5	6	7
f) Förkorta tiden till att patientens ÖLI läker ut är:	1	2	3	4	5	6	7
g) Förkorta durationen för ett besök pga ÖLI är:	1	2	3	4	5	6	7
h) Minska antibiotikaresistensen är:	1	2	3	4	5	6	7

14 Hur motiverad är Du att göra vad:

	Inte alls						***Mycket***
a) patienterna tycker att Du borde	1	2	3	4	5	6	7
b) slutenvårdskollegor tycker att Du borde	1	2	3	4	5	6	7
c) primärvårdskollegor tycker att Du borde	1	2	3	4	5	6	7
d) STRAMA anger att Du bör	1	2	3	4	5	6	7
e) publicerad litteratur anger att Du bör	1	2	3	4	5	6	7

15 Utan ett antibiotikum, hur säker är Du på Din egen förmåga att handlägga patienter med ÖLI som

	Inte alls självsäker						***Mycket självsäker***
a) har redan provat att självbehandla med antibiotika för sin ÖLI	1	2	3	4	5	6	7
b) förväntar sig att Du skriver ut ett antibiotikum	1	2	3	4	5	6	7
c) har KOL i anamnesen.	1	2	3	4	5	6	7

		Instämmer inte alls						***Instämmer helt***
16	**När en patient söker med ÖLI, jag planerar att handlägga honom/henne utan att skriva ut antibiotika.**	1	2	3	4	5	6	7
17	**Jag planerar att handlägga patienter med ÖLI utan att skriva ut antibiotika**.	1	2	3	4	5	6	7
18	**Min nuvarande standard metod att handlägga patienter med ÖLI är utan att skriva ut antibiotika**	1	2	3	4	5	6	7

19 Jag är: Kvinna ☐ Man ☐

20 Min ålder är : <35 ☐; 36-45 ☐; 46-55 ☐; >56 ☐

21 Min arbetslivserfarenhet efter legitimation är: <10 år ☐; 10-20 år ☐; >20 år ☐

Tack för Din medverkan!

Appendix B. Intervention med graderad uppgift (GTI)

A). Nedan finns en lista på fem situationer rörande behandling av halsont. Situationerna har rangordnats från lättast till svårast och bygger alla på allmänläkares erfarenhet av att behandla ÖLI.

Med början från nummer 1, titta på varje situation i tur och ordning. Bocka i rutan till höger för att ange hur säkert det känns för dig att kunna åstadkomma varje situation.

Kan du med säkerhet:

1. Avsluta en läkarkonsultation för en patient med ÖLI utan att ordinera antibiotika
2. Hantera patientfall med ÖLI utan antibiotika där patienten redan har provat att självmedicinera sig mot ÖLI.
3. Hantera patientfall med ÖLI utan antibiotika där patienten förväntar sig att du ordinerar antibiotika.
4. Hantera patientfall med ÖLI utan att antibiotika där symtomen är plågsamma för patienten.
5. Hantera patientfall med ÖLI utan antibiotika för patienter som har en tidigare sjukhistoria av kronisk obstruktiv lungsjukdom.

	Ja	Nej	Kanske
1			
2			
3			
4			
5			

B).

i) Om du har svarat JA på ALLA frågor, kan du tänka dig en situation där det hade varit svårt att hantera ett patientfall av ÖLI utan antibiotika? Var vänlig beskriv situationen nedan och **fortsätt sedan vidare till del C:**

ii) Om du svarat NEJ eller KANSKE på någon av eller på alla fem situationerna ovan, välj utifrån dem den situation du finner minst besvärligt.

Skriv numret på den valda situationen här (1 – 5) ..... och fortsätt **sedan vidare till del C**

C). Tänk dig själv i den ovan beskrivna eller valda situationen och tillsammans med en patient.

Gör en lista över alla möjliga alternativa strategier för att kunna hantera situationen.

……..

……..

……..

……..

……..

Med tanke på strategin eller strategier som du tror är mest kliniskt lämpade och användbara, gör upp en plan på vad du faktiskt gör för att i framtiden kunna hantera den utvalda situationen. Skriv ner planen nedan.

……..

……..

……..

……..

……..

Appendix C. Intervention med övertygande kommunikationssätt (PCI)

Primärvården innefattar stora och varierande kliniska beslut som oftast tas under tidpress. Dessa beslut har konsekvenser inte bara för patientens aktuella kliniska tillstånd utan även för hur patienten uppfattar behandlingens effektivitet och även allmänläkares roll i den pågående vården.

Nedan finns en rad bildscenarier som visar några av konsekvenserna av att allmänläkare beslutar att hantera ÖLI-fall med eller utan antibiotika.

I den första scenarieraden, **hanterar Dr A ÖLI-fall genom att ordinera antibiotika,** medan den andra scenarieraden visar hur **Dr B hanterar ÖLI-fall utan att förskriva antibiotika**.

Nedanför scenarierna finns frågor för att hjälpa er att överväga eventuella **konsekvenser av varje läkares förskrivningsvanor.**

Dr A hanterar patientfall med ÖLI genom att ordinera antibiotika

Dr B hanterar patientfall med ÖLI symtomatiskt

Med avseende på hantering av patientfall med ÖLI:

Vem strävar Du efter att vara som?

100% som Dr A ----------*100% som Dr B*

Vem är Du som egentligen?

100% som Dr A ----------*100% som Dr B*

Appendix D

Samtalsguide

till studien

Svenska allmänläkares uppfattningar om behandlingsrekommendationer

Del 1. Uppfattningar om lokala behandlingsrekommendationer (BR)

- Praktiska exempel från vardagen- Läkemedel och Skånelistan: frivilliga berättar
- Vad tror Ni syftet är med BR (Skånelistan)?
- Har ni kunskap om hur lokala BR utformas?
- Tycker Ni att lokala BR borde finnas? (versus nationella)
- Hur har Ni tillgång till lokala BR?
- Vad är bra/dåliga BR?
- Vilka är Era hinder mot att använda Skånelistan?
- Vad motiverar Er att använda BR?

Del 2. Uppfattningar om påverkan på patient-läkarrelationen

- Upplever Ni att lokala BR underlättar/försvårar i Ert arbete?
- Upplever Ni att lokala BR leder till en bättre/sämre patientkontakt?
- Hur upplever Du att Dina patienter påverkas av att Skånelistan finns?
- Upplever Ni att patienterna har kunskap om lokala BR?
- Vad skulle få Dig att använda lokala BR i mindre/större utsträckning?
- Något vi glömt?

Paper I

Drugs Aging (2013) 30:235–246
DOI 10.1007/s40266-013-0057-0

ORIGINAL RESEARCH ARTICLE

Improving the Quality of Pharmacotherapy in Elderly Primary Care Patients Through Medication Reviews: A Randomised Controlled Study

Veronica Milos · Eva Rekman · Åsa Bondesson · Tommy Eriksson · Ulf Jakobsson · Tommy Westerlund · Patrik Midlöv

Published online: 14 February 2013

Abstract
Background Polypharmacy in the Swedish elderly population is currently a prioritised area of research with a focus on reducing the use of potentially inappropriate medications (PIMs). Multi-professional interventions have previously been tested for their ability to improve drug therapy in frail elderly patients.
Objective This study aimed to assess a structured model for pharmacist-led medication reviews in primary health care in southern Sweden and to measure its effects on numbers of patients with PIMs (using the definition of the Swedish National Board of Health and Welfare) using ≥10 drugs and using ≥3 psychotropics.
Methods This study was a randomised controlled clinical trial performed in a group of patients aged ≥75 years and living in nursing homes or the community and receiving municipal health care. Medication reviews were performed by trained clinical pharmacists based on nurse-initiated symptom assessments with team-based or distance feedback to the physician. Data were collected from the patients' electronic medication lists and medical records at baseline and 2 months after the medication review.
Results A total of 369 patients were included: 182 in the intervention group and 187 in the control group. One-third of the patients in both groups had at least one PIM at baseline. Two months after the medication reviews, the number of intervention group patients with at least one PIM and the number of intervention group patients using ten or more drugs had decreased ($p = 0.007$ and $p = 0.001$, respectively), while there were no statistically significant changes in the control patients. No changes were seen in the number of patients using three or more

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psychotropic drugs, although the dosages of these drugs tended to decrease. Drug-related problems (DRPs) were identified in 93 % of the 182 patients in the intervention group. In total, there were 431 DRPs in the intervention group (a mean of 2.5 DRPs per patient, range 0–9, SD 1.5 at 95 % CI) and 16 % of the DRPs were related to PIMs. *Conclusions* Medication reviews involving pharmacists in primary health care appear to be a feasible method to reduce the number of patients with PIMs, thus improving the quality of pharmacotherapy in elderly patients.

1 Background

1.1 The Challenge of Drug Therapy in the Elderly

The elderly population is increasing worldwide, and statistical demographic data estimate that 20 % of the global population will be older than 65 by 2025 [1]. According to the Swedish Central Bureau of Statistics, the proportion of the population aged 65 years or older was 18.8 % in Sweden in 2011. Aging is known to be associated with an increased prevalence of multiple chronic diseases and therefore the use of complex therapeutic regimes. Age-related changes in pharmacokinetics and pharmacodynamics [2], together with co-morbidity and polypharmacy, make the elderly a special group of patients who need to be treated with increased attention [1].

Polypharmacy is a controversial issue and has been found to be related to an increased risk of drug–drug interactions, higher morbidity in the older population, higher numbers of hospital admissions, lower compliance and increased institutionalisation [3]. A comprehensive literature review on the topic shows that polypharmacy is increasing in the elderly and is a major cause of morbidity and mortality in the elderly population worldwide [4]. Lack of continuity in physician contacts, lack of a consistent drug list, and inadequate prescribing and monitoring of drug therapy are some of the reasons for drug-related problems and the need for emergency hospital contacts [4]. A drug-related problem (DRP) has previously been described as "an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome" [5].

1.2 Potentially Inappropriate Medication

Well-defined criteria (Beers' criteria) for potentially inappropriate medications (PIMs) in the elderly that use toxicological aspects and risk of adverse drug reactions have been described and were updated in 2012 [6]. The lack of good nationally adapted alternatives has led to the wide use in studies of the internationally accepted definition criteria in order to create tools for identifying PIMs. About half of the drugs listed as PIMs in the Beers criteria are, however, unavailable in Europe. Therefore, criteria corresponding to European drug formularies have been developed, such as the Swedish quality indicators developed by the Swedish National Board of Health and Welfare [7]. They can work as a support for the prescriber in choosing appropriate medications but can even be used by drug and therapeutics committees to follow up doctors' prescribing habits or to assess the quality of prescribing at the local or national level.

A nationwide register-based study in Sweden showed a strong correlation between the number of prescribed drugs and the number of PIMs, such as anticholinergic drugs, long-acting benzodiazepines, and three or more psychotropic drugs [8]. Use of multiple psychoactive drugs has been identified as particularly problematic in nursing home patients [9].

1.3 Medication Review

Optimisation of drug therapy in the elderly can be challenging, and different tools have been tested, such as educational outreach visits [10], medication reports at hospital discharge [11] and pharmaceutical care programmes using community pharmacists and medication reviews [12].

Currently, there is no well-established definition of the term "medication review" but Pharmaceutical Care Network Europe has suggested the following definition: "Medication review is an evaluation of patients' medicines with the aim of managing the risk and optimising the outcome of medicine therapy by detecting, solving and preventing drug-related problems" [13].

Collaboration between physicians and pharmacists to identify drug-related problems has proven to be useful and led to better patient safety, as well as cost savings [14, 15]. Multi-disciplinary approaches have proved to be very satisfactory in the elderly patient, being appreciated by physicians and nurses, and had long-term effects on the patient's drug therapy [16].

1.4 Multi-dose Drug Dispensing

Community-dwelling elderly individuals and nursing home residents in Sweden use on average eight to ten different drugs [7]. A large proportion of them use multi-dose drug dispensing (MDD). The goal of MDD is to create safer drug therapy, improve the patients' drug management and adherence, get a complete picture of the patient's drug prescriptions from different health-care providers as well as to improve communication between hospitals, primary care and communities. However, this service is used

primarily in Sweden and there are no studies to support evidence for such positive effects compared to traditional prescribing. According to data from 2005, 19 % of women and 13 % of men aged ≥75 years use MDD [8] and a majority of them live in nursing homes. The same study showed that 40 % of these patients were treated with at least one PIM. However, MDD led to fewer dangerous drug–drug interactions and may thus have advantages if used optimally. Disadvantages, including managing difficulties and uncritical renewal of prescriptions, have been mentioned [17]. A majority of the nursing home patients and community-dwelling patients with municipally provided home care in Sweden receive MDD because of high age, co-morbidity, cognitive impairment, polypharmacy and therefore increased care need. The medication is dispensed to the patient by the nurse and the intake is documented, leading to a high level of compliance.

1.5 The Medication Review in Primary Care in Southern Sweden

An integrated approach in which pharmacists help in the clinical routine has been developed in hospital care in Skåne County in southern Sweden (the Lund Integrated Medicines Management [LIMM] model) [18] and has been shown to reduce PIMs and drug-related hospital admissions [11]. This model of medication reviews for elderly patients with multiple illnesses originates from an early Swedish study in nursing homes, where medication reviews including the pharmacist in the multidisciplinary team produced a significant reduction in the number of psychotropic drugs [19]. In primary health care in Skåne County, medication reviews have been conducted during the past 10 years in different projects, both in nursing homes and community-dwelling elderly patients with multiple illnesses, and several models and approaches have been tried. The goal of medication reviews has been improved patient safety and quality of medication use, according to the Swedish National Board of Health and Welfare's indicators for good drug therapy in the elderly [7]. The instruments used in the LIMM model have been adapted to work in primary care. The main aim of adapting the instruments for primary care was to implement a new model of care with medication reviews before the patient's annual visit in order to improve the quality of elderly patients' pharmacotherapy in both community-dwelling and nursing home patients.

2 Objectives

The primary objective was to assess a structured model of care by studying the impact of pharmacist-led medication reviews on the number of the patients using PIMs. Secondary objectives were to assess if this intervention model led to a decreased number of patients using ≥10 drugs and ≥3 psychotropics. The study also intended to classify and describe the types of DRPs identified during the intervention period and the medication reviews' impact on the patients' medication therapy.

3 Methods

The study received ethical approval from the Regional Ethical Review Board in Lund (no: 2011/245).

3.1 Study Setting and Design

Skåne County is situated in the southern part of Sweden and has approximately 1,150,000 inhabitants. Primary care is provided by public or private primary health care centres (PHCCs). There are 90 public and approximately 40 private PHCCs in Skåne. Due to practical reasons, such as to minimise the number of different electronic medical records (EMRs) we invited all public PHCCs to participate in this study. Four pharmacists were selected and were assigned to one area each. The pharmacists had at least 4 years' experience of performing medication reviews. Patients eligible for inclusion were users of the multi-dose drug dispensing system aged 75 years or older, living in nursing homes or their own homes with municipally provided home care. Patients were included in the study after they provided written consent (directly or through relatives in cases of severe cognitive impairment). The patients were included between 1 September and 16 December 2011 with follow-up data collection continued until 16 February 2012. An overview of the actions in the study is presented in Fig. 1.

3.2 Implementation

Prior to the patient's annual visit and medication renewal by the GP, nurses collected the patient's written consent for participation in the study and conducted a specific symptom evaluation and health status check including blood pressure, pulse, weight, tendency to fall and confusion, using a validated symptom assessment form (Phase-20) [20]. After inclusion, the pharmacist used closed, non-transparent envelopes to randomise the patient to one of two groups: control or intervention (Fig. 2). The randomisation was performed using a random number generator and stratified only for geographic area. Medication lists (MDD cards) were printed by the pharmacists who had received permission to access patients' EMR as well as the electronic MDD record.

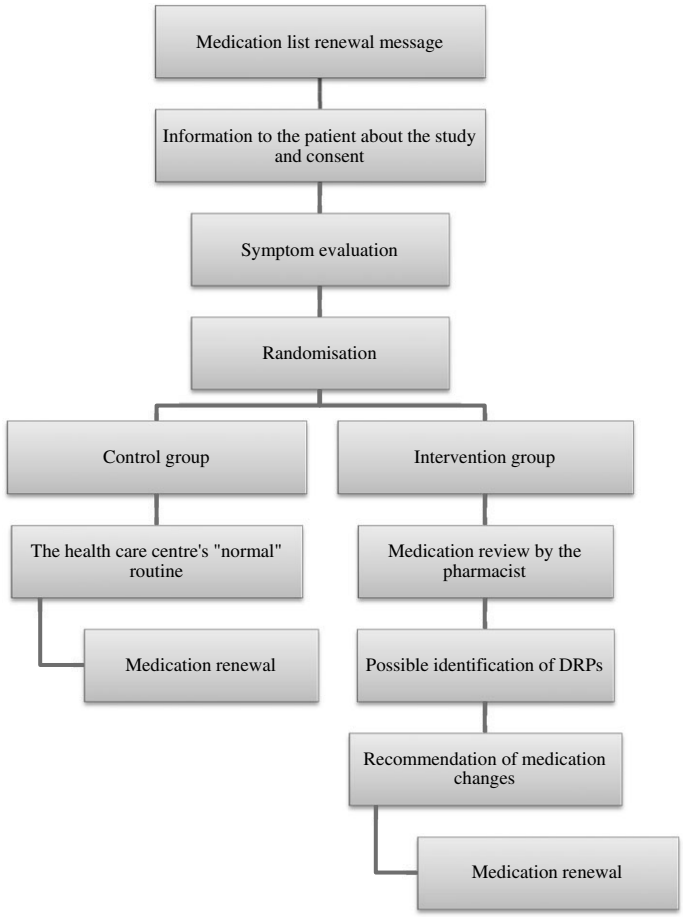

Fig. 1 Overview of the study. *DRPs* drug-related problems

3.3 Intervention

For patients in the intervention group the pharmacists performed a systematic medication review without personal patient contact. The medication review included assessment of relevant parts of the EMR and collection of data on the patient's blood sample results for creatinine, estimated glomerular filtration rate (eGFR), cystatin C, haemoglobin, sodium and potassium plasma levels.

To identify DRPs the clinical pharmacist initiated medication reviews based on the background information (symptom assessment form and the MDD cards). The working process was carried out in a structured way with formularies compiled from the LIMM model [18].

The following predetermined risk categories for identifying DRPs were taken into account by the pharmacist and documented by the student:

- Drugs that required therapeutic monitoring
- Inappropriate drugs for elderly according to The National Board of Health and Welfare (PIMs)
- Drugs that are not recommended according to the regional drug and therapeutics committee
- Problems with administration/handling of the drugs (crush, cut, inhalation technique)
- C/D drug–drug interactions (C interactions are those involving a drug combination that could require dose

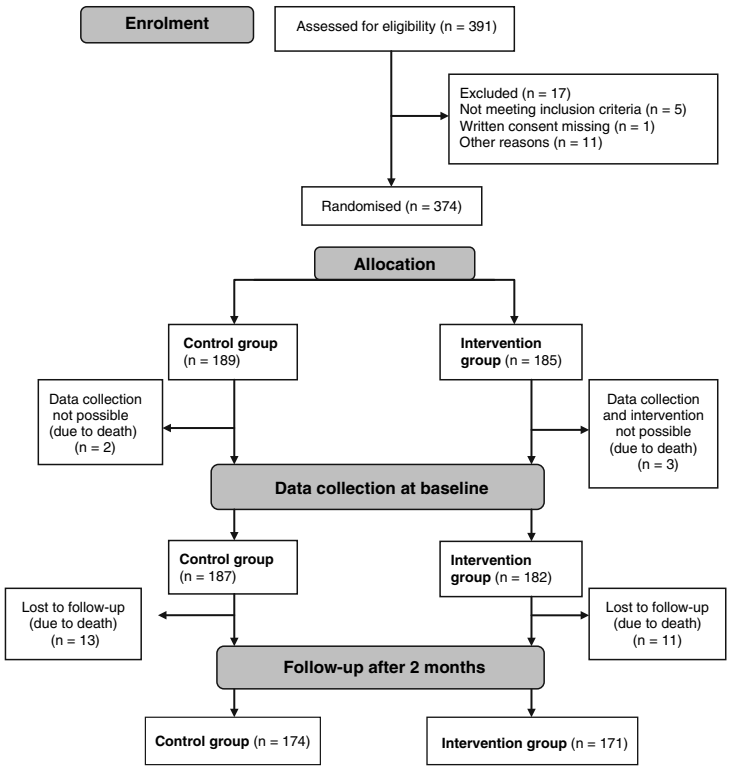

Fig. 2 CONSORT study flow chart of the inclusion and assessment process

adjustment; D interactions are those involving a drug combination that ought to be avoided)
- Drug type or drug dosage not adjusted for the patient (renal function, liver function)
- Unclear indication for drug treatment
- Suboptimal treatment
- Drugs causing potential adverse drug reaction.

The check list including the nine risk categories was an instrument to facilitate the medication review.

PIMs were identified according to the national guidelines of the Swedish National Board of Health and Welfare regarding drug therapy in the elderly [7].

The pharmacists' recommendations were documented in patients' EMRs. The feedback to the physician varied depending on the PHCC's routines and organisation and consisted of team rounds, written contact, personal contact and telephone contact.

To ensure that the pharmacists worked similarly, they were formally instructed in one tutorial by the head pharmacist (E.R.) about the method of medication review, had monthly meetings with the data collector (S.W.) and had one meeting with the head researcher (V.M.). In addition, the head pharmacist was available for consultation throughout the entire study.

3.4 Data Collection and Statistical Analysis

The required sample size was estimated to be at least 160 patients ($n = 80$ per group) by power calculation analysis ($p = 0.05$; power: 0.80) based on the assumption that 40 % of respondents would have at least one inappropriate drug. The intervention was expected to reduce this proportion to 20 %. The calculation was based on previous studies on drug consumption in the elderly [8].

For the intervention patients, S.W. and V.M. compiled drugs associated with the DRPs and assigned categories of risk and type of suggested change in collaboration with the consulting research pharmacist (Å.B.). Medication lists were not assessed for DRPs for the control patients for ethical reasons.

During the data collection, medication lists and patients' EMRs were reviewed at baseline and after 2 months. Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [21].

The documented DRPs were further classified by S.W and V.M into the seven categories used by Cipolle, Strand and Morley [22]: need for additional therapy, unnecessary drug therapy, wrong drug, dosage too low, adverse drug reaction, dosage too high and compliance problems.

Both S.W. and V.M. participated in the ongoing review meetings of the research team, where the input method was discussed continuously, in order to assure the quality of the collected data.

If a drug prescription was for both continuous use and as needed, it was counted as one drug. Drugs for topical use such as eye drops, moisturisers and topical steroids were included; short-term antibiotic prescriptions were not.

The primary outcome measure was change in the proportion of patients taking PIMs [7] including one or more of the following drugs: intermediate- or long-acting benzodiazepines (ATC group N05BA01, N05CD02 and N05CD03), antipsychotics [N05A, excluding lithium (N05AN)], tramadol (N02AX), propiomazine (N05CM) and drugs with anticholinergic effects (R06, G04 and N05BB). Secondary outcome measures were percentage of patients taking ten or more medications (regularly or as needed) and percentage of patients taking three or more psychotropic drugs (from one or more of the following ATC groups: N05A, N05B, N05C and N06A) regularly or as needed before and after the intervention. The secondary outcome measures are based on the definition of "polypharmacy" as described by the Swedish National Board of Health and Welfare.

Intermediate- and long-acting benzodiazepines prescribed in Sweden are nitrazepam, flunitrazepam and diazepam.

The average age and sex distribution of the patients were determined, as were the average number of drugs per patient and the proportion of patients using drugs in the different ATC subgroups. Data on DRPs, if recommended changes were performed or not and actions taken were also collected. Identification of DRPs was a part of the intervention and thus not made in the control group. The DRPs were identified based on the symptom assessment performed by the nurse at baseline. This was not repeated after the intervention. Focus was on the medication changes in the medication lists with data collection before and after the medication reviews.

Data were analysed according to the "intention-to-treat" principle with the last value carried forward using a single imputation method [23]. A significance level of $\alpha = 0.05$ was used. Statistical tests were performed for both intention-to-treat and per-protocol analyses using Student's *t* test and McNemar's test for pairwise observations using IBM SPSS version 20.0 UK.

4 Results

A flow chart of the inclusion and assessment steps is presented in Fig. 2. Baseline characteristics are presented in Table 1. In the intervention group the pharmacist had a face-to-face encounter with the physician during team sessions in 20 % of cases. Distance medication reviews were performed in 80 % of the cases. The control and intervention groups were similar, and a majority of patients were females and lived in nursing homes.

4.1 PIMs

A total of 391 patients were assessed, and 369 were included in the intention-to-treat analysis. The proportion of patients with at least one PIM decreased in the intervention group (by 6 %; $p = 0.007$) but not in the control group ($p = 1.0$) (Table 2). Similarly, the number of patients taking ten or more drugs decreased in the intervention group but not in the control group (Table 2). No differences in mortality between the groups were seen after the medication reviews: 6.8 % of patients in the control group and 5.9 % of patients in the intervention group died during follow-up (Fig. 2). Nearly one-third of the patients in both the control and intervention groups had at least one PIM for elderly patients at baseline (Table 2). The total number of drugs and number of continuous drugs decreased significantly between baseline and follow-up in the intervention group (Table 3). No significant decreases after the medication reviews were noted in the medication subgroups (antipsychotics, benzodiazepines, etc.). Similar results were found in both intention-to-treat and per-protocol analyses.

4.2 DRPs

DRPs were identified in 93 % of the 182 patients in the intervention group. The total number of DRPs in this group was 431 with a mean of 2.5 DRPs per patient [range 0–9 (SD = 1.5)]. No difference between the number of DRPs in community-dwelling patients [mean 2.55 (SD = 1.29)] and nursing home patients [mean 2.53 (SD = 1.33)] was seen ($p = 0.767$).

Drugs acting on the nervous system (26 %), cardiovascular system (25 %) and blood and blood-forming organs (15 %) were the most common ATC classes involved in DRPs.

The distribution of the seven main categories of DRPs identified when data were collected is shown in Fig. 3. Of

Table 1 Baseline characteristics of intervention and control group patients

Characteristic	Control group	Intervention group	*p* value
Female, *n* (%)	142 (75.9)	138 (75.8)	0.980[a]
Age, mean (SD)	87.7 (5.5)	87.0 (5.8)	0.662[b]
Place of residence, *n* (%)			
Community	47 (25.1)	43 (23.6)	0.736[a]
Nursing home	140 (74.9)	139 (76.4)	
No. of drugs, mean (SD)	12.1 (4.7)	11.4 (4.2)	0.903[b]
No. of continuous drugs, mean (SD)	9.7 (3.9)	9.3 (3.7)	0.528[b]
No. of drugs as needed, mean (SD)	2.2 (1.8)	2.1 (1.7)	0.399[b]
No. of antipsychotics, mean (SD)	0.11 (0.36)	0.14 (0.35)	0.137[b]
No. of intermediate- or long-acting benzodiazepines, mean (SD)	0.06 (0.25)	0.10 (0.29)	0.070[b]
No. of anticholinergics, mean (SD)	0.12 (0.34)	0.08 (0.26)	0.040[b]
No. of propiomazine, mean (SD)	0.04 (0.19)	0.04 (0.19)	0.918[b]
No. of tramadol, mean (SD)	0.06 (0.24)	0.07 (0.27)	0.873[b]
No. of psychotropics, mean (SD)	1.93 (1.37)	1.71 (1.37)	0.750[b]

SD standard deviation

[a] Chi-square test

[b] Student's *t* test

the identified DRPs, 67 (16 %) were related to PIMs, as follows: antipsychotics (27), intermediate- or long-acting benzodiazepines (15), tramadol (11), anticholinergics (9) and propiomazine (5).

The two most common intervention recommendations the pharmacist presented to the physician were withdrawal of drug therapy (30 %) and reduced dosage (28 %) (Fig. 4).

Fifty-six percent (241) of the presented DRPs (Fig. 4) resulted in actions taken by the physician such as changes in medication, with a minimum of one and maximum of seven changes for the same patient [mean 1.44 (SD = 1.33)] with no difference between the community-dwelling and the nursing home patients ($p = 0.946$) or between the group receiving team-based medication reviews compared to the distance medication reviews ($p = 0.363$).

The changes in the actions taken by the physician regarding PIMs were significant ($p = 0.003$) for "lowered dosage" (Table 4) and there was a clear tendency to withdraw the PIMs, although it was not significant. There were no significant differences in actions taken on PIMs between the group receiving team-based medication reviews and the group receiving distance medication reviews.

5 Discussion

Our study showed that medication reviews involving pharmacists in primary health care reduced the number of patients with PIMs.

The majority of the patients in the present study were women, were living in nursing homes, were old and were using a large number of drugs, characteristics similar to those in other studies [24–26]. The results demonstrate that the assessed care model led to a reduction in the number of intervention group patients taking PIMs and the total number of drugs these patients were taking and identified common DRPs [27–29], such as overprescribing or unclear reasons for medication use.

Similar to another study using a multidisciplinary approach [30], the present study did not show a decrease in

Table 2 Changes in number of patients with PIMs, patients with ≥10 drugs or ≥3 psychotropic drugs

Variable	Group	Frequency at randomisation (%)	Frequency at follow-up (%)	*p* value[a]
No. of patients with ≥10 drugs	Control group	123 (65.7)	120 (64.1)	0.549
	Intervention group	120 (65.9)	107 (58.7)	**0.001**
No. of patients with ≥3 psychotropics	Control group	60 (32.0)	64 (34.2)	0.219
	Intervention group	47 (25.8)	49 (26.9)	0.754
No. of patients with PIMs	Control group	58 (31.1)	57 (30.5)	1.000
	Intervention group	60 (33.0)	49 (27.0)	**0.007**

PIM potentially inappropriate medication

[a] McNemar's test

Table 3 Changes in medication in the control and intervention groups at follow-up

	Group	Mean number of drugs (range) at baseline	Mean number of drugs (range) at follow-up	*p* value[a]
No. of drugs	Control	12.1 (3–28)	12.1 (3–29)	0.782
	Intervention	11.4 (2–21)	10.8 (0–22)	**<0.001**
No. of continuous drugs	Control	9.7 (1–27)	9.6 (1–25)	0.327
	Intervention	9. 3 (1–20)	8.8 (1–18)	**<0.001**
No. of drugs as needed	Control	2.2 (0–12)	2.5 (0–12)	0.061
	Intervention	2.1 (0–10)	2.0 (0–8)	0.171
No. of antipsychotics[b]	Control	0.11 (0–3)	0.11 (0–3)	1.000
	Intervention	0.14 (0–1)	0.13 (0–1)	0.158
No. of intermediate- or long-acting benzodiazepine[c]	Control	0.06 (0–2)	0.06 (0–2)	1.000
	Intervention	0.10 (0–1)	0.10 (0–1)	0.556
No. of anticholinergics[d]	Control	0.12 (0–2)	0.10 (0–3)	0.319
	Intervention	0.08 (0–1)	0.08 (0–1)	1.000
No. of propiomazine[e]	Control	0.04 (0–1)	0.04 (0–1)	1.000
	Intervention	0.04 (0–1)	0.03 (0–1)	0.416
No. of tramadol[f]	Control	0.06 (0–2)	0.07 (0–1)	0.416
	Intervention	0.07 (0–2)	0.04 (0–1)	0.103
No. of psychotropics[g]	Control	1.93 (0–6)	1.96 (0–6)	0.224
	Intervention	1.71 (0–6)	1.69 (0–6)	0.082

Anatomical Therapeutic Chemical (ATC) classification system codes for medications are provided in footnotes b-g

[a] Student's *t* test

[b] N05A excluding lithium (ATC code N05AN)

[c] N05BA01, N05CD02 and N05CD03

[d] R06, G04 and N05BB

[e] N05CM

[f] N02AX

[g] N05A, N05B, N05C and N06A

the number of patients taking three or more psychotropics, possibly because of multiple illnesses and the remaining need for psychotropics due to cognitive or other psychiatric impairments in this group of patients. This conclusion is, however, only speculative and future research is required to explore a possible association between elderly patients' multiple use of drugs affecting the nervous system and psychiatric morbidity.

There was no difference in mortality after the performed medication reviews between the intervention and control groups, but the short follow-up period and multiple illnesses in this frail group of elderly patients should be taken into consideration.

Assessing the effect of optimisation strategies on the appropriateness of prescribing in elderly patients is currently a priority for both clinical and interventional health care research [31]. Multi-disciplinary approaches have been highlighted [32], although according to a meta-analysis of randomised controlled trials of pharmacist-led medication reviews, the evidence of an impact on clinical outcomes (e.g. morbidity) and health-care use was inconclusive [33]. The analysis excluded, however, interventions delivered by combinations of health professionals (e.g. physician and nurses) where the pharmacist was only partly involved. This accentuates the difficulties in measuring the effects of such interventions. Although there is broad knowledge of medication use in older people and tools exist to improve adherence to treatment guidelines, the prevalence of inappropriate prescribing remains high and further studies are needed to identify effective interventions [34].

A strength of our study is that the pharmacists were blinded to patient allocation but not blinded performing the medication reviews. The DRPs were identified by symptom assessment by a nurse working closely with the patient. This information was included by the pharmacist in the written feedback to the physician that was recorded in the patient's EMR and also faxed to the physician as a reminder regardless of medication review form. The MDD cards and EMRs were the central instruments for the assessment of drug therapy, giving current information to the pharmacist and responsible physician and therefore increasing the ability of pharmacists to make an accurate

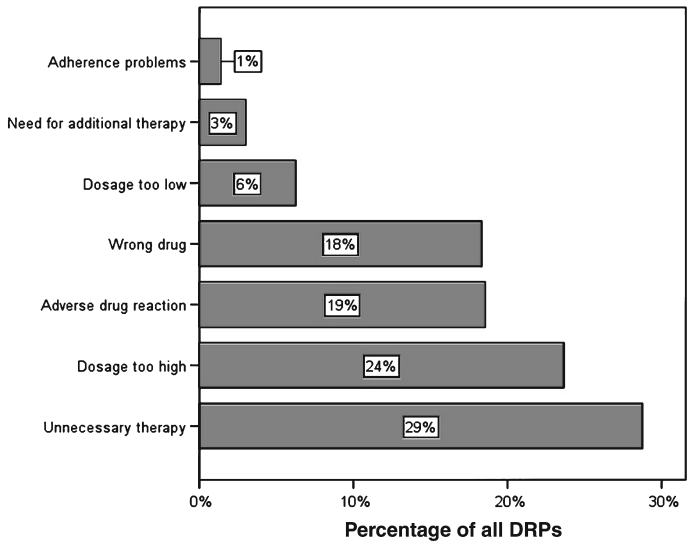

Fig. 3 Distribution of drug-related problems in the intervention group by category (N = 431)

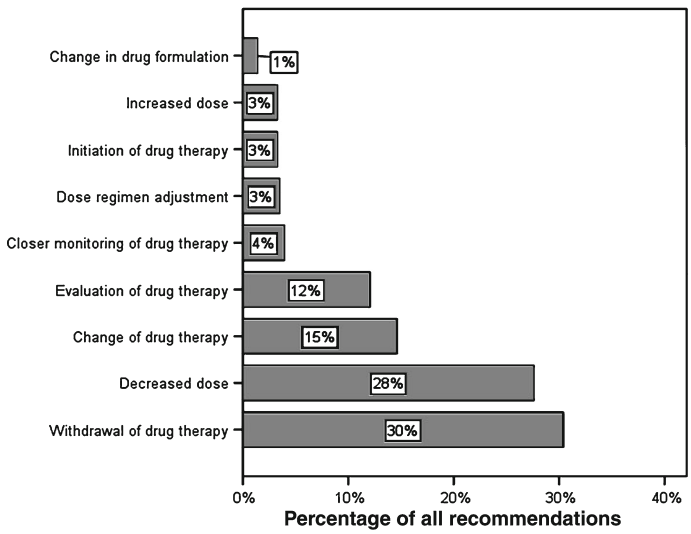

Fig. 4 Distribution of recommended changes in drug therapy in the intervention group (N = 431)

decision in recommending changes in medication. No other medication prescribing interventions were conducted in the districts at the time of the study that impacted on the results. Physicians' decision-making in medication changes was not influenced by patients' living form, implying that the present model of medication review could be applicable in both community-dwelling and nursing home patients with similar results.

The results from this study have to be interpreted with acknowledgement of its limitations. The pharmacists did not have any direct contact with the assessed patients. Therefore, the identified DRPs are only potential DRPs.

Table 4 Frequency of changes in PIMs in the control group versus the intervention group

Action taken by the physician on drug therapy	No. of cases (percent)		*p* value[a]
	Control	Intervention	
Dose not changed	56 (76.8)	45 (64.8)	0.349
PIM out	8 (11.5)	13 (17.5)	0.238
New PIM in	7 (10.1)	2 (2.7)	0.098
Lowered dose	0 (0.0)	10 (13.5)	**0.003**
Increased dose	1 (1.4)	1 (1.3)	0.995

PIM potentially inappropriate medication

[a] Student's *t* test

Feedback between the pharmacists and the physicians varied from team discussions to distance reviews, which may partly explain the low rate of physician response in performing medication changes. Fifty-six percent of the presented suggestions led to medication changes. These figures are low compared to those for team-based interventions including a responsible physician in secondary care (65–90 %) [35, 36]. In a British study of elderly nursing home patients, 75 % of the pharmacist's proposals were accepted and of these 76 % were implemented [37]. The present study assessed the implemented medication changes, with results similar to those from other studies performed in primary care [38, 39]. The medical literature supports the theory that valid clinical care recommendations do not always have the desired impact on physicians' behaviour due to cultural barriers [40, 41] or contextual factors (e.g. staffing and resources) [42]. Our study shows that the physicians responded in similar ways after the distance medication reviews compared to the team-based medication reviews.

Inter-professional medication reviews with pharmacists are often studied when performed in face-to-face team discussions [16, 27]. Despite this, distance reviews can have benefits such as accessibility despite large geographical patient distributions and have been performed in southern Sweden as an alternative to team-based medication reviews with positive results concerning quality and quantity of medication and drug costs [43]. Comparison with a model using team-based reviews in another Swedish region showed similar results and the possibility to implement the method should be taken into account in order to improve physicians' adherence to drug therapy guidelines and the inter-professional collaboration.

Medication reviews as interventions performed by pharmacists not primarily responsible for the prescribing decision have previously been criticised for not delivering clear positive outcomes or even potentially worsening health outcomes [44]. Despite this, the present study shows an effect on the primary outcome measure (number of patients with PIMs).

We estimated that physicians might be most prone to take action within 2 months after the medication review. A longer period to follow-up might also risk a larger dropout because of death in this group of frail patients.

However, the 2-month follow-up period after the intervention may have been too short to measure withdrawal of psychotropic drugs that need a slow reduction in dosage. The analysis of the actions taken by physicians showed a significantly higher frequency of PIM dosage reduction in the intervention group compared to the control group. Dosage reduction is a preferable and recommended step when withdrawal of psychotropics such as long-acting benzodiazepines or antipsychotics is planned.

It is important to mention that the pharmacist's role in reviewing the medication list must be weighed against the clinical reasoning in the final patient assessment and that the path from medication review to the actual implementation of the proposed changes is a complex process. This process starts with the nurses' observation and ends up with the physician's decision.

The assessed method addressed the complexity of prescribing in the elderly, where the professionals were able to collaborate and where use of information technology tools improved drug therapy.

Health outcomes such as improvement in quality of life or effect on hospital admissions were not investigated in this study but should be considered in future studies in order to demonstrate the effectiveness of this kind of intervention.

6 Conclusions

This study verifies that inappropriate prescribing is a problem in Swedish elderly patients living in the community or nursing homes, mirroring the results of international studies [26]. Medication reviews involving pharmacists in primary health care appear to be a feasible method to reduce the number of patients with PIMs, thus improving the quality of pharmacotherapy in elderly patients.

Acknowledgments The authors especially want to thank the four pharmacists who performed the medication reviews (Annika Dobszai, Karin Fält, Martina Haggren and Krister Karlsson), the pharmacist student who initially collected the data (Susan Wong) and the municipal care nurses. We are indebted to Stephen Gilliver for his expertise and invaluable advice in proofreading the manuscript.

Conflict of interest None declared

Disclaimer The opinions or assertions in this article are the views of the authors and are not to be construed as official or as necessarily

reflecting the views of the Swedish Medical Products Agency, where one of the authors is employed.

Funding The study was conducted with government funding for projects involving improvement of drug therapy in the elderly.

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Paper II

Milos et al. BMC Geriatrics 2014, 14:40
http://www.biomedcentral.com/1471-2318/14/40

BMC Geriatrics

RESEARCH ARTICLE Open Access

Fall risk-increasing drugs and falls: a cross-sectional study among elderly patients in primary care

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Abstract

Background: Falls are the most common cause of injuries and hospital admissions in the elderly. The Swedish National Board of Health and Welfare has created a list of drugs considered to increase the fall risk (FRIDs) and drugs that might cause/worsen orthostatism (ODs). This cross-sectional study was aimed to assess FRIDs and their correlation with falls in a sample of 369 community-dwelling and nursing home patients aged ≥75 years and who were using a multi-dose drug dispensing system.

Methods: Data were collected from the patients' electronic medication lists. Retrospective data on reported falls during the previous three months and severe falls during the previous 12 months were collected. Primary outcome measures were incidence of falls as well as numbers of FRIDs and ODs in fallers and non-fallers.

Results: The studied sample had a high incidence of both reported falls (29%) and severe falls (17%). Patients were dispensed a mean of 2.2 (SD 1.5) FRIDs and 2.0 (SD 1.6) ODs. Fallers used on average more FRIDs. Severe falls were more common in nursing homes patients. More women than men experienced severe falls. There were positive associations between number of FRIDs and the total number of drugs ($p < 0.01$), severe falls ($p < 0.01$) and female sex ($p = 0.03$). There were also associations between number of ODs and both total number of drugs ($p < 0.01$) and being community dwelling ($p = 0.02$). No association was found between number of ODs and severe falls. Antidepressants and anxiolytics were the most frequently dispensed FRIDs.

Conclusions: Fallers had a higher number of FRIDs. Numbers of FRIDs and ODs were correlated with the total number of drugs dispensed. Interventions to reduce falls in the elderly by focusing on reducing the total number of drugs and withdrawal of psychotropic medications might improve the quality and safety of drug treatment in primary care.

Keywords: Elderly, Falls, Prevention, Drug therapy, Fall risk-increasing drugs

Background

Drug prescribing in patients aged ≥75 years increased by nearly 70% in Sweden between 1990 and 2010 [1]. A comprehensive Swedish register-based study showed that a high number of drugs in elderly patients is related to a higher risk of prescribing potentially inappropriate medications, as well as higher risks of side-effects and drug-drug interactions [2]. A meta-analysis of prospective studies indicated that almost 17% of hospital admissions in the USA were caused by adverse drug reactions [3]. Meanwhile, both Swedish and international studies have shown that a majority of hospital admissions related to inappropriate drug use could potentially be prevented [4].

Falls are the most common cause of injuries among patients older than 65 years. Seventy-three percent of hospital admissions of patients older than 65 years are due to falls [5]. Upper extremity fractures and hip fractures are the most common fall-related injuries that lead to emergency department visits [6]. A Swedish study showed that treatment with fall risk-increasing drugs (FRIDs) was very common (93%) among older hip fracture patients both before and after the fracture [7].

Today, there is a consensus definition of falls [8]. Several risk assessment tools are available to assess a hospitalised

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[9,10] or community-dwelling [11,12] patient's risk of falling. The tools assess different clinical characteristics as confusion, dizziness, cognitive impairment or administered drugs. Although the causes of falls are multifactorial, medications are an important risk factor that it might be possible to influence. The most common FRIDs are different types of psychotropic drugs, such as sedatives, hypnotics, antidepressants and antipsychotic medications, which can cause sedation, impaired balance and coordination. The use of selective serotonin reuptake inhibitors (SSRIs) has been associated with falls regardless of the presence of depressive symptoms [13]. Due to age-related physiological changes in blood pressure-regulating systems and cardiovascular co-morbidity, cardiovascular drugs may cause or worsen orthostatic hypotension and falls [1,14,15]. Anti-Parkinson's disease and dopaminergic drugs might also increase the fall risk by causing or worsening orthostatic hypotension, dyskinesia or hallucinations [16]. Anticholinergic drugs, such as antihistamines and urological spasmolytics, may affect elderly patients' cognitive skills and cause blurred vision, thereby increasing the fall risk [16].

There is clear evidence that polypharmacy and the use of psychotropic drugs, especially when combined with cardiovascular medications or present as therapeutic duplications, increase the fall risk [16-19]. Medications for night-time sedation, such as lorazepam and zopiclone, have been found to be the most frequently prescribed medications before a fall in general medicine inpatient units in Canada [20].

A meta-analysis of interventions aiming to prevent falls in the elderly showed that slow withdrawal of psychotropics significantly reduced the risk of falling and that prescribing modification programs for primary care physicians significantly reduced risk of falling [21].

The National Board of Health and Welfare (NBHW) in Sweden has produced a FRID list, and also a list of drugs causing or worsening orthostatic blood pressure, which is relevant for assessing the fall risk (Table 1) [1].

According to the Swedish Central Bureau of Statistics, the proportion of the population 75 years or older was 9% in Sweden in 2012. Community-dwelling older adults and nursing home residents in Sweden use on average 8–10 different drugs [1]. A large proportion of them use the multi-dose drug dispensing (MDD) system. This system involves machine-packaging all the medications that the patient should take at any particular time together in small labelled plastic bags. This packaging is done at a regional pharmacy dispensing centre and means that nurses are not involved in drug dosage preparation [22]. The use of the MDD system ensures a more reliable source of a patient's active medication list [23].

This study aimed to explore the association between the drugs on the NBWH list of FRIDs and ODs and falls in Swedish elderly community-dwelling and nursing home patients.

Table 1 Fall risk-increasing drugs (FRIDs) and drugs that may cause or worsen orthostatism (ODs) according to the list from the Swedish National Board of Health and Welfare (NBHW)

ATC* code	Drugs/group of drugs
Increase the fall risk	
NO2A	Opioids
N05A (NO5AN excluded)	Antipsychotics (lithium excluded)
N05B	Anxiolytics
N05C	Hypnotics and sedatives
N06A	Antidepressants
May cause or worsen orthostatism	
C01D	Vasodilators used in cardiac diseases
C02	Antihypertensives
C03	Diuretics
C07	Beta blocking agents
C08	Calcium channel blockers
C09	Renin-angiotensin system inhibitors
G04CA	Alpha-adrenoreceptor antagonists
N04B	Dopaminergic agents
N05A (NO5AN excluded)	Antipsychotics (lithium excluded)
N06A	Antidepressants

*Anatomical Therapeutic Chemical classification system.

Methods

Patients and settings

Patients included in the study were users of the MDD system [23], aged 75 years and older, living in nursing homes or in their own homes with municipally provided home care.

Patient data were collected from a separate randomised controlled trial (RCT) examining whether multiprofessional drug reviews including a pharmacist could improve the quality of pharmacotherapy among elderly primary health care patients [24]. At baseline, nurses completed a symptom checklist using the Pharmacotherapeutical Symptom Evaluation 20 (PHASE-20) tool [25] and sent the results to a pharmacist participating in the study. PHASE-20 includes 20 questions and is designed to identify drug-related symptoms (Additional file 1) [25]. For this study, all intervention and control patients from the aforementioned study [24] were included. Information on baseline characteristics, such as age, sex, residency, locomotion and blood pressure, was extracted from the PHASE-20 responses.

The study received ethical approval from the Regional Ethical Review Board in Lund (no. 2011/245).

Data collection

The patients were recruited to the RCT between September 1 and December 16 2011.

Data collection for the present study was conducted between September 1 2012 and February 15 2013. Baseline drug lists were screened for FRIDs and ODs according to the NBHW list. To facilitate the identification of FRIDs and ODs, a list of all generic names and product names was created. All identified drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system [26]. Every drug was counted as one with its unique ATC code regardless of the dosage or number of pills for the individual patient. Data on FRIDs and ODs were collected and analysed separately due to the distinction made by the NBHW and the fact that drugs from certain ATC groups (e.g. antipsychotics) appear on both the FRID and OD lists.

The data for reported falls and severe falls were collected. Reported falls were defined as falls during the past three months reported by the nurse in the patient's PHASE-20 checklist evaluation. Severe falls were defined as falls leading to emergency visits at hospitals or hospital admission as a consequence of syncope, contusion or bone fracture during the previous year as documented in the patient's EMR. Data on hospital admissions and hospital emergency visits relating to falls during the year prior to inclusion in the study were collected from the patient's hospital electronic medical records (EMRs).

Data analysis

Primary outcome measures were incidence of falls as well as numbers of FRIDs and ODs in fallers and non-fallers. The secondary outcome measure was distribution of drug types among FRIDs and ODs. Data were analysed using Student's t-test and Fischer's exact test for two-group comparisons, and multiple linear regression (backward method) analyses. In the two regression analyses FRIDs and ODs were used as the respective dependent variables while age, gender, place of living, number of drugs and severe falls were entered as independent variables. A significance level of $a = 0.05$ was chosen. All data were analysed using IBM SPSS version 20.0.

Results

Seventy-six percent of the 369 included patients were women and the mean age was 87.4 (SD 5.7) years. A majority (76%) were living in nursing homes. Table 2 shows the baseline data for the patients.

The patients were prescribed a mean of 2.2 (SD 1.5) FRIDs according to the FRID list of the NBHW and 2.0 (SD 1.6) drugs from the OD list of the NBHW. Only 13% of the study sample had no drugs prescribed from the FRID or OD lists. Data collected from the PHASE-20 symptom checklist were available for all 369 patients.

Table 2 Baseline characteristics of the study sample

Characteristic	Patient sample
Patients, N	369
Female, N (%)	280 (76)
Age (years), mean (SD)	87.4 (5.7)
Residency, N (%)	
Nursing home	279 (76)
Community	90 (24)
Mean no. of drugs, N (SD)	11.8 (4.5)
No. of continuous drugs	9.5 (3.9)
No. of drugs as needed	2.3 (1.8)
Locomotion, N (%)	
Ambulatory	204 (72)
Chair-bound	76 (27)
Bed-bound	2 (1)
Blood pressure (mmHg), mean (SD)	
Systolic	130 (19.5)
Diastolic	70 (11.5)

Almost four in ten patients experienced moderate to severe dizziness, unsteadiness or fatigue. Data about reported falls from the PHASE-20 assessment were only available for 275 patients (75%). Twenty-nine percent of these patients reported at least one fall in the three months prior to the PHASE-20 evaluation. More men reported falls during the past three months. There were no differences between patients who reported falls and those who did not fall during the past three months with regard to age, total number of drugs and place of living (Table 3).

There were no significant differences between total number of drugs, number of FRIDs, number of ODs or blood pressure between community-dwelling and nursing home patients when performing a Student's t-test.

Data for severe falls collected from the patients' EMRs were available for all 369 patients. Seventeen percent had at least one severe fall during the previous year. Severe falls were more common in nursing home patients as compared to community-dwelling elderly patients. More women experienced severe falls.

Two multiple linear analyses with number of FRIDs and ODs as dependent variables were performed (Table 4). They showed positive associations between the number of FRIDs and the total number of prescribed drugs ($p < 0.01$) and severe falls ($p < 0.01$). Being female was associated with a higher number of FRIDs ($p = 0.03$). Associations were found between the number of ODs and both the total number of prescribed drugs ($p < 0.01$) and community dwelling ($p = 0.02$). No association was found between the number of ODs and the occurrence of severe falls.

Seventy-four different drugs were prescribed to patients among the total number of 1533 FRIDs. The five

Table 3 Comparisons between fallers and non-fallers regarding age, sex, place of living, number of drugs, FRIDs and ODs

Outcome variable	Falls during the last 3 months before the symptom evaluation			Falls leading to emergency visits or hospital admissions during the last 12 months		
	Falls	No falls	P value	Falls	No falls	P value
Sex, N (%)						
Male	31 (44)	39 (56)	<0.01*	4 (4)	85 (96)	<0.01*
Female	50 (24)	155 (76)		58 (21)	222 (79)	
Age, mean (SD)	87.2 (5.7)	87.2 (5.4)	0.97**	87.8 (5.6)	87.3 (5.7)	0.53**
Place of living, N (%)						
Nursing home	53 (26)	149 (74)	0.07*	56 (20)	223 (80)	<0.01*
Community	28 (38)	45 (62)		6 (7)	84 (93)	
No. of drugs, mean (SD)						
Total	11.5 (3.8)	11.8 (4.8)	0.58**	12.6 (4.4)	11.6 (4.5)	0.12**
Continuous use	9.5 (3.6)	9.2 (4.0)	0.64**	9.8 (3.5)	9.4 (3.9)	0.39**
As needed	2.0 (1.4)	2.5 (2.0)	0.01**	2.7 (2.1)	2.2 (1.6)	0.08**
No. of FRIDs[1], mean (SD)						
Total	2.4 (1.5)	2.0 (1.4)	0.06**	2.7 (0.7)	2.0 (0.6)	<0.01**
Continuous use	2.0 (1.4)	1.6 (1.2)	0.02**	2.1 (1.4)	1.6 (1.3)	<0.01**
As needed	0.4 (0.6)	0.5 (0.7)	0.41**	0.5 (0.7)	0.4 (0.6)	0.13**
No. of ODs[2], mean (SD)						
Total	1.8 (1.4)	2.0 (1.6)	0.26**	1.7 (1.5)	2.0 (1.5)	0.15**
Continuous use	1.6 (1.3)	1.7 (1.4)	0.38**	1.4 (1.2)	1.7 (1.3)	0.05**
As needed	0.2 (0.4)	0.2 (0.4)	0.28**	0.2 (0.4)	0.2 (0.4)	0.36**

*Fishers exact test.
**Student's t-test.
[1]FRIDs = Fall risk-increasing drugs according to the NBHW.
[2]ODs = Drugs that may cause or worsen orthostatism according to the NBHW.

most frequently prescribed drugs among the FRIDs and ODs in the NBHW lists had the ATC codes N (Nervous System) (54.1%) and C (Cardiovascular System) (45.6%). The frequency and percentage of the different ATC groups among prescribed FRIDs are presented in Table 5. For the FRID list of the NBHW, the five most frequent prescribed FRIDs were oxazepam (n = 151), citalopram (n = 113), zopiclone (n = 104), mirtazapine (n = 68) and zolpidem (n = 44).

Discussion

Main findings

Patients who had fallen were prescribed a higher number of continuous-use FRIDs than patients with no reported falls. A significant proportion (87%) of the study sample was taking FRIDs and ODs, as in other studies [27]. More men reported falls during the past three months; however, more women suffered from severe falls leading to emergency visits or hospital admission during the past year.

Table 4 Regression models with FRIDs and ODs as dependent variables

Model	Dependent variable: FRIDs				
	Unstandardised coefficients		Standardised coefficients	Sig.	Model summary
	B	Std. error	Beta		
Female sex	−0.340	0.162	−0.099	0.037	Adjusted R squared = 0.225
No. of drugs	0.145	0.015	0.442	<0.001	
Severe falls	0.515	0.187	0.130	0.006	
Dependent variable: ODs					
No. of drugs	0.191	0.015	0.542	<0.001	Adjusted R squared = 0.313
Severe falls	−0.432	0.186	−0.102	0.152	
Community living	0.392	0.162	0.106	0.016	

Table 5 Frequency and percentage of ATC groups for FRIDs and ODs according to NBHW lists

FRIDs		
ATC*code	**Frequency**	**%**
N06A (Antidepressants)	238	29.4
N05B (Anxiolytics)	194	24.0
N05C (Hypnotics and sedatives)	187	23.1
N02A (Opioids)	142	17.5
N05A (Antipsychotics)	47	5.8
Total	808	100
ODs		
ATC*code	**Frequency**	**%**
C03 (Diuretics)	251	24.9
N06A (Antidepressants)	238	23.6
C01D (Vasodilators used in cardiac diseases)	136	13.5
C07 (Beta blocking agents)	129	12.8
C09 (Renin-angiotensin system inhibitors)	118	11.7
C08 (Calcium channel blockers)	64	6.3
N05A (Antipsychotics)	47	4.7
N04B (Dopaminergic agents)	22	2.2
G04CA (Alpha-adrenoreceptor antagonists)	4	0.4
C02 (Antihypertensives)	1	0.1
Total	1010	100

*Anatomical Therapeutic Chemical classification system.

The study sample had a high incidence of both reported falls during the last three months (29%) and severe falls (17%). The results are similar to previously published results [28]. Data for reported falls during the past three months might have included severe falls and this explains the higher incidence of reported falls.

Fallers used a higher number of FRIDs, consistent with the findings of similar studies [29]. It is difficult to compare FRID data between different studies, since there are several different FRID classifications. Other international FRID lists include analgesics, hypoglycaemics and urinary antispasmodics [30-32]. Since drugs from these classes were not included in the Swedish NBHW lists, our results may differ from studies using more extensive FRID and OD lists. We chose not to merge the FRID and the OD lists from the NBHW but to present the results separately, because some drugs (e.g. antipsychotics) are classified both as FRIDs and as ODs.

Female sex and residency in nursing homes were associated with severe falls. Due to low bone mass, the presence of osteoporosis and low muscle strength, females are more likely than males to experience a fall-related injury [33,34]. In our study, female sex was associated with a higher number of FRIDs and this might explain the association with severe falls. Nursing home patients have increased care needs due to cognitive impairment, multiple illnesses and the use of a high number of drugs, and might therefore be more prone to fall. Numbers of FRIDs and ODs were associated with the total number of drugs and with severe falls. This is in agreement with previous studies showing strong evidence of an association between the use of psychoactive drugs and falls in the elderly [18], as well as between polypharmacy and falls [10,35,36].

A majority of the patients were females, lived in nursing homes and had a high number of drugs, as in other studies [37].

Antidepressants and anxiolytics were the most frequently used FRIDs and have been previously found to predispose elderly patients to falling [38]. The most frequently prescribed FRID in the study sample was oxazepam. Due to their muscle-relaxing effects, benzodiazepines have been associated with an increased risk of hip fractures in the elderly [39]. Cardiovascular drugs such as the commonly prescribed diuretic furosemide can cause or worsen orthostatic hypotension. However, there was no association between the numbers of ODs and falls in this study.

Almost a third of the patients complaining of moderate to severe symptoms of dizziness or unsteadiness reported falling in the three months prior to the study, compared to less than 10% of those who had no complaints. This suggests that the PHASE-20 symptom checklist might be a useful tool to predict falls among elderly patients. One strength of this study is that the drug lists are accurate and compliance with prescribed drug therapy was high due to the use of the MDD system. The reliability of the data is high since it was collected in a standardized manner by a single individual. The studied sample was from several different geographic regions in Skåne, Sweden, which increases the generalizability of our results. PHASE-20 was found to have acceptable consistency, test-retest reliability and internal validity [25]. Nurses that used the symptom checklist (PHASE-20) had direct contact with the patients, which ensured more accurate description of their symptoms.

Limitations

A major limitation of the study is the cross-sectional design with collection of retrospective data about falls. Since no risk assessment tool was used, we are unable to stratify patients into low and high risk for falls. Data on patients' diagnoses were not collected. It is therefore hard to draw a firm conclusion as to whether the cognitive impairment itself or the treatment of its symptoms is associated with falls.

Another major limitation of the study is also the lack of geriatric assessment. The identification of cognitive impairment, comorbidity and functional disability would clarify the contribution of other potential factors in increased fall risk.

Another limitation is that we assessed data about number of FRIDs and ODs regardless of the defined daily dosage of each drug. More detailed drug information might have provided better understanding of whether drug dosage affects fall risk.

All patients were included in the fall evaluation, even though some of them were not ambulatory. This may have caused some bias, since the chair-bound and bedbound patients were not able to walk freely and were possibly less prone to falling.

Since the study is retrospective, it is not known what each study patient's drug profile was during the period prior to the PHASE-20 evaluation.

Future research

Interventions to optimize drug therapy in elderly patients with an emphasis on preventing falls would need to use a fall risk assessment tool including FRIDs to be able to stratify the patients into low and high risk of falling. A prospective study design would also confirm the strength of the association between exposure to FRIDs and subsequent falls.

All our patients used the MDD system. Although this system was originally developed to improve patient safety and drug compliance among those with multiple chronic co-morbidities, studies indicate that the use of the MDD system may be associated with a higher number of drugs, especially psychotropics [40], and poorer drug treatment. Future research should assess the possible effect of medication reviews with an emphasis on FRIDs and falls as a method to increase the quality of drug treatment in the elderly.

Conclusions

Falls were common in this study sample. Nursing home patients and women had higher rates of falls requiring emergency room visits or hospitalisations. The number of FRIDs and ODs were associated with the total number of drugs. Fallers had a higher number of FRIDs but there was no association between number of ODs and falls. Antidepressants and anxiolytics were the most frequently used FRIDs. Interventions to prevent falls in elderly patients with a focus on reducing the total number of drugs and withdrawing psychotropic medications might improve the quality of drug treatment in elderly primary care patients.

Additional file

Additional file 1: PHASE-20. PHArmacotherapeutical Symptom Evaluation, 20 questions.

Abbreviations

ATC: Anatomical therapeutic chemical; FRIDs: Fall risk-increasing drugs; MDD: Multi-dose drug dispensing; NBHW: National board of health and welfare; ODs: Drugs that may cause or worsen orthostatism.

Competing interests

The authors declare no competing interests.

Authors' contributions

VM, ÅB and MM participated in study design and coordination, data collection and statistical analysis, and drafted the manuscript. UJ, TW and PM participated in the design of the study and choosing of statistical analyses. All authors reviewed and approved the final manuscript.

Acknowledgements

We are indebted to Stephen Gilliver for his expertise and invaluable advice in proofreading the manuscript.

Disclaimer

The opinions or assertions in this article are the views of the authors and are not to be construed as official or as necessarily reflecting the views of the Swedish Medical Products Agency, where one of the authors is employed.

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Received: 20 August 2013 Accepted: 18 March 2014
Published: 27 March 2014

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doi:10.1186/1471-2318-14-40
Cite this article as: Milos *et al.*: Fall risk-increasing drugs and falls: a cross-sectional study among elderly patients in primary care. *BMC Geriatrics* 2014 **14**:40.

Paper III

Family Practice Advance Access published August 19, 2013

Family Practice
doi:10.1093/fampra/cmt043

Theory-based interventions to reduce prescription of antibiotics—a randomized controlled trial in Sweden

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Received 8 February 2013; Revised 24 June 2013; Accepted 18 July 2013.

Background. Upper respiratory tract infections (URTIs) are the most common reason for consulting a GP and for receiving an antibiotic prescription, although evidence shows poor benefit but rather increasing antibiotic resistance. Interventions addressing physicians have to take into consideration the complexity of prescribing behaviour.

Objective. To study whether interventions based on behavioural theories can reduce the prescribing of antibiotics against URTIs in primary care.

Setting and subjects. GPs at 19 public primary health care centres in southern Sweden.

Methods. We performed a randomized controlled study using two behavioural theory-based interventions, the persuasive communication intervention (PCI) and the graded task intervention (GTI), which emerged from social cognitive theory and operant learning theory. GPs were randomized to a control group or one of two intervention groups (PCI and GTI).

Main outcome measures. Changes in the rate of prescription of antibiotics against URTIs in primary care patients of all ages and in patients aged 0–6 years.

Results. No significant differences were seen in the prescription rates before and after the interventions when patients of all ages were analysed together. However, for patients aged 0–6 years, there was a significant lower prescription rate in the PCI group ($P = 0.037$), but not the GTI group, after intervention.

Conclusion. Theory-based interventions have limited impact on reducing the prescription of antibiotics against URTIs in primary care. Future studies are needed to draw firm conclusions about their effects.

Keywords. Antibiotics, behavioural change interventions, primary health care, upper respiratory tract infections.

Introduction

The use of antibiotics leads to both the emergence and spread of resistant bacteria.[1] Data from 26 European countries demonstrated a correlation between the use of antibiotics and the level of antibiotic resistance.[2] A Cochrane analysis from 2005 showed that there is no evidence for any benefits of antibiotic treatment against unspecific upper respiratory tract infections (URTIs) and that the risk of side effects outweighs the benefits.[3]

The danger of increasing antibiotic resistance has been recognized globally, resulting in extensive campaigns aimed at both prescribers and the public and in the development of treatment guidelines.[4]

URTIs are the most common reason to visit a doctor and to receive antibiotic prescriptions in Swedish primary care.[5] Although antibiotic prescribing has decreased and knowledge and awareness of resistance has increased among prescribers and the public, there is a need for strong actions both nationally and internationally to reduce the spread of antibiotic resistance. Different interventions to reduce prescribing that have been tested include educational programs for care givers,[6] web-based decision support tools[7] and even multifaceted strategies with audits, clinical

guidelines, patient education and point-of-care tests.[8] These interventions have had varying results.

A comprehensive 2005 Cochrane review of various interventions in primary care showed that efficient methods must be targeted to physicians, patients and the public and must also aim to influence barriers in the form of prescribers' behaviour and local therapy traditions.[9]

A recently published study from south-west Sweden on general physicians' perceptions of the treatment of infections in primary care showed a strong conviction of the importance of strict indications for the prescription of an antibiotic to maintain its effectiveness and for the benefit of the patient in the long run. The study also showed that doctors may have different views and may need different types of support.[10]

Application of psychological theories of behaviour[11,12] in order to understand and influence GPs' attitudes and behaviour in the prescribing situation is an exciting new approach that has not been sufficiently explored. Three theories have come into focus: the theory of planned behaviour, social cognitive theory (SCT) and operant learning theory (OLT).[13]

Assessing behaviour with a theory-based approach has been used, for example to increase knowledge of British GPs' attitudes towards testing and the factors that influence behaviour.[14] Such knowledge of the mechanisms underlying behaviour can be used to develop useful tools that can lead to a change of attitude and thus a change in behaviour.

Experimental studies have designed and validated survey instruments based on the three aforementioned theories of human behaviour.[15] In one study, examining physicians' knowledge, attitudes and self-efficacy and reinforcing it through targeted interventions improved behaviour in prescribing antibiotics for URTIs.[16] Two questionnaire-based instruments validated in a British–Canadian study[16] were designed to influence the attitudes that had previously been identified as important predictors of antibiotic prescribing by GPs for URTIs (self-efficacy, anticipated consequences and risk perception).

The aim of this study was to determine whether interventions based on behavioural theories can reduce the antibiotic prescription rate for URTIs in primary care in southern Sweden.

Methods

Design and participants

The study was designed as a randomized controlled trial (RCT) with a control group and two intervention groups.

Study population

Primary care in southern Sweden is provided by 91 public and ~40 private primary health care centres (PHCCs). For practical reasons, as to facilitate inclusion, we invited all public PHCCs to participate in this study by informing their managers by mail and in meetings. Twenty-two PHCCs agreed to participate and were blindly randomized into three groups. The randomization was performed at the PHCC level to ensure that the participants within each practice received the same intervention and was stratified by the number of listed inhabitants for each PHCC. Each PHCC was blindly allocated to one of the three groups consecutively starting with the largest one. The smallest PHCC was allocated to the group with least listed inhabitants totally to ensure equivalence of groups. The randomization at the PHCC level was used to avoid contamination by applying the changed behaviour in treating not included patients that might have happened by using individual patient randomization.

Interventions

Questionnaire-based behaviour change interventions that had been validated in a previous experimental study were translated into Swedish, back-translated into English for verification and sent to the GPs by mail. All groups received a questionnaire assessing attitudes, beliefs and subjective norms.[16] The control group received only this questionnaire. In addition to this, the first intervention group also received the graded task intervention (GTI)[16] addressing the GP's belief in his/her capabilities to manage URTIs without prescribing an antibiotic. GTI had a first part including a set of questions and a second part asking the GP to describe a difficult situation of managing a patient with URTI without prescribing antibiotics and how to handle it. It used graded task behaviour change techniques: rehearsal and action planning (SCT). The aim of this intervention was to reinforce GP's confidence in their ability to manage URTIs without antibiotics. The second intervention group received the questionnaire addressing attitudes, beliefs and subjective norms and also the persuasive communication intervention (PCI)[16] with the aim of influencing the GP's belief about the positive consequences of managing URTIs without prescribing an antibiotic (OLT and SCT). The skill acquisition approach as a training method and therefore an intervention was thus based on the questionnaires.

The questionnaire survey ran from 1 December 2011 to 15 February 2012 and was posted to GPs with a letter of invitation. Anonymous completed questionnaires were collected by the PHCCs' managers and were returned by post to the head researcher in order to maintain the group randomization. Two reminders were sent by mail during the data collection.

URTIs were defined in the questionnaires as common cold, pharyngitis, tonsillitis, acute otitis media, sinusitis and laryngitis.

Outcome measures

The main outcome measure was the prescription rate (the number of antibiotics for URTIs per 1000 inhabitants listed at the PHCC) in primary care patients of

all ages and in patients aged 0–6 years old. Prescription rates were compared before and after the intervention and between the groups. The following antibiotics, classified by therapeutic group based on the World Health Organization's Nordic Anatomical Therapeutic Chemical Classification Index codes,[17] were included: tetracycline (J01A), beta-lactamases sensitive penicillin (J01CE), combinations of penicillins (J01CR), macrolides (J01FA), lincosamides (J01FF), broad-spectrum penicillin minus mecillinam (J01CA) and first- to fourth-generation cephalosporins (J01DB-DE). Secondary outcome measures were GP's gender and years of experience. The predictive measures emerging from the theoretical constructs were as follows: behavioural intention, attitudes, subjective norm, perceived behavioural control, risk perception, self-efficacy, anticipated consequences, evidence of habits and prior planning. Different items in the questionnaire measured these variables on a 7-point Likert scale from *Strongly Disagree to Strongly Agree* or from 0 to 10, as designed in the experimental model.[16] A composite variable was created as a behavioural intention score from items with different scales by converting the item scores to *z*-scores and summing them (Table 1).[16]

Statistical analysis

The study was powered to detect a 10% difference between the control group and the intervention groups. There are ~400 antibiotic prescriptions per 1000 inhabitants in Skåne every year, of which 250 are antibiotics for URTIs. At least 10 500 inhabitants were required in each group to have 80% power to detect an effect size of 0.8 with a significance level of 5%. In Sweden, the size of a PHCC can vary between 4000 and 16 000 listed inhabitants, and we estimated that at least five PHCCs in each group would be sufficient.

Prescribing data on dispensed drugs were collected from the Swedish National Pharmacy Register. Antibiotic prescription data for the three groups for January–June 2011 were compared with data for January–June 2012 (after the intervention) in order to eliminate confounding due to seasonal variation URTI incidence during the year.

Table 1 *Summary of the theoretical constructs used as predictive measures*

Variable (number of questions)	Example item(s)
Theory of planned behaviour (TPB) Ajzen[11]	
Behavioural intention (3 & 4). Two summary scores: sum of three and four items	I intend to manage patients with URTIs without prescribing an antibiotic (scored 1 to 7) Given 10 patients presenting for the first time with an URTI, how many patients would you intend to manage without prescribing an antibiotic? (Scored 1 to 10)
Attitude: Direct (3); Indirect (8 behavioural beliefs (bb) multiplied by 8 outcome evaluations (oe). The score was the mean of the summed multiplicatives.)	*Direct*: In general,: The benefits of managing patients with URTIs without prescribing antibiotics outweighs the harm *Indirect*: In general, managing a patient with an URTI without prescribing an antibiotic would reassure them (bb) × reassuring the patient is (oe: un/important)
Subjective Norm: I (5 normative beliefs (nb) multiplied by 5 motivation to comply (mtc) items. The score was the mean of the summed multiplicatives).	I feel under pressure to manage patients with an URTI without prescribing an antibiotic: from published literature (nb) × How motivated are you to do what the published literature states that you should (mtc: very much/not at all)?
Perceived behavioural control: direct (4); indirect (6)	*Direct*: Whether I manage patients with an URTI without prescribing an antibiotic is entirely up to me *Indirect*: I find it difficult to manage patients presenting with an URTI without prescribing an antibiotic who: Expect me to prescribe an antibiotic
SCT (Bandura[12])	
Risk Perception (3)	It is highly likely that patients with an URTI will be worse off if I manage them without prescribing an antibiotic
Outcome Expectancies: Behaviour (8×8). The score was the mean of the summed multiplicatives	*Behaviour*: See Attitude (Theory of Planned Behaviour)
Self-efficacy: Specific (6)	*Specific*: Without an antibiotic: How confident are you in your ability to manage patients with URTIs who have tried to self-medicate?
OLT	
Anticipated consequences (3)	If I routinely manage patients with URTIs without prescribing an antibiotic then, on balance, my life as a GP will be easier in the long run
Evidence of habit (2)	When I see patients with URTIs, I automatically consider managing them without prescribing an antibiotic

Data were analysed by analysis of variance (ANOVA), chi-square test and Student's *t*-test using IBM SPSS version 20.0. Outcome variables derived from the theoretical construct were measured using sum scores or *z*-scores.

Results

Twenty-two (35%) PHCCs were included in the study and were randomized (Fig. 1). All practices were multipractitioner surgeries. Completed questionnaires were returned by 84 (60%) of the 139 GPs. Nineteen practices (86%) responded with 60 365 (PCI), 51 077 (GTI) and 69 887 (control) inhabitants, respectively. The response rate was 68% (34 GPs) in the PCI group, 60% (21 GPs) in the GTI group and 54% (29 GPs) in the control group.

The PCI intervention was completed by 71% of the GPs in the PCI group. The first part of the GTI intervention was completed by 100% of the respondents; however, only 33% completed the second part.

The randomized groups did not differ significantly in terms of measures derived from the theoretical behaviour construct or demographic measures using chi-square test and Student's *t*-test(Table 2).

The rate of prescription tended to be higher in the control group and the GTI group post-intervention, and unchanged or lower in the PCI intervention group (Fig. 2). We used the test ANOVA to compare the antibiotic prescription rates in the three groups before and after the interventions.

ANOVA showed no effect of the interventions on prescription rates in patients of all ages. However, in patients aged 0–6 years, there was a significant lower prescription rate in the PCI group (P = 0.037) compared with the control group.

Discussion

This RCT found no significant changes in antibiotic prescription rate in the intervention groups compared with the control group when analysing patients of all ages, whereas a significantly lower rate in individuals aged 0–6 years in the PCI group compared with the control group. This result might be due to a higher incidence of viral URTIs in this age group and, thus, a higher proportion of unnecessary antibiotic prescriptions.

The first part of the GTI questionnaire was completed by all participants, while the second part, which included written reflection on and description of the strategies, showed a much lower rate of completion (33%). This is not surprising in a busy primary care setting, where time-consuming paperwork is not highly prioritized. It is difficult to know whether the low rate of completion of the questionnaire may explain the lack of effect on the prescription rate. Future studies should, however, take into consideration the importance of time when implementing interventions in primary care.

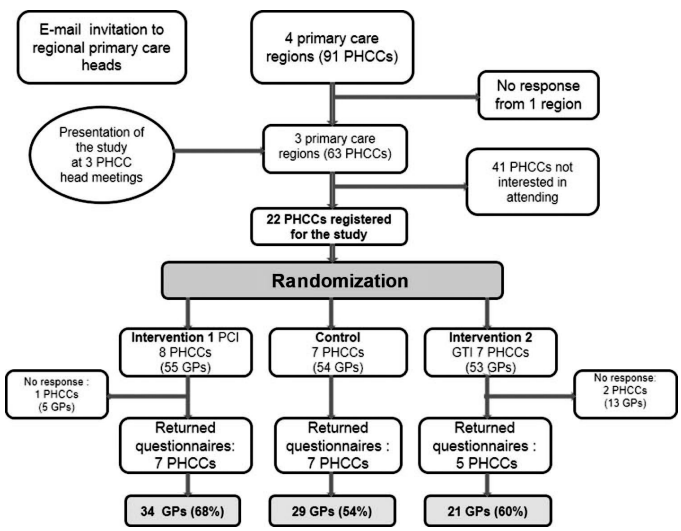

FIGURE 1 *Consort flow chart of the randomization process*

Table 2 *Baseline characteristics of the studied population*

Outcome measure	Control group	GTI	PCI	*P*-value
Demographic measure				
Age (%)				
<35	34.5	33.3	20.6	0.307[a]
36–45	27.6	23.8	23.5	—
46–55	17.2	9.5	20.6	—
>56	20.7	33.3	35.3	—
Gender, female (%)	72	47	55	0.185[b]
No. of GPs at the practice; mean (range; SD)	8 (4–11; 2.3)	7 (4–10; 2.1)	7 (1–12; 2.5)	0.272[b]
No. of ordinary GPs; mean (range; SD)	5 (1–8; 2.6)	5 (2–8; 2.1)	5 (3–7; 1.4)	0.955[b]
Years of experience (%)				
<10	41.4	52.4	35.3	0.306[b]
10–20	34.5	23.8	23.5	—
>20	24.1	23.8	41.2	—
Measures derived from the theoretical constructs; mean (range; SD)				
Behavioural intention	0.15 (–4.2 to 1.1; 1.5)	0.1 (–5.6 to 19.4; 4.8)	–0.18 (–4.9 to 1.1; 1.5)	0.881[b]
Attitudes—direct	10 (3–16; 2.5)	10.5 (9–14; 1.7)	10.1 (7–16; 2.4)	0.726[b]
Attitudes—indirect	188 (109–251; 34)	189 (90–281; 45)	184 (103–261; 43.6)	0.893[b]
Subjective norm	87.7 (18–180; 51.1)	69.2 (12–169; 44.7)	87.1 (22–158; 38.6)	0.281[b]
Perceived behavioural control—direct	16.7 (7–27; 5.6)	16.1 (6–26; 6)	16.4 (7–26; 4.5)	0.938[b]
Perceived behavioural control—indirect	15.2 (4–21; 4.2)	15.9 (1–20; 4)	16.5 (9–22; 3.8)	0.437[b]
Risk perception	3.3 (2–14; 2.6)	3.5 (2–10; 2.2)	3.8 (2–14; 2.6)	0.678[b]
Self-efficacy	31.1 (16–39; 5.6)	31.5 (23–41; 4.9)	30.8 (23–41; 4.6)	0.869[b]
Anticipated consequences	7.7 (2–10; 1.6)	6.9 (2–9; 1.9)	7.9 (4–14; 1.8)	0.112[b]
Evidence of habit	10.6 (2–14; 3.2)	9.5 (2–14; 3.1)	10.9 (7–14; 2.2)	0.213[b]
Prior planning	6.1 (3–7; 1.2)	5.7 (1–7; 1.5)	6 (2–7; 1.1)	0.639[b]

[a]Chi-square test.
[b]Student's *t*-test.

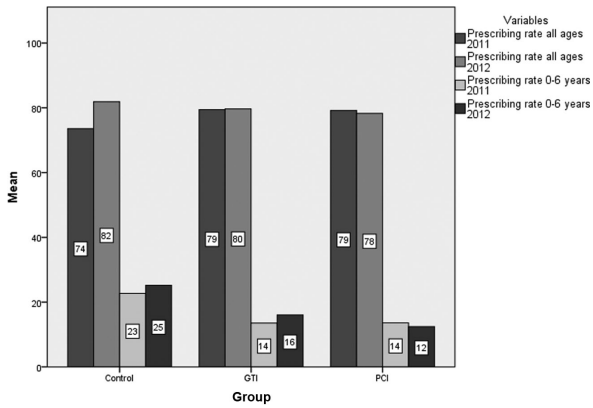

Figure 2 *The prescription rates (number of prescriptions/1000 listed inhabitants in 6 months) in 2011 (before the interventions) and in 2012 (after the interventions)*

A strength of this study is the randomization process, which ensured equivalence of the studied groups in terms of demographic variables and variables derived from the theoretical construct. Another strength of this intervention was the possibility to study the effect on everyday clinical work and to reach a large number of

GPs in a large geographical area by means of e-mail questionnaires. An Irish study showed that postal prescribing feedback had the same effect on antibiotic prescription rate and the same cost-effectiveness as academic detailing,[18] indicating that this kind of intervention might have a large impact on the prescribing behaviour.

Only 60% of the GPs returned their questionnaires, a similar response rate to that in an experimental study evaluating the intervention instruments.[16] It is important to mention that the instruments were developed for and tested on British GPs using simulated patient cases. Using British intervention materials means that we are assuming that the predictors of clinician behaviour are the same in Sweden as they are in the UK. This might be true, but further research with Swedish GPs is needed to develop interventions targeted for this group. Lack of similar studies upon the effect of these instruments in GPs' everyday work makes it difficult to compare results. Furthermore, we cannot draw conclusions if our theory-based interventions are better than non-theory-based interventions. We have only comparisons with a control group.

A major limitation of our study is that the outcome measure was the rate of prescription of antibiotics used against respiratory tract infections, which also includes prescriptions for lower respiratory tract infections. At the time of the study, there was no possibility to collect data on antibiotic prescribing related to patient diagnose and therefore to assess more accurately the cause of prescribing. This could have affected the results for individuals of all ages, in which there were minor differences after the interventions. A better effect was noticed in individuals aged 0–6 years, in whom the majority of respiratory infections are URTIs and therefore an assumed antibiotic overprescribing.

Another limitation of the study is that the outcome measure (antibiotic prescribing rate) was for whole practice populations, regardless of the number of GPs who were exposed to the training intervention.

The study is assessing the effect of clinician training using theory-based behavioural change techniques and the actual delivery as an effect of the interventions is difficult to measure.

Audit-based methods to enhance GP learning and behavioural change in antibiotic prescribing have shown effects;[19] however, it is important to mention that the high rate of prescription of antibiotics against URTIs is a complex phenomenon. Different interventions to improve compliance to guidelines for rational use of antibiotics have been tested, but it is not yet clear which is the most effective and why.[20] Interventions to change it should be multifaceted and must address health care providers, patients and decision makers at governmental level. Apart from engaging GPs in creating flexible and feasible guidelines in primary care, future studies need to focus even on implementing the interventions in a multinational scale.[21]

A meta-ethnographic assessment of different interventions concluded that it is important to allow GPs to reflect on their own prescribing, and to educate GPs about appropriate prescribing and the benefit of implementing it in practice, in order to enhance the acceptability of the interventions.[22] However, theory-based interventions have not previously been tested in clinical everyday practice and therefore it is difficult to compare results. Future research should focus on evaluating this model of approach to reduce the prescription of antibiotics against URTIs.

Conclusion

Theory-based interventions for reducing prescribing of antibiotics against URTIs in primary care are of limited value, however, an interesting yet insufficiently explored approach that might improve adherence to treatment guidelines and rational use of antibiotics.

Acknowledgements

We want to thank Susan Hrisos and associates for giving permission to use the questionnaire booklets and providing important suggestions for the evaluation of the results.

Declaration

Funding: STRAMA (Strategic Programme against Antibiotic Resistance in Sweden).
Ethical approval: Declaration of Helsinki Regional Ethical Review Board, Lund, Sweden (2011/431).
Conflict of interest: none.
Disclaimer
The opinions or assertions in this article are the views of the authors and are not to be construed as official or as necessarily reflecting the views of the Swedish Medical Products Agency, where one of the authors is employed.

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Paper IV

Title page

Swedish general practitioners' attitudes towards treatment guidelines – a qualitative study

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Abstract

Background Drug therapy in primary care is a challenge for general practitioners (GPs) and the prescribing decision is influenced by several factors. GPs obtain drug information in different ways, from evidence-based sources, their own or others' experiences, or interactions with opinion makers, patients or colleagues. The need for objective drug information sources instead of drug industry-provided information has led to the establishment of local drug and therapeutic committees. They annually produce and implement local treatment guidelines in order to promote rational drug use. This study describes Swedish GPs' attitudes towards locally developed evidence-based treatment guidelines.

Methods Three focus group interviews were performed with a total of 17 GPs working at both public and private primary health care centres in Skåne in southern Sweden. Transcripts were analysed by conventional content analysis. Codes, categories and themes were derived from data during the analysis.

Results We found two main themes: *GP-related influencing factors* and *External influencing factors*. The first theme emerged when we put together four main categories: *Expectations and perceptions about existing local guidelines*, *Knowledge about evidence-based prescribing*, *Trust in development of guidelines*, and *Beliefs about adherence to guidelines.* The second theme included the categories *Patient-related aspects*, *Drug industry-related aspects*, *and Health economic aspects*. The time-saving aspect, trust in evidence-based market-neutral guidelines and patient safety were described as key motivating factors for adherence. Patient safety was reported to be more important than adherence to guidelines or maintaining a good patient-doctor relationship. Cost containment was perceived both as a motivating factor and a barrier for adherence to guidelines. GPs expressed concerns about difficulties with adherence to guidelines when managing patients with drugs from other prescribers. GPs experienced a lack of time to self-inform and difficulties managing direct-to-consumer drug industry information.

Conclusions Patient safety, trust in development of evidence-based recommendations, the patient-doctor encounter and cost containment were found to be key factors in GPs' prescribing. Future studies should explore the need for transparency in forming and implementing guidelines, which might potentially increase adherence to evidence-based treatment guidelines in primary care.

Keywords

Qualitative research, focus groups, guidelines, attitudes, primary care, GPs, adherence, drug therapy

Background

Drug therapy in primary health care is a large field and a challenge for the medical world, pharmacists, related authorities and, most important of all, patients. The elderly population is increasing and so therefore is the need and importance of safe pharmacotherapy, with a focus on evidence-based medicine.

The broad skills of Swedish general practitioners (GPs) allow them to manage a vast spectrum of diseases and problems, with care accounting for patients' complex needs. Following evidence-based medicine principles while maintaining the holistic view of the individual without risking patient safety are aspects a GP needs to consider in every prescribing decision. The challenge of continuously improving drug therapy while also meeting increasing pharmaceutical costs has resulted in both national and regional reforms in Sweden. These reforms include prescribing guidance and financial incentives in order to improve adherence to drug therapy recommendations [1]. Evidence-based treatment guidelines have been developed and are available for both primary and secondary care in Sweden.

GPs work in a broad medical field and therefore have a complex way of seeking medical information, with more direct patient-oriented care questions, which might differ from those of colleagues in other specialities who search for information from journals and other literature or by corresponding with colleagues [2]. However, GPs also base their decisions on "mindlines", which are collectively reinforced, internalized, tacit guidelines, developed from own experiences or from interactions with colleagues, patients or pharmaceutical industry representatives [3]. This suggests that both formal and informal networking might influence prescribing behaviour.

Although GPs are aware of the guidelines, clinical inertia can lead to a conservative attitude [4]. Prescribing behaviour can vary a lot and the causes of the variation can be complex. Unlike GPs in other European countries such as the Netherlands, Denmark and Norway, Swedish GPs work in public or tax-financed private multidisciplinary surgeries with several physicians, registered nurses and physiotherapists. Each surgery is given economic responsibility by the county council. While the structure of primary care demands financial responsibility on the part of physicians, there are efforts to meet patients' needs and wishes and also to increase confidence in GPs. Due to the patient-centred approach used in Swedish

primary care during recent decades, non-medical factors can influence the prescribing decision, such as organisation structure or patient age and gender [5]. Another aspect is that although GPs believe that costs should be taken into account when prescribing, they are considered secondary to clinical effectiveness and safety, whilst individual patient need is emphasized above other forms of rationality or notions of opportunity costs. Conflict might be apparent between a policy of cost containment and GPs' resistance to cost-cutting [6]. At the same time, influences from both patients and the pharmaceutical industry put pressure on the doctor [7]. An interesting phenomenon is that physicians deny changing their prescribing habits according to patients' wishes as a result of advertising from the pharmaceutical industry addressed directly to the public, but feel pressure to justify their prescribing habits [8]. Meanwhile, doctors with the most visits per week are the most likely to prescribe medicines according to patients' wishes, even though they do not consider finding a medical reason for that [9]. Another important aspect is that GPs in Sweden do not have a gatekeeper role and the patients are free to consult other specialists without a referral [10]. The patients' drug list might thus contain drugs prescribed by several physicians. According to the regulations of the Swedish National Board of Health and Welfare, the GPs have the responsibility for their own prescribed drugs, but should even, if possible, inform themselves about other drugs that the patient uses and assess whether the current prescription is appropriate [11]. However, GPs' understanding of responsibility for patients' medication lists varies [12] and lower adherence to medication guidelines could potentially arise. The prescribing decision is therefore multifaceted and strategies that influence prescribing patterns must take the abovementioned underlying factors into account.

In the Swedish county of Skåne, the local drug and therapeutic committee (DTC) develops treatment guidelines and publishes an annual list containing recommended drugs based on medical evidence but also economic considerations. The DTC works within multidisciplinary networks including GPs, secondary-care specialists, district nurses and pharmacists. The networks provide medication guideline lists for different specialities such as urology, psychiatry and dermatology, and sub-specialties of internal medicine such as endocrinology and ischemic heart diseases. They present the guidelines in a small booklet. More detailed background information is available in print and on the internet. Each network includes at least one GP. There is a special section for drug therapy in the elderly, including dosage reduction recommendations and a list of potentially inappropriate medications in elderly patients. This is especially important since multi-morbidity and polypharmacy are common in the elderly, which means that multiple treatment guidelines have to be taken into account.

In addition to the published list, the guidelines are also spread through academic detailing at primary care centres and an annual local informative conference.

There is no clear evidence that locally developed guidelines have a better effect on GPs' adherence to evidence-based medicine compared to national guidelines, and there is an ongoing debate in Sweden as to whether the DTCs should focus on a consensus national list instead of each providing one list [13]. However, the role of knowledge exchange through professional networking has been suggested to be an important factor for transferring evidence into practice [14].

To increase compliance with local treatment guidelines, it is important to get a deeper understanding of GPs' attitudes to them. Previous Swedish research has explored Swedish GPs' attitudes towards evidence-based guidelines in general using focus groups as the study approach [15]. The aim of this study was to explore GPs' attitudes towards locally developed treatment guidelines and the factors that affect adherence.

Methods

In previous studies we assessed the effects of different intervention methods on GPs' adherence to medication guidelines [16] [17]. The qualitative design of the present study was chosen in order to get a deeper understanding of Swedish GPs' attitudes towards local guidelines.

Focus groups have been widely used as an effective technique to explore the attitudes and needs of medical staff [18]. The method uses open-ended questions, allowing participants to approach the studied issues from a personal point of view. However, the debate within the group facilitates expression of beliefs and attitudes left undeveloped in an individual interview.

For practical reasons we chose to invite pre-existing focus groups of GPs with different experiences and genders, working at both private and public health care centres. The GPs didn't interact with each other on a daily basis but had regular meetings every month. Formal approval was obtained from the local DTC, which develops and publishes treatment guidelines annually.

Three focus group interviews were held. The first interview was performed by a moderator (ELS) with prior experience of leading focus group interviews. An assistant (VM) took notes during the interviews in order to recall impressions of non-verbal communication between the participants during the analysis. The researchers switched roles in the second and third

interviews. All three interviews were performed using a semi-structured interview guide.

Participants

The GPs in the focus groups were recruited to the study through an invitation letter. In Skåne, GPs from both public and private health care centres have the possibility to meet regularly in previously established continuing medical education (CME) groups to discuss patient cases or different medical, practical or scientific issues [19]. Because of the assumed difficulty in creating new groups, we strategically invited all the pre-established CME groups in Skåne to participate in the study. The groups usually contain 6-12 GPs of different age, gender and experience, from different public and private health care centres. The groups are used to interacting and debating, and feel comfortable expressing and sharing opinions. The invitation letter, sent by e-mail, contained information about the aim of the study and an informed consent form, and offered the possibility to perform the interviews at the CME group's regular time and place of meeting.

Interview questions were created with an emphasis on the following themes:

- Attitudes towards guidelines
- The impact of using guidelines on the doctor-patient relationship

Analysis

The interviews were audio recorded, transcribed verbatim and studied by the first and last authors using thematic content analysis [20] [21]. After the transcribed interviews and additional notes had been read, the text was divided into meaning units and condensed. Units with similar content were compiled into different sub-categories, categories and themes, and the results were discussed until a consensus was reached. The method is conventional inductive content analysis with codes and categories derived from data during analysis [22].

Ethical approval

The study has received ethical approval from the Regional Ethical Review Board in Lund (case no: 2013/392).

Results

Three focus group discussions were held with a total of 17 participants, with 5, 5 and 7 GPs in groups 1, 2 and 3, respectively. The characteristics of the participants are shown in Table 1. An example of the text condensation in meaning units is shown in Table 2.

Seven categories emerged during the coding process (Table 3). The categories were grouped into two main themes: **GP-related influencing factors** and **External influencing factors**.

GP-related influencing factors

The first category included in this theme was ***"Expectations and perceptions about existing local guidelines"*** (Table 4). GPs stated unanimously during the discussions that they perceive guidelines as a form of support, that they do not feel bound by them but feel safe when using them. They also stated that they feel free to deliberately deviate from guidelines if necessary and expected the existence of second and third choice drug on the list of recommended drugs. Several GPs expressed a belief that the aim of guidelines was cost containment and also that guidelines focus primarily on drug costs and not on the patient. A majority of GPs perceived the local guidelines as time saving.

The second category was ***"Knowledge about evidence-based prescribing"***. Although participants unanimously agreed that drug treatment should be evidence based, all of them reported a lack of time to self-inform about new drugs or therapy recommendation changes. They also revealed different levels of knowledge about the existence of and use of IT-based guidelines. All the GPs reported easy access to guidelines in a paper folder and welcomed the annual DTC-arranged conference with information about guidelines.

The category ***"Trust in development of guidelines"*** showed that all the GPs welcomed the detailed background information following the guidelines. They reported that they felt more prone to adhere to guidelines when informed about the decision process presented by the DTC based on background research about the recommended drugs. A historic change in attitude towards the DTC among GPs was described, with a more positive attitude and greater trust during recent years. Different levels of knowledge about how the guidelines were formed were revealed; however, trust in the DTC was described as being more important. Several GPs expressed curiosity about the structure of the local DTC and its work on developing guidelines.

A recurrent subject, spontaneously discussed by all three groups, was the existence of local guidelines, with emphasis on the risk for unequal care in Sweden. Even if most GPs agreed about the importance of local experience and increased adherence if guidelines were local, some GPs were concerned with different prescribing habits in different regions and the consequences for the patients, such as different access to expensive drugs.

An interesting aspect is that most of the GPs reported caution with trying new drugs, using patient safety as an argument; however, they agreed that the introduction of new therapies might be delayed if primary care waits for secondary-care specialists to prescribe them, e.g. drugs for treatment of diabetes.

The category ***"Beliefs about adherence to guidelines"*** revealed several dimensions with attitudes towards both GPs' own and others' prescribing. Most of the GPs agreed that prescriptions should be based on guidelines. The frequency of guideline updates was discussed and some GPs requested more frequent updates than the current annual ones, with faster introduction of new drugs. However, a majority of GPs reported lower adherence if recommendations changed often.

The first focus group had longer experience in primary care practice (Table 1). The second group included physicians with a great range of experience and the debate within the group was dominated by the more experienced GPs, the youngest having a more passive and confirmatory role. The third group, which included younger physicians with shorter experience, expressed a greater concordance of opinions regarding the acceptance of guidelines as a prescribing tool, explaining it as the result of early training in following evidence-based practice.

A majority of the participants expressed concerns about having difficulties managing other doctors' prescribing and feeling uncomfortable changing prescriptions according to guidelines if the patient had multiple prescribers. Some GPs described strong beliefs that guidelines were directed to primary care and were not compulsory for hospital doctors or private secondary care specialists.

External influencing factors

The first category in this theme was ***"Patient-related aspects"*** (Table 5), where patient safety was described as an important factor influencing the prescribing decision. A majority of GPs reported deviation from guidelines if a drug caused adverse drug reactions or if changing the drug would result in lower compliance with treatment. Patient safety was ranked as more important than maintaining a good patient-doctor relationship, e.g. regarding prescription of antibiotics. GPs reported the belief that patients' expectations might sometimes be different from those of doctors; however, it was unusual for patients to be unwilling to change drug therapy. A majority of GPs reported a belief that patients have more trust in drugs prescribed in hospitals, leading to difficulties in changing therapy according to guidelines in primary care. Some GPs felt uncomfortable about not being able to always meet patients' expectations. GPs also believed that patients might feel safe knowing that GPs adhere to guidelines but that patients usually have little knowledge about the existence of guidelines. Patient-adapted information about guidelines was believed to increase compliance and safety, to benefit the patient-doctor relationship, and to be a better alternative to drug advertising from the pharmaceutical industry. The importance of dialogue with the patient was a recurrent

issue and a majority of the GPs reported that guidelines facilitated the patient-doctor relationship.

The category ***"Drug industry-related aspects"*** included GPs' statements about difficulties in managing direct-to-consumer commercials about drugs and their impact on patients. Some GPs wondered about possible influences of the drug industry on the local DTC. The GPs described an historical change in how GPs get information about new drugs as a shift from information from the drug industry to objective academic detailing from the DTC.

The category ***"Health economic aspects"*** included GPs' statements about how economic considerations should or should not influence adherence to guidelines. The GPs expressed a feeling of economic responsibility for both patients and society, revealing a two-sided attitude and a dilemma faced in the prescribing situation.

Some GPs reported a belief that guidelines take cost efficiency into account more than patients' individual needs. A subject largely discussed in the groups was economic aspects in forming the guidelines. GPs expressed both reluctance and understanding, describing the economic perspective as both a barrier and a motivator for adherence to guidelines. A majority of the GPs reported understanding of the necessity of priorities in primary care, but also a negative attitude towards the influence of economic terms on the prescribing decision.

The core motivators for adherence to guidelines were found to be the time-saving aspect, trust in evidence-based market-neutral guidelines, patient safety and the feeling of economic responsibility for both patients and society. Main barriers to adherence were cost containment as a decision factor in developing guidelines, multiple prescribers with unclear responsibility for patients' medication lists and drug industry information addressed directly to the public.

Discussion

Main findings

We found two main themes describing GPs' attitudes towards local treatment guidelines: **GP-related influencing factors** and **External influencing factors**.

The attitudes were grouped into seven main categories: ***Expectations and perceptions about existing local guidelines, Knowledge about evidence-based prescribing, Trust in development of guidelines, Beliefs about adherence to guidelines, Patient-related aspects, Drug industry-related aspects, and Health economic aspects***. To rely on evidence-based guidelines and the time-saving benefit of using local guidelines were described as key motivating factors for adherence, suggesting that understanding of the development process

and easy access to local guidelines are factors with big implications for future guideline design and implementation. Patient safety was reported to be more important than adherence to guidelines or maintaining a good patient-doctor relationship. GPs described both positive and negative attitudes to cost containment, which was perceived both as a motivating factor and a barrier for adherence to guidelines. GPs expressed concerns about difficulties with adherence to guidelines while managing drugs from other prescribers and drug industry information addressed directly to the public.

Strengths and limitations

Previous research has focused on GPs' adherence to nationally developed guidelines [23] [24] [25], using a questionnaire-based approach. We found no previous qualitative research with focus groups studying GPs' attitudes towards adherence to local guidelines, which is a novel aspect of this study.

Focus groups as a qualitative research method have been approached from different theoretical point of views. For instance, social contextual constructivist researchers address the "process" of interaction among individuals, in a specific context in which people live and work, and recognize that the researcher's own background shapes their interpretation [26]. Social contextual constructivists emphasize the importance of the researcher's reflexivity and the context-dependent method. The realist theoretical framework focuses on reliability and validity in qualitative studies in order to present the presumed only existing reality [27]. Methodological tensions have been described between contextual constructionist and realist theory frameworks behind focus groups [28]. According to contextual constructionism, pre-existing groups may provide "naturalistic" exchanges by encouraging participation by people who are reluctant to be interviewed or feel they have nothing to say [18]. From a realistic point of view pre-existing groups should be avoided given their potential for bias [29]. We believe that the strategic use of pre-existing groups of GPs with different experience and gender, working at both private and public health care centres and with previous contact and familiarity with the debate within the group was a strength of the study. Five to seven participants are recommended for focus groups and we managed to include at least five GPs in each group. Since the aim of the study was to understand the factors that affect adherence to guidelines, and not to generalize the results, we consider 17 participants to be satisfactory. There was a general concordance of opinions within the groups; however, the interviews created a debate allowing the participants to express a great variety of attitudes towards particular issues, such as the frequency of updates and economic aspects, which increased the credibility of the results. These interesting aspects of different group dynamics suggest that

even if heterogeneous groups might facilitate a debate, great variation in professional experience is a possible limiting factor, less experienced doctors being more hesitant in expressing their opinions. However, including GPs with different levels of experience might have increased the transferability of the results of this study.

One of the researchers (VM) knew 12 of the 17 participants as colleagues, which could be both an advantage and an obstacle. Her role as a GP might have encouraged free debate due to an assumed mutual understanding of the cultural context the participants worked in. However, no specific reactions on this matter were discussed or observed. VM is also a member of the local DTC and her role as an objective researcher in the study with no links of an economic or employment nature was stressed prior to the interviews. She also explained her role as a researcher in order to avoid addressing debate questions related to her pre-understanding of the discussed topic. However, even if data collection and analysis were performed with objective reflexivity and with continuous awareness of her pre-understanding of the topic taken into account, this might have been a limitation of the study. The second researcher present during the interviews (ELS) had a background as a social worker and had no previous contact with the participants or pre-understanding of the studied subject. Due to the researchers' different levels of pre-understanding, they switched role during the interviews. This might have served as a strength by increasing the dependability of the results.

The GPs in this study reported strong adherence. However, international data show that GPs overestimate their adherence to guidelines, suggesting that self-reported adherence might not correlate well with actual prescribing behaviour and should not be used as the sole measure of guideline adherence [30]. No prescribing data were collected as we did not aim to assess prescribing behaviour. This means that we cannot draw any conclusions from this study about Swedish GPs' adherence to local guidelines.

Comparison with existing literature

As previously described in other studies, Swedish GPs often believe that treatment guidelines are useful in practice and generally have a positive attitude to them [24]. They see prompt and pragmatic benefits as a strong motivating factor, though differences exist between GPs [15]. However, a meta-analysis of qualitative research shows that GPs' attitudes towards treatment guidelines may be influenced by the purpose of the guidelines and that trust might be more important than access when implementing them [23], similar to the results in our study.

The GPs in this study did not report that adherence to guidelines would lead to a poorer patient-doctor relationship. The results are different from international data. A Canadian study showed that the use of recommendation lists based on a controlled replacement model led to

poorer patient contacts, increased stress for doctors and increased the frequency of contacts with the healthcare system [31]. A British study showed that a strong feeling of clinical autonomy and resistance to economic decisions caused a sceptical attitude towards clinical guidelines and that emphasis on cost-effectiveness might be counterproductive [32]. The participants in our study reported concerns about the negative effect of economic aspects in forming guidelines, findings similar to those of other studies [33]. However, cost containment was not frequently reported to be a negative factor in decision making or to affect the patient-doctor relationship. These findings, unlike those from other studies, might be due to the unique social and professional context Swedish GPs work in, in larger multi-professional surgeries with shared economic responsibility. However, the impact of different organisational contexts on GPs' attitudes towards adherence to guidelines was not studied in this paper. The results might also mirror the historical change in attitudes towards drug information. The participants described a paradigm shift in GPs' attitudes towards drug information sources during recent decades, with an increasingly positive attitude towards academic detailing provided by the local DTC instead of drug industry-supplied information. Younger GPs reported higher adherence to local guidelines. This is consistent with findings from a recent Swedish study [34], which showed that Swedish GPs who were older or had more experience were more positive to drug industry-supplied information than younger GPs. Frequent changes in recommendations were viewed both positively and negatively, with great variation between the participants. GPs reported trust in evidence-based guidelines, but also interest in the operations of the local DTC. However, they did not express opposition to a top-down managerial initiative about prescribing quality. Our findings indicate that transparency in forming guidelines, such as information about the structure and methods of the local DTC together with regular academic detailing about the guidelines, might increase confidence in the local DTC and thus enhance adherence. A recent Canadian study showed that GPs believe that involvement of frontline practitioners in developing guidelines might facilitate implementation by maximizing the objectivity of recommendations [35]. This suggests that increased knowledge among Swedish GPs about the structure of DTCs, which involve GPs in the development of guidelines, might further enhance adherence.

GPs described the patient-doctor encounter, with emphasis on informing the patient about guidelines if necessary, as very important. This factor has been found to enhance adherence to guidelines, such as recommendations for prudent antibiotic prescribing [36].

Conclusions

The Swedish GPs in this study reported that patient safety, the time-saving aspect, trust in evidence-based market-neutral guidelines and the patient-doctor encounter, with emphasis on informing the patient were core motivators for adherence to guidelines. Main barriers to adherence were cost containment as a decision factor in developing guidelines, multiple prescribers with unclear responsibility for patients' medication lists and drug industry information addressed directly to the public. Future studies should explore the need for transparency in forming and implementing guidelines, which might potentially increase adherence to evidence-based treatment guidelines in primary care.

List of abbreviations used

GP: General practitioner

DTC: Drug and therapeutic committee

CME: Continuing medical education

Competing interests

The authors declare that there is no conflict of interest. The first author (VM) was at the time of the study a member of Skåne County's DTC. The study was financed by funding from the Southern Medical District and Lund University.

Disclaimer: The opinions or assertions in this article are the views of the authors and are not to be construed as official or as necessarily reflecting the views of the Swedish Medical Products Agency, where one of the authors is employed.

Authors' contributions

VM and ELS were involved in the conception and design of the study, the acquisition, analysis and interpretation of data and the drafting of the manuscript, and have given final approval of the version to be published. TW and PM were involved in the conception and design of the study and the regular revision of manuscript drafts, and have given final approval of the version to be published.

Acknowledgements

We are indebted to Stephen Gilliver for his expertise and invaluable advice in proofreading the manuscript.

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Tables

Table 1. Characteristics of the participants

Focus group	Participant	Sex	Age	Age, median	Years of practice	Years of practice, median	Practice
1	A	F	57	54	20	20	Public
	B	F	54		25		Public
	C	F	50		15		Public
	D	F	45		16		Public
	E	F	58		30		*Private*
2	A	M	53	53	10	10	Public
	B	F	61		33		Public
	C	F	64		35		Public
	D	F	34		4		Public
	E	F	38		3		Public
3	A	F	35	40	7	5	Public
	B	F	48		5		Public
	C	M	41		10		Public
	D	F	48		5		*Private*
	E	M	35		5		Public
	F	F	40		8		Public
	G	M	33		2		Public

Table 2. Example of text condensation and coding

Theme	**GP-related influencing factors**		
Category	Beliefs about adherence to guidelines		
Final coding	Reported adherence behaviour in everyday practice		
Initial coding	High adherence if guidelines similar to own experience	Lower adherence if more frequent changes to guidelines	High adherence when feeling unsure
Condensed meaning unit	In the case of migraine drugs, when I did not have enough experience to say that the more expensive drugs were better, I supported my argument with the guidelines.	It was decided that the insulin kind would change to another, cheaper one, and soon afterwards it would change back again, but I have learned from previous experience and have not changed anything yet.	When I feel unsure I stick to the guidelines.
Meaning unit	"… and an area where I've benefited from them … (guidelines) … in agreement with the patient or against the patient's will … is when they want migraine drugs, triptans, more expensive ones … and when I didn't have enough experience to say that that the more expensive ones were better, I supported my argument with the guidelines then …"	"… we were supposed to change from the usual insulin that we had used many years to a cheaper one, and it is a lot of work if you are going to change it for all patients, and then after a couple of months they lowered the price of the first one, so there was no difference any more. But I have some previous experience and have not changed anything yet, but will wait and see what happens."	"You feel sometimes that you should be more informed, but if I feel unsure I stick to the guidelines."

Table 3. Categories and themes

Categories	Themes
Expectations and perceptions about existing local guidelines	**GP-related influencing factors**
Knowledge about evidence-based prescribing	
Trust in development of guidelines	
Beliefs about adherence to guidelines	
Patient-related aspects	**External influencing factors**
Drug industry-related aspects	
Health economic aspects	

Table 4. Categories and quotations for the theme "GP-related influencing factors"

GP-related influencing factors
Expectations and perceptions about existing local guidelines "… and then I feel free, that if it doesn't work with these basic drugs, it's not a problem to prescribe something else …" "… it is easy to check with the list … and maybe I don't have the same critical judgement as before, but on the other hand I save time, because I perhaps wouldn't have had the time anyway …"
Knowledge about evidence-based prescribing "It has a lot to do with our stress, that we don't have the time to sit and read *Läkartidningen*[a] or to look at our drugs, what there is and what the options are … it is about our time … that we actually don't have time to do it. Instead it is easier to reach for something like this … just as you say …" "A good thing to bring up, I think, is the new electronic medical records system, PMO, that [the prescriptions] are there, so it is very easy to prescribe a recommended drug, which is very positive." "I didn't even know that the guidelines were there, where do you find them?"
Trust in development of guidelines "… then I wonder a little bit…they are after all human beings … these groups who sit and write the guideline, I mean … we don't know how active and good the doctors in these groups are …" "…then I wonder, why does it have to be local, does it have to be different … in every region … are the patients different?" "The background information? Yes, it is very robust and good. If I didn't have that book I perhaps wouldn't have been as … satisfied or had the same confidence, because I can … read about what they considered and how the drugs work." "But it feels quite uncomfortable, because they're new drugs that we've heard so many good things about, and they cost a lot, but you sit there and wonder … well … nobody else tries it …"
Beliefs about adherence to guidelines "A barrier would also be, as I said, a lack of options. It is a barrier to following guidelines, because you don't know whether it will work in the next step …" "Sometimes they come with different pills from the hospital, which they don't need, and then we are supposed to withdraw them and prescribe the recommended ones. I can say that often the patient goes along with it, because I have the book there with the guidelines …" "It is actually aimed at GPs; hospital doctors don't read it." "Sometimes it feels that they don't know what we are doing … they are supposed to follow the guidelines for the drug … but I don't think they do…" "Yes, I agree with you, C … if a patient has a drug that works I don't change it either just because they change the guidelines. Because … I don't want to make the poor old patients more confused than they already are…"

[a]A Swedish-language medical periodical

Table 5. Categories and quotations for the theme "External influencing factors"

External influencing factors
Patient-related aspects
"Yes, you should never experiment with patients … or expose them to risk of injury. It is very important. This is why I think that we GPs are very careful with new drugs. I prefer to wait a while with a new drug before I prescribe it …"
"You might think so, but the patient may think differently …"
" … I think it is very important not to give in, at least in those cases with tetracycline versus penicillin, it feels important to explain to the patient the risk of bacterial resistance and so on … so there you can compromise a bit on the patient-doctor relationship …"
Drug industry-related aspects
"A conflict arises sometimes. Some patients are so well-read and influenced by the media and sometimes want another drug and … insist …"
"We don't know anything about that. We don't know if somebody there is on Pfizer's board … or is biased …"
"… and then you think about how life was before the [local] guidelines even existed. … we were drug industry indoc … formed … (laughs)"
Health economic aspects
"…I think that it is OK to save money on things you can save money on … maybe to be able to do more tests of that kind or something else … the budget is not unlimited, so I usually think that this is not a problem."
"… but there is a lot of focus on economy here, more focus on economy than on the pharmacological benefit compared to other drugs … so from that point of view it is highly controlled …"
"I am not really sure if the economy part motivates us …"
"The goal is to save money, I suppose, and more and more of the drug costs are transferred to the primary health care centres … so of course it matters …"