A systematic approach to improving pharmacotherapy in the elderly

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A SYSTEMATIC APPROACH TO IMPROVING PHARMACOTHERAPY IN THE ELDERLY

by

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Contents

Original articles

The thesis is based on the following articles, which are referred to by their Roman numerals:

I. Midlöv P, **Bergkvist A**, Bondesson Å, Eriksson T, Höglund P. Medication errors when transferring elderly patients between primary health care and hospital care. *Pharmacy World and Science* 2005; 27 (2): 116-120.

II. **Bergkvist A**, Midlöv P, Höglund P, Larsson L, Eriksson T. A multi-intervention approach on drug therapy can lead to a more appropriate drug use in the elderly. LIMM-Landskrona Integrated Medicines Management. *Journal of Evaluation in Clinical Practice* 2009; 15 (4): 660-7.

III. **Bergkvist A**, Midlöv P, Höglund P, Larsson L, Bondesson A, Eriksson T. Improved quality in the hospital discharge summary reduces medication errors-LIMM: Landskrona Integrated Medicines Management. European *Journal of Clinical Pharmacology* 2009; 65 (10): 1037-46.

IV. **Bergkvist Christensen A**, Holmbjer L, Midlöv P, Höglund P, Larsson L, Bondesson Å, Eriksson T. The process of identifying, solving and preventing Drug Related Problems in the LIMM-study based on the collaboration between pharmacists and physicians. *Submitted September 2010.*

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Abbreviations

ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ApoDos	A specific multi-dose medication dispensing system
ASA	Acetylic Salicylic Acid
ATC	Anatomical Therapeutic Chemical classification system
COX	Cyclooxygenase
DRP	Drug Related Problem
GP	General Practitioner
IMM	Integrated Medicines Management
LIMM-model	Lund Integrated Medicines Management – model
LIMM-study	Landskrona Integrated Medicines Management – study (where the LIMM-model was tested)
MAI	Medication Appropriateness Index
NSAID	Non-Steroidal Anti-Inflammatory Drug
RCT	Randomized Controlled Trial
Vd	Volume of distribution

Introduction

The elderly population in Sweden, 65 years or older, has been fairly constant since the 1990s and comprises 17% of all inhabitants, however, this proportion is expected to increase to 21% in 2020 [1]. In 2006, 6.2% of all people 65 years or older lived in nursing homes and 8.9% lived in their own home with help from the community health care [2, 3]. Now the number of beds in nursing homes is decreasing and more patients are living in their own home with help. In 2007, 5.9% of the elderly lived in nursing homes and 9.6% lived in their own home with help from the community health care [2, 3].

As the elderly population is growing, so is the population of elderly with multiple medical conditions, of which the majority is 80 years or older [1]. The elderly consume a large proportion of medications and those 75 years or older represent 9% of the Swedish population but use more than 25% of all medications [4]. Drugs are important in the treatment of elderly patients, and in Swedish nursing homes patients have been reported to use on average 9-12 medications per person [5-8]. Those 65-74 years old use on average 11 medications and the drug use then seems to decrease somewhat with age as those 90 years or older use 9,8 drugs per person [6].

The elderly use many drugs and are more prone to suffer from adverse drug reactions [9]. Therefore it is important to address the quality of their drug therapy, otherwise the harmful consequences of inappropriate drug use will become a growing problem.

The aging process and its effect on drug therapy

With age, the risk of becoming ill increases and many elderly suffer from several diseases, making pharmacotherapy in the elderly a complicated task. In addition to this, physiological alterations in the human body takes place as we grow older, making pharmacotherapy even more difficult. Changes in the body's pharmacokinetic and pharmacodynamic parameters begin in early adulthood but is not clinically significant until the age of sixty or later [10] and leads to changes in the effects and side-effects from drug therapy.

Pharmacokinetics, the way the body affects the drug, can be divided into: absorption, distribution, metabolism and elimination. The way aging affects these functions differ from minor to major impact. Even though the gastrointestinal function changes with age, no or small effects have been seen in drug absorption after oral administration [11]. Distribution, however, can differ with age as the elder person has a higher amount of body fat in relation to muscle mass. The volume of distribution (Vd) of lipophilic drugs can therefore increase, which can result in a prolonged elimination half-life as it is dependant on the Vd [12, 13]. Correspondingly, hydrophilic drugs can present decreased Vd. Some drugs bind extensively to plasma proteins, ex albumin, and as the elderly can have altered protein concentrations this can change the free, unbound drug concentration and potentially affect both distribution and elimination of the drug [11]. Plasma clearance describes the overall ability of the body to eliminate drugs, particularly metabolism of drugs in the liver and elimination of drugs in the kidneys. The most important age-dependant changes in the body are seen in these systems. Changes in metabolism in the liver can also be caused by stress and illness in the elderly [12]. An age related decrease in metabolism is due to a decrease in hepatic mass, blood flow and enzymatic capacity [11]. Decrease in the liver function reduces clearance and can lead to an accumulation of drugs and a higher plasma concentration when dosage is maintained, resulting in an increased risk of side-effects. Therefore tranquilizers, tricyclic antidepressants and antiarrhythmics are examples of drugs that should be used with caution in the elderly [11]. The final elimination of drugs takes place in the kidneys, were the drugs are extracted into the urine. Creatinine clearance can be used as an estimate of the glomerular filtration and thus the kidneys' function. The kidneys ability to eliminate drugs decrease with age and this decline starts already at the age of 30 [12]. As the elimination declines so do clearance and the risk of drug accumulation increases. Therefore, dose adjustments in the elderly are often necessary [12]. Digoxin and ACE-inhibitors are example of drugs needing adjustment when the elimination decreases [11].

Changes in pharmacodynamics, the way the drug affects the body, are also seen in the elderly. The change in drug sensitivity varies with the drug in question and generalizations are difficult. With age, there is an increase in sensitivity for warfarin [14] and it is therefore important to be careful when administering warfarin as well as drugs affecting the pharmacokinetics of warfarin [15]. Further, the elderly are also more sensitive to drugs with their effect in the central nervous system. This is seen for bensodiazepines, and dosage reductions are recommended in order to avoid negative side-effects [15]. The increased sensitivity for neuroleptics can lead to adverse effects, such as delirium, extrapyramidal symptoms, arrhythmias and postural hypotension [14].

Inappropriate drug use and its consequences in the elderly

The use of inappropriate drugs in the elderly is a widespread problem. In Swedish nursing homes, over 70% of the residents with ApoDos had one or more potentially inappropriate prescription according to quality indicators published by the Swedish National Board of Health and Welfare [8]. Every fifth person in nursing homes was prescribed medications with anticholinergic effects, risking side effects for the patient, such as confusion [6, 8]. However, the use of drugs differs among the elderly. In general, patients in the age 65-79 years had a lower quality in their drug treatment than those 80 years or older [6, 8]. The use of inappropriate drugs in the elderly is of course not only a Swedish problem. Beers criteria have been used internationally to measure inappropriate drugs. For example, a Portuguese survey among elderly outpatients showed that more than 25% of the studied population used at least one or more inappropriate drugs [16] and in a region in Italy, 18% of elderly outpatients had one or more potentially inappropriate drug [17]. A study set in an American ambulatory setting, showed that 74% of the drugs prescribed to the patients had one or more inappropriate rating according to the Medication Appropriateness Index (MAI) and that all patients took at least one drug with an inappropriate rating [18].

As previously described, the elderly use many drugs and the number of medications per patient has been shown to correlate to the number of prescribing doctors [6, 8]. For every additional physician involved in the prescribing to a patient, the drug use increased with on average 0.5 medications [6]. A high number of prescribers was associated with more drugs and lower quality of drug therapy [6, 8] and unnecessary drug use [19]. An increase in physicians involved in the prescribing showed a decrease in the quality in the patient's drug treatment regarding long acting benzodiazepines, anticholinergic drugs, drug duplication, the use of three or more psychoactive drugs and drug interactions [6], and an increased risk of patients self reporting an adverse drug event (ADE) [20]. The risk of experiencing an ADE also increases with being female, higher age, indicators of poorer health, the number of medications [21] and inappropriate prescribing [22]. In a similar way, inappropriate drug use was significantly associated with being female and the total number of medications [23]. In elderly outpatients the use of inappropriate medications also increased with an increased disease burden [23], the total number of drugs [16, 24] and age, total number of drugs and chronic conditions [17].

As described above, the use of many drugs and inappropriate drugs can lead to decreased quality in the patients' drug treatment and the risk for negative side effects. An American expert panel concluded that the most common medication

related risk factors for an adverse drug reaction (ADR) to occur in elderly out-patients were the use of opioid analgetics, warfarin, non-ASA non-COX-2 NSAIDs, anticholinergics and bensodiazepines [25]. Many of these drugs are also listed on Beers criteria of inappropriate drugs to the elderly [26] and the quality indicators published by the Swedish National Board of Health and Welfare [27]. Patient related risk factors were considered to be polypharmacy, multiple chronic medical problems, prior ADR, dementia and renal insufficiency [25].

Inappropriate drug use can thus lead to ADRs and further on an ADR can lead to the need for health care contacts. Meta-analysis have shown ADRs to be the cause of about 5% of all admissions to hospital [28-30]. An English study confirms the result as ADRs being the cause of 6.5% of all hospital admissions [31] and a Swedish study showed that 35% of admissions to geriatric wards were caused by ADRs and that those with severe ADRs were older than average [32]. In an American study, hospital admission as a consequence of ADR was found in one of every seven nursing home residents and seemed to be related to polypharmacy and inattention to patient history of contraindications and previous ADRs [33].

Problems with inappropriate drug use and ADR do not only occur in outpatients, but also in patients during their hospital stay. However, the frequency of ADRs in inpatients is not as well described in the literature as ADRs in outpatients. A meta-analysis shows that 1–24% of all patients acquire ADRs during their hospital stay [28]. An English study confirms this result, as 15.8% of patients experienced one or more ADRs during their hospital stay [34]. When looking at inappropriate drug use, an American study showed that 43% of all elderly inpatients were prescribed at least one drug without valid indication and that 47% of the patients were prescribed drugs with inappropriate duration [35]. At discharge from hospital, 44% of the frail and elderly patients in an American study had at least one unnecessary drug, most commonly caused by lack of indication [19].

ADRs have also been shown to be a risk factor for death and are among the six most common causes of death in American hospitals [28]. When looking at patients admitted to the hospital due to an ADR, 0.13% was fatal [28]. In English hospitals this is confirmed as 0.15% of all ADRs at admission were fatal [31]. The majority of these ADRs can be avoided [28, 31] and in the elderly as much as 90% of the ADRs can be avoided [30]. A high rate of avoidable ADRs is also seen in Swedish studies [36-38].

Using drugs in an inappropriate way is not only a medical risk for the individual patient but also expensive, and for every dollar spent on drugs in American nursing homes, it was shown to cost 1.33 dollars to take measures against problems directly related to drug use [39]. In an American review, hospitalisation

was considered to be the most expensive part of healthcare in the elderly, responsible for more than 40% of the health care costs [10]. In England, admissions to hospital caused by ADRs are estimated to cost £466m annually [31]. A Swedish report states that drug therapy in the elderly causes many to suffer unnecessarily, that it needs substantial improvement and that drug related problems are very costly for the community [40]. Already in the late eighties, adverse effects of drugs in the elderly led an expert panel to declare them as one of the most prioritised topics for quality assurance activities within this population [41].

Assessment of inappropriate drug therapy

Different classification systems and tools for assessing the appropriateness of a drug therapy have been developed. One tool widely used is Beers criteria, developed in the United States in 1991 [42], expanded in 1997 [43] and revised and updated in 2003 [26]. This tool uses explicit criteria to assess a drug's appropriateness and states certain drugs that should be avoided in the elderly. In Sweden, the National Board of Health and Welfare developed quality indicators for the use of drugs in the elderly in 2003 [44] and updated these in 2010 [27]. These indicators also use explicit criteria to list inappropriate medications. Being tools based on explicit criteria, the drugs are considered inappropriate regardless of the effect in the individual patient. The classifications of inappropriate or appropriate drugs are made on group level.

The MAI was developed in 1992 in order to assess the appropriateness in a patient's drug treatment [45, 46]. This instrument combines implicit and explicit criteria when determining a drug's appropriateness [45]. By adding implicit criteria in the MAI, the individual patient's experience of the drug therapy affects whether the drug is inappropriate or not. Therefore, a drug considered inappropriate according to explicit criteria could be appropriate using implicit criteria, if the patient does not experience negative side-effects from the treatment. Several aspects on a drug treatment are addressed in the MAI, such as: indication, effectiveness, dosage, correct directions, practical directions, drug–drug interactions, drug–disease interactions, duplication, duration and expense; and it has been validated for evaluating drug therapy in the elderly [46]. However, the original version does not take the underuse of drugs in account. By using a weighing scheme each drug then receives a score, from 0 (no inappropriate ratings) to 18 (only inappropriate ratings) [46]. A patient MAI-score can then be calculated by summing the MAI-medication scores for the patient's drugs [47]. MAI has been proved, by tests of inter-rater agreement, to be a reliable method in evaluating drug therapy appropriateness [45, 48].

An updated version from 2010 deals with over and underdosing separately [49]. However, there is yet no published study where the updated version of MAI has been used.

Pharmaceutical Care and Clinical Pharmacy

Pharmaceutical care, has been defined by Hepler and Strand, as 'the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life' [50]. The approach is based on identifying, resolving and preventing drug related problems (DRP) for the patient [50]. Pharmaceutical care can be performed by pharmacists and other health care personnel. Clinical pharmacy on the other hand can be defined as 'a health specialty, which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of medicinal products and devices' [51] and is performed by clinical pharmacists. These activities can be performed both in an inpatient- and an outpatient setting.

A model for pharmaceutical care, an integrated medicines management (IMM), has been developed in Northern Ireland. Medicines management has earlier been defined as a practice that seeks to maximise health through the optimal use of medicines [52]. The IMM-model is a systematic approach to optimize the drug treatment for the individual patient and involves pharmaceutical care at admission, during the hospital stay and at discharge as well as a cooperation between hospital and community health care [53]. A randomized controlled trial (RCT) showed that patients receiving the IMM-model had a significantly shorter length of hospital stay, decreased rate of readmission over a 12-month follow-up period and an increased time to readmission [53]. Further investigation shows that the model resulted in a significant improvement in the appropriateness of medications on discharge [54].

Studies in to clinical pharmacy have also been performed in Sweden and recent findings from a RCT showed that clinical pharmacy services in elderly inpatients significantly reduced the number of hospital visits after discharge and drug-related readmissions. This approach was also proved to be cost-effective [55].

The definitions of medication error, ADE, ADR and DRP

Medication errors have been defined by Leape as ‘any error in the process of prescribing, dispensing or administering a drug, whether there are adverse consequences or not’ [56]. As such, medication errors are by far the largest group of incidents described here.

An ADE was defined by Leape as ‘an injury related to the use of a drug’ [56]. An American study showed that 0.9% of all medication errors resulted in an ADE [57]. Potential ADEs were defined by Bates et al as ‘medication errors with potential for injury but in which no injury occurred’ [57]. If the incident has no potential for injury, it is merely a medication error. A Danish study showed that of medication errors identified, in worst case as much as 20–30% were assessed as potential adverse drug events [58]. A preventable ADE is ‘an injury that is the result of an error at any stage in the medication use’, compared to non-preventable ADEs where there is no error in the process [59]. The vast majority of ADEs are dose-dependent and therefore preventable [57]. Non-preventable ADEs are also known as ADRs [59].

An ADR is defined by WHO as ‘a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man’ [60]. They can be either predictable and therefore often possible to avoid (type A reactions) or unpredictable and thereby of course difficult to foresee (idiosyncratic or type B reactions) [61]. As described above, ADRs are commonly occurring both in out-patients and inpatients and can lead to mortality and morbidity in the elderly.

Strand et al have defined a DRP as ‘an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome’ [62]. Several definitions of DRPs and systems for further classification of DRPs into subgroups exist, none of which meets the ideal criteria for an optimal system (i.e. clear definition, published validation, usable in practice, open hierarchical structure and focus on the drug-use process and outcome) [63]. Our research group has chosen to use the model published by Cipolle et al with the following seven subgroups [64]: unnecessary drug therapy, need for additional drug therapy, ineffective drug, dosage too low, ADR, dosage too high and non-compliance. Furthermore, a DRP can be either actual or potential, as monitoring might be needed in order to prevent a potential DRP to become an actual one. One drug may introduce more than one DRP, for example, an unnecessary drug therapy can also result in an adverse drug reaction. DRPs caused by errors can be considered to be medication errors as they meet the definition presented above. However, not all DRPs are the result of an error as an unpredictable ADR can

occur. According to a symposium held by the Pharmaceutical Care Network Europe, actual DRPs overlapped with ADEs and potential DRPs overlapped with potential ADEs [65].

Risks for the patient in the transition of care

In Sweden, the health care system is divided into community health care, primary care and hospital care. When a patient is discharged from hospital but still needs help from society, the patient is discharged to the primary care with help from the community health care. Either the patient is discharged to a nursing home or to his or her own home with help from the community health care system. The community health care does not have their own general practitioners (GPs) as they are employed by the primary care. At discharge a medication summary is sent to the GP with whom the patient is listed. When in primary care, the patient is free to use as many GPs as he or she wants. Even though the patient is listed at a medical centre, there are no regulations on visiting other GPs. The consequence of this system is that no GP or physician can be certain of possessing the complete information on a patient's drug therapy. Most commonly, the primary care and the hospital care do not have the same system for medical records and therefore do not have direct access to the same information on the patient. As a step towards better access of information, it is now possible to achieve information on what medications the patient has been dispensed at the pharmacy. This is however based on consent from the patient. Improvements on harmonising the journal systems have been made and in 10 of 21 Swedish counties it is now possible for the hospital and the primary care to access the same information [66].

Medication errors in the transfer of information between care levels have been proven to be wide spread. A review stated that 60-67% of all patients had at least one omission or commission error in the medication history regarding prescription medications at admission to hospital and that 11-59% of the errors were considered clinically important [67].

In 2006, The Council of Europe highlighted insufficient quality in the transfer of information on a patient's medications as an important problem in health care [68]. The Institute for Healthcare Improvement, claims that poor communication of medical information at transition points causes as many as 50% of all medication errors and 20% of adverse drug events in the hospital [69]. There is a substantial risk for negative patient outcomes in these transitions, as there is a high risk of discontinuity in care when discharged from hospital to primary care which might lead to an increased risk of rehospitalisation [70]. Correspondingly, when the GPs have received the discharge summary in time for the patient's assessment in

primary care following hospitalisation, the risk for rehospitalisation seems to decrease [71]. Medication reconciliation is a process that involves comparing the medications a patient is receiving to what he or she actually should be receiving and then resolving the discrepancies [69]. This approach has been introduced as one of the solutions to decrease medication errors and increase patient safety [69, 72, 73].

Lund Integrated Medicines Management – the LIMM-model

Our research group has put together and developed systematic and validated instruments for use in clinical pharmacy services during the patient's hospital stay and beyond, as shown in Figure 1. The activities are performed by a multi-professional team consisting of physicians, nurses and pharmacists among others.

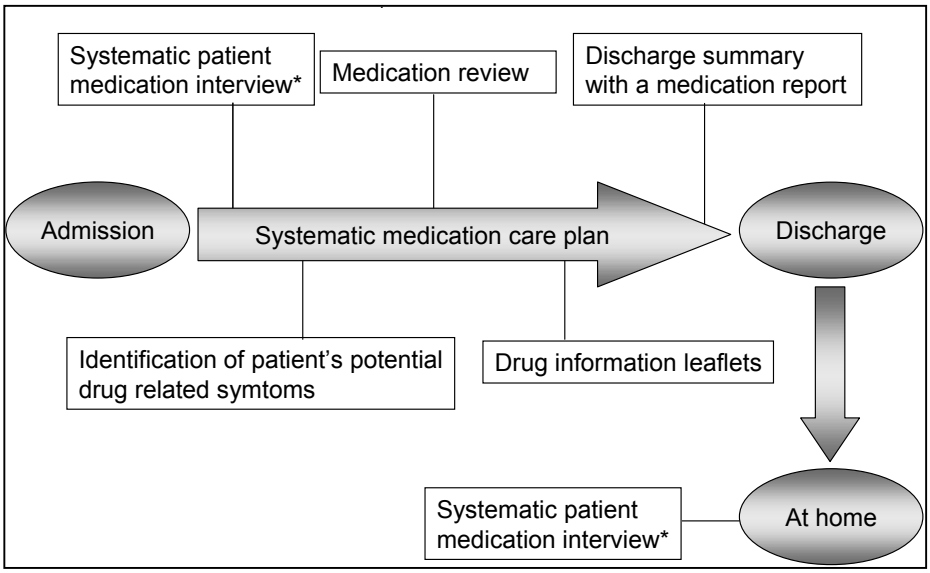

Figure 1. Description of instruments in the LIMM-model. Interventions marked * are performed only with patients who handle their drug therapy on their own.

Based on our experience, the following instruments have been developed and put together:

At admission - Patient medication interview
This structured medication questionnaire has been developed in order to assess the correctness of the medication list at admission, the patient's knowledge about the drug treatment, the patient's attitudes towards disease and drug treatment (beliefs

about medication questionnaire, specific BMQ [74]) and patient compliance (Morisky 4-item scale [75]). The instrument includes medication reconciliation at admission and is used by pharmacists [76].

In addition to this, an identification of patient's potential drug related symptoms is performed by a nurse or a pharmacist.

During hospital stay - Medication review
Structured checklists for the pharmacists and the care team have been developed in order to individualise and monitor a patient's drug treatment during the hospital stay. To systematically identify DRPs in the medication review, the following issues are addressed by the pharmacists: decrease in renal function, drugs with narrow therapeutic index, problems with swallowing drugs, drug allergies, drug-drug interactions and inappropriate drugs in the elderly. The following drugs are considered to be inappropriate in the elderly, drugs with anticholinergic effects, long-acting bensodiazepines, the use of ticlopidine, quinidine, quinine and po theophylline, treatment with more than one drug from the same Anatomical Therapeutic Chemical (ATC)-group, $\geq$ three psycholeptics and psychoanaleptics and inappropriate doses of psycholeptics and psychoanaleptics.

During the hospital stay, the pharmacist also helps the patients with information regarding new drugs. This is done by discussing the new drug with the patients and providing them with leaflets containing short information on the drug. Hoping that the more the patients understand about their drug therapy and the necessity to take them as directed, the more likely they will be to show compliance [10].

At discharge - Discharge summary with a Medication report
The medication report is part of the discharge summary and has been constructed in order to provide the patient and the GP with information on changes in the patient's drug therapy [77]. The document is written by the physician for the patient and contains the following [77]:

- General information (i.e. reason for admission to hospital, name of patient's physician at the hospital, GP in primary care as well as planned follow-up)
- Medication report (a section with information on changes that were made in the drug therapy and reasons for these changes)
- Medication list (a list of current medications, dosages and indications for each medication)

This document is given to the patient at discharge and, if applicable, sent to the community health-care provider and the patient's GP.

Where applicable, the pharmacists perform a medication interview with the patients after discharge from hospital.

Rationale for the studies

This thesis emphasises the importance of individualising drug therapy in the elderly in order to prevent the patients from suffering from negative side effects due to their treatment, to communicate information on drug therapy accurately and to approach this in a structured and systematic way. We have focused on the elderly as they are the patient population with most diseases and therefore those to be seen in hospitals, use many drugs and in addition to this, those most sensitive to positive and negative effects from drug therapy.

The first study presented in this thesis showed that medication errors in the transition of care are common. These results contributed to the development of the LIMM-model. The opportunity to study the full model arose as the department of internal medicine at Landskrona Hospital was interested in improving drug therapy in the elderly by using clinical pharmacy services. We therefore started the Landskrona Integrated Medicines management – the LIMM-study. Although it is important to address these problems both in outpatients and inpatients, as the LIMM-study took place at a hospital, this thesis manly focuses on improvements made in the hospital setting.

Medication errors in the transition of care

In discussions with nurses in the community health care in Landskrona it became apparent that the medication list received from the hospital at patient discharge often was incomplete. We therefore wanted to study how information on drug therapy was transferred between primary care and hospital care, i.e. at admission to hospital and at discharge to primary care. By doing so we hoped to better understand the process and to find possible solutions to the problem.

A systematic approach on drug therapy and a more appropriate drug use in the elderly

The use of inappropriate drugs in the elderly is widespread. In the Swedish health care system, several physicians and GPs can be involved in a patient's drug

therapy. This can unfortunately result in unclear responsibilities and that no one takes the full responsibility of evaluating and ending drug therapy when it is no longer relevant. More and more is known on the difficulties of drug therapy in the elderly and tools to address this have been developed. We had put together and developed the LIMM-model that addressed problems at admission, during the hospital stay and at discharge and wanted to study the model's effect on the appropriateness in drug use in the elderly.

Improved quality in the hospital discharge summary and medication errors in the transition of care

Based on the findings in Paper I, a process to improve communication on information on drug therapy started. This resulted in the Medication report which has been shown to reduce both the total number of medication errors as well as the number of medication errors with risk for clinical consequences [77] as well as morbidity and the need for medical care due to medication errors [78]. However, in these studies the quality of the Medication report had not been studied and it was not known whether the Medication report contained relevant and accurate information. Therefore we wanted to study how the Medication report was written, its contents and if evaluation and improvement in the Medication report further could reduce medication errors at discharge from hospital.

The process of identifying, solving and preventing DRPs and attitudes towards the LIMM-model

The cornerstones in pharmaceutical care and clinical pharmacy are to identify, solve and prevent DRPs and as such, this was also a part of the LIMM-model. As the pharmacist only is advisory to the physicians and nurses regarding drug therapy, it is important that the process in which the pharmacists work are structured and distinct. Otherwise, health care personnel can have difficulties in understanding the benefits with the advice and deny making relevant alterations in the drug therapy. Establishing good relations between the pharmacists and the health care personnel is also important in order to make the communication process and thereby the process of solving and preventing identified DRPs as successful as possible. In this study we therefore wanted to study identified DRPs, DRPs put forward by the pharmacist and DRPs adjusted by the physicians as well as the health care personnel's attitudes towards the LIMM-model.

Aims of the thesis

The general aim of this thesis was to investigate whether a systematic approach on drug therapy as well as on transfer of information on drug therapy between care levels would lead to a more appropriate and accurate drug use in the elderly.

The aims of the specific studies were to:

- Investigate the nature and frequency of medication errors when patients are transferred between hospital and primary care. (Paper I)
- Evaluate if an integrated medicines management (the LIMM-model) can lead to a more appropriate drug use in the elderly according to MAI. (Paper II)
- Evaluate whether an integrated medicines management (the LIMM-model) improves the quality of the discharge summary and reduces medication errors when patients are discharged from hospital to community health care. (Paper III)
- Describe the process behind the improvements in patients' drug therapy due to an integrated medicines management (the LIMM-model), based on identifying, solving and preventing DRPs and to evaluate the health care personnel's attitudes towards the model. (Paper IV)

Material and methods

Different methods have been used in the presented articles and detailed descriptions are provided in each publication.

Paper I

This was a descriptive study where patients 65 years or older who had been discharged from Landskrona Hospital or any of the departments of internal medicine, neurology or orthopaedics at Lund University Hospital and discharged to the community health care in the town of Landskrona were eligible for inclusion. Inclusion to the study was performed by nurses in the community health care and took place during the period 1 September 2000 until 1 June 2001. After inclusion, documents on drug use prior to the hospital stay, during the hospital stay, at discharge and after return to the community health care were collected. Two pharmacists then separately compared the medication lists in order to identify medication errors at admission and discharge. A discrepancy was considered a medication error if the drug was added, missing or the total dosage over 24 hours was changed and documentation on the reasons for the change was lacking.

Papers II, III and IV

Papers II, III and IV are based on the LIMM-study which consists of several intervention groups and control groups, as described in Figure 2. It is possible for a patient to be included in more than one study.

The LIMM-study was a longitudinal study at a department of internal medicine where patients 65 years or older were eligible for inclusion. The control groups were included at the same three wards as where the interventions took place, but were done prior to the interventions. Due to practical reasons it was not possible to include all patients at the three wards. Therefore a systematic procedure was constructed, in order to make sure that inclusion was done systematically. Every day, Monday to Friday, all newly admitted patients were identified. Inclusion was then performed throughout the corridors beginning with room number one. At all

wards there were single rooms in the start and in the end of the corridor, preferably for the patients most ill. In the middle of the corridor, there were rooms with two or four beds for patients in a not so critical state. The inclusion process thereby made sure that no selection was done regarding how ill the patients were. This process was used for the inclusion to the control group in the study of MAI and for inclusion to the intervention groups in the study of MAI and the study of medication errors (when the LIMM-model was launched). Regarding the inclusion to the control group in the study of medication errors, all patients that met inclusion criteria were eligible for inclusion.

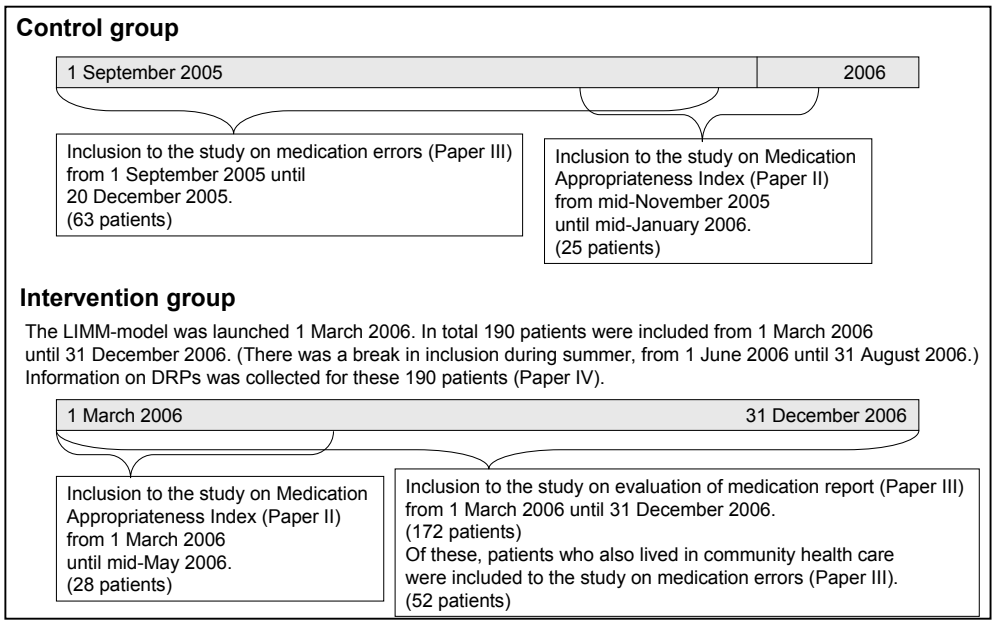

Figure 2. Inclusion to the LIMM study.

During the intervention period the pharmacists took part in the daily work at the wards and performed interventions during the patients' hospital stay. The interventions were the interventions previously described for the LIMM-model, including medication interview, check of patient's symptoms, medication review, medication care plan, drug information leaflets and evaluation of the medication report. A systematic medication care plan was created in which DRPs and changes in drug therapy were noted. The care plan was updated continuously and was decided on by the team. The DRPs identified by the pharmacist were put forward to the care team and discussed.

Paper II

The pharmacists collected information on the patients' drug therapy from medical records and from information achieved through the interventions. MAI-scores were then systematically determined by the pharmacists according to specific instructions for the MAI [45]. First, a MAI-score for each of the patient's drugs was calculated [46]. Then, a MAI-score for the patient was calculated by adding the MAI-scores for all drugs [47]. This was done for each patient in the intervention group and control group at admission, discharge and by telephone interviews 2 weeks after discharge. First, one of two pharmacists determined MAI-scores for each patient. Then both pharmacists went through all MAI-scores together to reach consensus.

Paper III

In addition to the inclusion criteria for the LIMM-study, patients also had to be discharged to the community health care in the cities of Landskrona or Svalöv to be eligible for inclusion. Patients in the intervention group were included by the pharmacists at the three wards. Inclusion to the control group was made by nurses in the community health care, after receiving information from the pharmacists regarding which patients that were relevant to ask.

For both the control group and the intervention group, a physician completed the discharge summary, including the medication report and a medication list, at the day of discharge. For the intervention group, the discharge summary was then evaluated by a pharmacist according to a developed checklist, focusing on the medication report and the medication list. Discrepancies found between the information in the discharge summary and medical records from the hospital stay were analysed. The evaluation process was performed according to the following subgroups in the discharge summary: general information and layout, medication report – changes made, medication report – reasons for the changes, medication list – current medications and medication list – indication for current medications. The pharmacists notified the physicians on identified discrepancies, who then had a possibility to adjust the discharge summary before the patient was discharged.

The first medication list used after discharge was sent in by the nurses in the community health care. The medication list in the discharge summary was then compared with the first medication list used by the community health care in order to study whether the transfer of information was done correctly or not. The same definition of medication error was used as in Paper I.

The base for inclusion was the intervention group in the LIMM study, as described in Figure 2.

Information on DRPs identified and put forward by the pharmacists within the clinical pharmacy service described above, as well as DRPs adjusted by the physicians were collected and analysed. When a DRP was not put forward or not adjusted, information on the reason for this was noted. DRPs were classified according to Cipolle et at [64] with the addition of the following groups: transferring errors and suboptimal monitoring of drug treatment. In order to see which drugs that were most commonly associated with DRPs, the drugs were grouped according to the ATC-system [79]. To make sure that DRPs were classified uniformly one pharmacist was responsible for all classifications.

To evaluate the health care personnel's attitudes towards the clinical pharmacy service, a questionnaire was sent out to physicians and nurses employed at the department of internal medicine during the study period. The questionnaire had previously been developed by our research group and used six-point ordinal scales, from 1 (no benefit) to 6 (great benefit) [80].

Results

Medication errors in the transition of care (Paper I and Paper III)

In the first study investigating medication errors when transferring patients to and from hospital from the community health care, information on 19% of all drugs was transferred erroneously (Paper I). After introducing the medication report and then improving its quality in Paper III, medication errors at discharge decreased. Results found in Paper I and Paper III regarding patients without medication errors, drugs with medication errors and medication errors per patient are shown in Table 1.

Table 1. Medication errors on drug level and patient level in Paper I and Paper III.

		Patients without medication errors (%)	Drugs with medication errors (%)	Medication errors per patient
Paper I[a]	At admission	5/34 (14.7)	80/389 (20.6)	2.35
	At discharge	16/35 (45.7)	62/369 (16.8)	1.77
Paper III[b]	Control group	40/63 (63.5)	66/549 (12.0)	1.05
	Intervention group	38/52 (73.1)	25/520 (4.81)	0.48

[a]In Paper I, 34 patients were included at admission and 35 patients at discharge.

[b]In Paper III, 63 patients were included in the control group and 52 patients in the intervention group. Analysis was performed at discharge. Three patients were included both in the intervention group and the control group.

At admission to hospital from the community health care, 14.7% of the patients had no medication error at all. The corresponding value for discharge from hospital to community health care was 45.7% (Paper I). With few exceptions, the same patients were studied both at admission to the hospital and at discharge to community health care. An improvement in the proportion of patients without medication errors was seen when evaluating the medication report, from 63.5% in the control group to 73.1% in the intervention group (Paper III). This was however not significant (P=0.319).

On average the number of medication errors per patient was 2.06 in the first study (Paper I). In the intervention study, the control group had 1.05 medication errors per patients compared to 0.48 in the intervention group. This was a significant decrease by 45% (P=0.012) (Paper III).

In both studies, the usage of a specific medication dispensing system (ApoDos) at discharge, showed a significant risk for medication errors. In the first study an odds ratio 18 (CI 1.9–169) (Paper I) was seen and in the second study, after improving the discharge summary, patients with ApoDos had a 5.9-fold higher risk of suffering from a medication error (P<0.001) (Paper III).

In the first study, 69.2% (18/26) of patients with ApoDos had at least one medication error, whereas only 11.1% (1/9) of patients without the medication dispensing system had at least one medication error (Paper I). Similar findings were seen in the intervention study and in the intervention group 78.6% (11/14) of patients with ApoDos had at least one medication error. For patients without ApoDos, 7.89% (3/38) had at least one medication error (Paper III).

Improved quality in the hospital discharge summary (Paper III)

Of 172 discharge summaries, only one was without discrepancies according to the evaluation checklist developed at Lund University hospital. When disregarding discrepancies in general information and layout 46 discharge summaries were complete. Most discrepancies were found in the medication report - reasons for the changes. Discrepancies in the medication list were the ones most often adjusted by the physicians, 59.1% (94/159).

As the time schedule often was tight, pharmacists chose to put forward only discrepancies that risked having a major negative effect for the patient. This lead to the pharmacists not informing the physicians regarding 33% of the medication reports with discrepancies and in these cases the physicians were given no chance to adjust the information.

A more appropriate drug use in the elderly (Paper II)

The intervention group contained 28 patients and the control group 25 patients. No one was included both in the intervention group and the control group. During hospital stay and until 2 weeks after discharge, 5 patients in the intervention group and 2 patients in the control were lost to follow up. Data was analysed as intention to treat and last observation carried forward was used when observations were missing.

There was a significant decrease in MAI-score per drug and MAI-score per patient for the intervention group from admission to discharge and from admission to 2 weeks after discharge. This was not seen for the control group. As patients in the control group had a significantly higher mean MAI-score per drug and MAI-score per patient at admission we also wanted to investigate the relative decrease in order to see if this differed between the groups. This was however not the case.

Almost all patients had at least one drug with an inappropriate rating at admission, 96% of the patients in the control group and 86% in the intervention group. When looking at the number of drugs with at least one inappropriate rating, the control group had significantly more drugs with at least one inappropriate rating at admission ($P=0.014$), discharge ($P<0.001$) and two weeks after discharge ($P<0.001$). The number of drugs with at least one inappropriate rating at discharge was found to be dependent on the number of drugs with inappropriate ratings at admission and whether the patient was in the control group or the intervention group. The intervention group had more drugs without inappropriate ratings at discharge ($P=0.049$) and 2 weeks after discharge ($P=0.031$). This difference was not seen at admission.

There were more patients in the intervention group with no change or decrease in the number of drugs with inappropriate ratings from admission to discharge than in the control group ($P = 0.049$). There were no differences regarding the change in the number of drugs without inappropriate ratings or the total number of drugs.

The MAI-dimensions that received most inappropriate ratings were indication, duration and expense. Psycholeptics were the group of drugs most often involved in inappropriate ratings.

Seven patients in the control group and four patients in the intervention group were also in the study for medication errors in the transition of care.

The process of identifying, solving and preventing DRPs (Paper IV)

Of the 1227 DRPs identified in 190 patients, a third was considered to be actual (35.9%). Unnecessary drug therapy was the DRP most frequently identified by the pharmacists, in almost every sixth case, and proton pump inhibitors were the drugs most often involved in this unnecessary drug use.

Some of the identified DRPs could be solved directly by the pharmacists (4.4%), some were not put forward (14.4%), not relevant to put forward after investigation (11.7%) and for some DRPs it was not known whether they were put forward or not (13.7%). The pharmacists put forward and discussed 55.8% of the identified DRPs with the physicians, who then adjusted 63.9% of the DRPs put forward. Only 16.6% of the discussed DRPs were rejected by the physicians. The remaining DRPs were considered no longer relevant to adjust (9.5%), unknown whether adjusted or not (4.8%) or solved by the pharmacists after discussion with the physicians (5.1%).

Statistical analyses were performed to see whether there was a difference in which DRP subgroups the pharmacists put forward to the physicians and which subgroups the physicians adjusted. No differences were seen in the analysis, resulting in that the pharmacists did not prioritise a specific DRP subgroup when discussing DRPs with the physicians and physicians did not prioritise a certain subgroup when choosing which DRPs to adjust.

The health care personnel's attitudes towards the LIMM-model (Paper IV)

The response rate to the questionnaire was high; in total 84.0% (68/81) of the questionnaires were returned.

The health care personnel were first asked to estimate the benefits of the clinical pharmacy service in general, both for themselves and for the patients. These benefits were considered to be very high, with a median of 6 on the six point ordinal scales. Then, the health care personnel were asked to estimate the benefits of eight specific activities within the clinical pharmacy service. Six of these activities were estimated to be of great benefit, with a median of 6 and two of the activities were given a median of 5. When estimating the benefit of a pharmacist in the health care team, four statements were used, all of which were thought to be of great benefit, with a median of 6.

Discussion

Medication errors in the transition of care

We found medication errors in the transfer of information on drug therapy to be common at admission to and discharge from hospital. Information on almost one fifth of all drugs was transferred erroneously (Paper I). When introducing a medication report and improving the hospital discharge process, medication errors decreased significantly from 1.05 errors per patient in the control group to 0.48 in the intervention group (Paper III). These results are comparable to other studies performed by our research group [77]. Information on only 4.8% of the drugs was erroneously transferred at discharge in the intervention group (Paper III). Medication errors in the transition of care are common, which has been proven in many studies and a review concludes that the communication and transfer of information between care levels at hospital discharge are insufficient and may affect patient care in a negative way [81].

Several approaches on improving the transfer of information have been launched, one of them being medication reconciliation. In order to achieve the correct medication list, medication reconciliation can be performed at admission to and discharge from hospital. Evidence suggests that pharmacist-lead medication reconciliation at hospital admission identifies more pre admission drugs and medication discrepancies than those lead by physicians [82]. Evaluation of medication reconciliation at admission by National Institute for Health and Clinical Excellence (NICE) suggests that pharmacist-led reconciliation at admission were likely to prevent most medication errors and to be most cost-effective (although the study design in the evaluated studies were not optimal) [83]. The time from discharge until the right information was achieved by the primary care was shortened when using computer generated discharge summaries with the patient as a courier and the quality of the discharge summary increased when using a standardised format [81]. Our model meets some of these criteria as reconciliation at admission is performed by pharmacists, the discharge summary is based on a standardised format and uses the patient as a courier as well as sending it to the physician. Improvements can still be made regarding the automatic generation of information in our discharge summary from the computer based medical records.

A discharge summary specifically adapted to the frail elderly patients has just been developed in a Canadian setting [84]. This model includes, for instance, a specific section for the changes in drug therapy as do the discharge summary developed by our research group. It will be interesting to see if the approach to adjust information to the frail elderly will be more beneficial for this population.

Finding ApoDos a risk factor for medication errors in Paper I was clearly a surprise (albeit a small study population and a large confidence interval). When we also saw this relationship in Paper III, it made us wonder whether ApoDos is a risk factor or a confounder. Perhaps we were more observant on patients with ApoDos? But we do not believe that we categorised medication errors differently in patients with or without ApoDos. One risk with ApoDos could be that the health care personnel do not always know that the patient uses this system. ApoDos is not linked to the medical records and an automatic alert is therefore not provided. The system has been based on communication by telephone and telephax, making it time-consuming. Over the past years improvements in the system have been made as an internet based service has been introduced. This makes it easier to find out if the patient uses ApoDos and to make adjustments in the drug therapy. However, other risk factors with the ApoDos-system have been identified as those using this system may be more exposed to potential inappropriate drug use according to criteria from the Swedish National Board of Health and Welfare [85]. This indicates that the system still needs to be properly evaluated regarding safety and quality of the patient's drug therapy.

As previously described, a discrepancy was considered a medication error if the medication was added, missing or the total dosage over 24 hours was changed and documentation on the reason for the change was lacking. This deals with lack in the quality of documentation. It is important to note that we do not equal this with lack in the quality of the patient's treatment. The consequences of the discrepancies are not known and we do not know if the patient has suffered any harm. We have not separated clinical relevant medication errors from errors being only administrative. However, the mere lack of quality in documentation always poses a potential risk for the patient and is therefore important to address and improve. Other studies on our medication report show that contacts with the health care system due to medication errors decrease by half after the introduction of the medication report [78], so medication errors found with this method seem to be clinically relevant.

It is possible that some selection bias has occurred as we only have included patients in the community health care. Therefore the situation for patients living in their own home without help is unknown. But maybe medication errors are not a major problem in this group? When you live on your own, without help from the

community health care, you are probably more independent and able to understand and evaluate information regarding your drug therapy. In our studies we choose to focus on patients dependent on the system to work in order to achieve the accurate drug therapy. These patients had a medication list used by the community health care, facilitating our evaluation. For patients in their own home without help, such a medication list is not always available. Another possible source for selection bias is that we in both Paper I and Paper III relied on nurses in the community health care to send in medical records used after discharge and in Paper I to also include the patients. We experienced difficulties in achieving the medical records and the nurses might have included the worst cases. Therefore we could have ended up with a selected group with many medication errors, not representative for all elderly in the community health care.

Improved quality in the hospital discharge summary

We found the vast majority of the discharge summaries to be insufficient and lack information. The checklist used in the evaluations dealt with the entire discharge summary and not only the accurateness of the medication report and the medication list, which were our focus in the clinical pharmacy service. As time is a limited resource in the everyday work at the wards, we focused on discussing only problems that could have negative consequences for the patients relating to the medication report and the medication list. Therefore, not many discharge summaries were altogether correct even at the evaluation after adjustment by the physician. Although, the correctness in the medication report and the medication list was improved.

As described above, 190 patients were included in the LIMM-study, but only 172 discharge summaries were evaluated. This is due to patients being discharged in late afternoons, evenings and weekends, when pharmacists did not attend the wards.

It is also important to evaluate the discharge summary and the medication report from the user's perspective. During the autumn in 2010 evaluation of the medication report is performed in the primary care and the community health care. Addressed areas are the clinical use of the medication report and whether it is time-saving and if it increases patient safety.

A more appropriate drug use in the elderly

The LIMM-model resulted in a more appropriate drug use in the elderly at discharge from hospital and at the two week follow-up, as MAI-scores and the number of drugs with inappropriate ratings decreased in the intervention group (Paper II). Most patients in both the control group and the intervention group had at least one drug with at least one inappropriate rating at admission to hospital. This is also seen elsewhere [22, 35, 86]. Models for pharmaceutical care and clinical pharmacy have been shown to improve MAI-scores during hospital stay [54, 86, 87].

High MAI-scores have been shown to relate to hospital admissions and unscheduled ambulatory or emergency care visits [88] and an increase in MAI-scores after discharge (in those not receiving help from a pharmacist transition coordinator at discharge) to relate to more emergency department visits and hospital readmissions [89]. However, contradictory evidence of relationships between MAI-scores and negative patient outcomes have been shown in a review article [90]. More recent findings claim that inappropriate prescribing according to a modified MAI-index predicts ADEs in the elderly [22]. To be able to make more reliable predictions this relationship ought to be studied further.

Validations of the MAI have been published by other researchers. In these validations there seemed to be higher values on intra-rater reliability than inter-rater reliability suggesting that the same persons should determine MAI-scores before and after the intervention [45, 46, 91-93]. As the inter-rater reliability is lower, it would have been preferable if we had made our own reliability calculation when analysing our results. Unfortunately, this has not been made and is not possible to determine retrospectively from the study material. We have instead relied on existing reliability studies.

One advantage with the MAI is that it combines implicit and explicit criteria when determining a drug's appropriateness, instead of only using explicit criteria (as in Beers criteria). The comparison of an explicit and an implicit measurement of appropriateness in drug therapy is therefore very interesting. Do they judge drug therapy equally? One comparison showed an overall agreement between Beers criteria and MAI when comparing the inappropriateness on drug-level of 78% and when comparing patients with inappropriate drug use of 49% [94]. Using the same criteria in another comparison showed that 48.7% of the patients had at least one inappropriate drug according to Beers criteria and 98.7% of the patients had at least one inappropriate drug using MAI [22]. Discrepancies occur and it is therefore important to know which of the methods that has been used when comparing studies on drug appropriateness.

When not using a randomised controlled design, there is always the risk that the intervention group and the control group differ at baseline. This was the case for the MAI-investigation. There can be several explanations for this difference. First, the control group was included prior to the intervention group and the pharmacists attended the wards from the start of the control period until the end of the intervention period. It could therefore be possible that the presence of the pharmacists at the wards and the forming of relationships with the physicians led to an increased awareness of problems in drug therapy over time. Then, at the start of the interventions, the health care personnel could already have been aware of the problems and therefore, intentionally or unintentionally more prone to identify and adjust the problems themselves. Second, as this is an open study, the pharmacists knew which group the patient belonged to when determining MAI-scores and could therefore unintentionally have affected the scoring of the MAI. To minimise the influence of subjective assessments, standardised tools and checklists were used in the process and the same approach was used in both groups. MAI-scores were also first determined by two pharmacists individually and then discussed together to reach consensus.

MAI-scores can be calculated for each drug and then summated to a MAI-score per patient. Summating ordinal data and then treating it as a continuous variable is questionable. In addition to this, a drug is either appropriate to an individual or not. Therefore we were also interested in looking at the number of drugs with at least one inappropriate rating per patient. When designing the study, available articles used median and SD when presenting their MAI-scores. Therefore we had to use Students T-test for our study size calculation. But as MAI-scores can not be considered as normally distributed data, we would have preferred Wilcoxon.

When analysing the results many analysis were performed on both groups, who were relatively small. This can of course be questionable. When performing many analysis there is always the possibility that something becomes significant by random. Perhaps a Bonferroni correction should have been made or the limit of significance lowered. However, we declared early on that we were going to perform many analysis, as we had to perform analysis according to the study size calculation even though we were more interested in the number of drugs with or without inappropriate ratings. Then, when the groups differed at baseline, we could not only compare the absolute figures but had to look at changes as well.

The process of identifying, solving and preventing DRPs

The presence of DRPs in the elderly is extensive. Of all patients included in the LIMM-study 97.4% had at least one DRP and on average 6.5 DRPs were found in each patient. The pharmacists discussed 55.8% of the identified DRPs with the physicians and solved 4.4% of the identified DRPs themselves without discussion with the health care personnel. The physicians then chose to adjust 63.9% of those discussed with the pharmacist. Of all DRPs put forward to the physicians, the pharmacist could solve 5.1% after discussion with the physicians. The number of identified DRPs per patient was somewhat lower than another study performed by our research group [80] but higher than found in other studies [55, 95].

The acceptance of the advice put forward by the pharmacists also differs between the studies. In the study by Gillespie et al the hospital physicians accepted 69% of the pharmacists' suggestions [55], Blix et al reports a 91.8% acceptation rate [95] and Bondesson et al found the physicians to accept 93% of the pharmacist's suggestions [80]. A review article stated that physicians on average accept 85.5% of the advice put forward by the pharmacists [96]. In our study, physicians accepted 63.9% of the suggestions put forward by the pharmacists. The lower acceptation rate could possibly be due to lack of documentation as it was uncertain whether 4.8% were adjusted. Another possible contributing factor could be that the pharmacists themselves solved 4.4% of identified DRPs without discussing with the physicians and 5.1% of the DRPs discussed with the physicians. A DRP could thereby have been adjusted although it was not discussed with the physicians or adjusted by them.

In the clinical pharmacy service used by Blix et al, pharmacists extracted information from medical records, team meetings with physicians and nurses and patients, performed drug reviews and participated in daily team meetings discussing DRPs [95]. A standard data recording form was designed. The study design used by Gillespie et al is more similar to ours as it also includes medication reconciliation at admission and discharge [55]. Standard operating procedures were also developed [55]. However, it is difficult to compare methods as the development and the exact design of the tools used in these studies are not fully described. We have launched a structured questionnaire to use in the medication reconciliation at admission [76] and the medication report at discharge [77], aiming to maintain a correct medication list throughout the hospital stay and beyond.

In this study, we were also interested in better understanding how the pharmacists and the physicians prioritise between different DRPs. The results showed that the

pharmacists and physicians did not prioritise a specific DRP subgroup for another, but discussed and adjusted all subgroups to the same extent. However, some DRPs must be considered more important than others, as 14.4% were not put forward to the physicians and 16.6% were rejected by the physicians. But this selection does not seem to be based on DRP subgroup. Even dividing DRPs into extremely important clinical significance and minor clinical significance does not shed light on how the prioritising takes place, as the physicians left DRPs with clinical significance unadjusted [95]. Perhaps other factors should be considered. Is it so that the relationship between the pharmacist and physician in question affects the physician's will to adjust the DRP? Zillich et al have suggested this and developed an instrument to measure the collaboration from the physician perspective [97].

Many definitions of DRPs and further classification into subgroups exist, some of which are validated and others not [63]. In order to be consistent with other studies performed by our research group, the definition of DRP by Strand et al [62] and the classification system with subgroups published by Cipolle et al [64] were used. However, these were not found to match the ideal classification system, as defined by van Mil et al [63]. The wide variety of classification systems makes it difficult to compare studies on DRP. It is therefore important to know which system that has been used when comparisons are made.

The health care personnel's attitudes towards the LIMM-model

The LIMM-model was very appreciated by the health care personnel and considered to be highly beneficial both for themselves and for the patient. This is comparable to the attitudes towards the LIMM-model in another setting [80].

When using a questionnaire as an evaluation model there is always the risk of selection bias, as the people who are indifferent tend not to answer and you only get answers from those very positive or very negative. A high response rate is needed when drawing conclusions from the answers. We had a response rate of 84.0% and therefore consider these results to be reliable.

We used a six point ordinal scale. Using an equal number of statements forces the respondents to take a stand, either positive or negative, and not just agree with the one in the middle when uncertain.

Qualitative methods to evaluate the health care personnel's attitudes could also have been used. However, our research group lacked resources to perform such evaluations.

The study design in the LIMM-study

The LIMM-study was initiated as the department of internal medicine at Landskrona Hospital wanted to start clinical pharmacy services on an everyday basis at its three wards. In this arrangement it was difficult to use the optimal study design for an intervention study (randomised) as the intervention was based on a new profession and a new process. We chose to design the study in the most favourable way regarding the prerequisites we were given, combining the services asked for by the hospital with an evaluation of our interventions. The control group was included at the same hospital prior to the interventions. The advantage with this procedure was that the hospital, staffing and patient clientele were identical. It is always preferable to have parallel intervention and control groups. However, having the same hospital as the setting for both groups at the same time is not preferable, as there is a substantial risk for carry over effects. Instead, we could have chosen a department of internal medicine at another hospital, but then it would be difficult to know whether the difference between the groups would be due to our interventions or to the different environments.

At inclusion, when it was not possible to communicate with the patient, a next of kin was asked instead. There is a potential problem when a next of kin gives consent to participate in a study, as one can not be sure that the next of kin has the patients best interest in mind. However, this procedure was not questioned by the ethics committee.

As it was not possible to include all patients, there is a risk for selection bias. In order to reduce the risk for this bias the inclusion was performed according to a specific scheme which was the same in both the intervention group and the control group.

Another difficulty with the study design is that it is the same persons who perform the interventions, collect and analyse the data and draw the conclusions. Due to lack of resources it was however not possible to design the study in any other way. Over time, more and more research groups in Sweden focus on clinical pharmacy and therefore the possibility increases to have one group performing the interventions and another one independently evaluating them.

The benefits of the LIMM-model so far

So far, the different components in the LIMM-model have proven beneficial in several areas during and after a patient's hospital stay. In addition to the studies presented in this thesis, the following results exist.

At admission, the patient medication interview performed by the pharmacists helps to identify medication errors [76, 98], DRPs [98] and problems with compliance, knowledge and attitudes towards the drug therapy [76]. The medication reconciliation performed by the pharmacist at admission seems to identify DRPs not identified by other health care personnel [99].

During the hospital stay, the medication review performed by the pharmacists identifies DRPs, the physicians accept the majority of the pharmacists' suggestions for improvement [100] and the majority of identified DRPs are considered clinically significant [101]. The use of the pharmaceutical care plan reduced the number of DRPs [102], the total number of drugs [102], the number of unidentified DRPs [80] as well as the number of inappropriate drugs [103]. The number of drug-related hospital revisits were reduced in patients treated in the LIMM-model [104]. The addition of pharmacists to the health care team is highly appreciated by the health care personnel [80].

At discharge, the medication report reduced medication errors in the transition of care and medication errors with risk for clinical consequences [77] as well as the need for medical care after discharge due to medication errors [78].

In addition to his, the medication report and medication reconciliation has been acknowledged nationally as The Swedish Association of Local Authorities and Regions has initiated a programme for improving patient safety where medication reconciliation has been introduced as a method to prevent medication errors [105].

Benefits of Clinical Pharmacy

A review article, evaluating the effects of interventions performed by clinical pharmacists on inpatients, stated that the addition of clinical pharmacy services generally resulted in improved care [106]. Interventions such as participating on patient rounds, interviewing patients, reconciling medications and providing patient discharge counselling and follow up resulted in improved outcomes [106]. Medication reviews by pharmacists and working in multidisciplinary teams were in a review found to be among the interventions that improved prescribing in the elderly [107]. Further, clinical pharmacy services in American hospitals have

shown to be associated with a reduction in ADRs and the greatest effects were seen in hospitals where pharmacists provided admission drug histories [108]. A reduction in mortality rates has also been associated with several clinical pharmacy services in American hospitals where pharmacists provided drug use evaluation, in-service education, ADR-management, drug protocol management, admission drug histories and where the pharmacist participated on the cardiopulmonary resuscitation team and on medical rounds [109]. It is important that the clinical pharmacy services are performed in close collaboration with the health care personnel. A Swedish report concluded that medication reviews alone is not the solution to problems related to pharmacotherapy in the elderly, instead many different actors need to take actions on several levels in order to come to terms with these problems [40].

Recent evaluations concluded that for every dollar invested in clinical pharmacy services, 4.81 dollars was achieved in economic benefits [110]. Therefore, the introduction, development and validation of these services is of utmost importance in order to improve drug therapy in the elderly, reduce negative patient outcomes and minimize health care costs for the society.

Conclusions

The studies presented here add information and knowledge on clinical relevant topics regarding drug therapy in the elderly, as great room for improvement has been shown to exist in this field. A structured and systematic approach on improving pharmacotherapy in the elderly with the addition of clinical pharmacists to the hospital setting, the LIMM-model, can help improve the drug therapy in the individual patient.

- Medication errors in information on drug therapy are common in the transition of care (Paper I).
- The introduction of the LIMM-model, including an evaluation of the discharge summary, reduces medication errors at discharge from hospital to the community health care (Paper III).
- The use of inappropriate drugs in the elderly is widespread. The LIMM-model, a systematic approach on improving drug therapy in a hospital setting, results in a more appropriate drug therapy in elderly patients (Paper II).
- The LIMM-model helps to identify DRPs in the elderly and the pharmacists' suggestions on how to solve these problems are well accepted by the physicians (Paper IV).
- The LIMM-model is highly appreciated by the health care personnel and is considered very beneficial both for the health care personnel and for the patients (Paper IV).

Svensk sammanfattning (Swedish summary)

Ett systematiskt sätt att förbättra läkemedelsbehandlingen av de äldre

Den äldre befolkningen i Sverige ökar i antal och med det ökar även antalet äldre med många sjukdomar som behöver läkemedel. Personer som är 75 år eller äldre utgör 9% av Sveriges befolkning men använder mer än 25% av alla läkemedel.

I takt med att man blir äldre sker en del förändringar i kroppens funktioner som kan påverka effekten av läkemedel. De största förändringarna är nedsatt metabolism i levern och nedsatt elimination i njurarna. Detta kan leda till att läkemedel ackumuleras i kroppen vid bibehållen dosering och att patienten löper större risk att drabbas av biverkningar. En ökad känslighet för vissa läkemedel har också setts vid stigande ålder och det gäller bland annat sömnmedel. Det finns också de läkemedel som är direkt olämpliga till äldre, som långverkande bensodiazepiner och läkemedel med antikolinerga effekter. Studier på svenska särskilda boenden visar att användningen av olämpliga läkemedel till äldre är utbredd. Detta är inte bara ett svenskt problem utan ses över hela världen. Användningen av många läkemedel och olämpliga läkemedel kan leda till negativa konsekvenser för patienten. De negativa konsekvenserna omfattar biverkningar, sjukhusinläggningar och död men är i de flesta fall möjliga att förhindra. Olämplig läkemedelsanvändning är också kostsam för samhället.

Eftersom äldre personer är sjukare har de också ett större behov av vård och kan behöva läggas in på sjukhus eller flytta till särskilt boende. I övergångarna mellan vårdformer har det visat sig att information om läkemedel kan bli felaktig och läkemedel tillkomma eller försvinna av misstag.

För att komma till rätta med både olämplig läkemedelsbehandling och osäker informationshantering vid förflyttning mellan vårdformer har vi utvecklat Lund Integrated Medicines Management (LIMM-modellen). Modellen omfattar kliniska apotekare på sjukhusavdelningar som en del i vårdteamet med fokus på att identifiera, lösa och förebygga läkemedelsrelaterade problem (LRP).

Syftet med denna avhandling var att undersöka om en systematisk och strukturerad modell för läkemedelsbehandling (LIMM-modellen) leder till en lämpligare läkemedelsbehandling av de äldre och en säkrare överföring av information om läkemedelsbehandling vid utskrivning från sjukhus.

I det första arbetet undersökte vi överföringsfel i äldres läkemedelsordinationer vid inskrivning och utskrivning från sjukhus till särskilt boende. Det räknades som fel om ett läkemedel tillkommit, försvunnit eller om dygnsdosen ändrats utan att detta fanns dokumenterat. Vi såg att information om i snitt vart femte läkemedel överfördes felaktigt. Vid inskrivning hade 85% av patienterna minst ett överföringsfel och vid utskrivning sågs överföringsfel hos 54% av patienterna.

I det andra arbetet jämförde vi en grupp patienter som fick traditionell vård med en grupp patienter som vårdades på avdelningar där LIMM-modellen fanns. Vi mätte olämplig läkemedelsbehandling vid inskrivning, utskrivning och två veckor efter utskrivning genom att använda Medication Appropriateness Index. Nästan alla patienter hade minst ett olämpligt läkemedel vid inskrivning. Vid utskrivning och två veckor efter utskrivning sågs signifikant färre olämpliga läkemedel hos den grupp patienter som hade vårdats i LIMM-modellen.

I det tredje arbetet infördes en kvalitetssäkrad läkemedelsberättelse som en del i utskrivningsinformationen inom ramen för LIMM-modellen. Vi jämförde en grupp patienter som hade fått traditionell utskrivningsinformation med en grupp som vårdats i LIMM-modellen. De som fått en kvalitetssäkrad utskrivningsinformation hade signifikant färre överföringsfel i sina läkemedelsordinationer vid utskrivning från sjukhus till särskilt boende och kommunal hemsjukvård.

I det fjärde arbetet kartlade vi apotekarnas arbete med att identifiera och föra fram läkemedelsrelaterade problem till läkarna i LIMM-modellen. Vi fann att apotekarna identifierade i genomsnitt 6.5 LRP per patient. Mer än hälften av dessa diskuterades med läkarna som sedan åtgärdade majoriteten av de framförda problemen. Vi utvärderade också läkares och sjuksköterskors attityder till LIMM-modellen. Läkarna och sjuksköterskorna ansåg att LIMM-modellen var till mycket stor nytta både för patienterna och för dem själva.

Sammanfattningsvis har LIMM-modellen visat sig leda till lämpligare läkemedelsbehandling av de äldre och en säkrare överföring av information om läkemedelsbehandlingen vid utskrivning från sjukhus. LIMM-modellen är mycket uppskattad av hälso- och sjukvårdspersonal och tillför stor nytta för patienter, läkare och sjuksköterskor.

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Appendix I-IV