Aspects on optimisation of drug therapy in the elderly

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by

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To my family

'Primum est non nocere'

Hippocrates

Contents

Original articles

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

I. Midlöv P, **Bondesson Å**, Eriksson T, Petersson J, Minthon L, Höglund P. Descriptive study and pharmacotherapeutic intervention in patients with epilepsy or Parkinson's disease at nursing homes in southern Sweden. *European Journal of Clinical Pharmacology* 2002; 57: 903-10.

II. **Bondesson Å**, Midlöv P, Eriksson T, Höglund P. Pharmacotherapeutic interventions by a multi-speciality team: opinions of the general practitioners and nurses. *European Journal of Clinical Pharmacology* 2003; 59: 65-9.

III. 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: 116-20.

IV. **Bondesson Å**, Hellström L, Eriksson T, Höglund P. A structured questionnaire to assess patient compliance and beliefs about medicines taking into account the ordered categorical structure of data. *Journal of Evaluation and Clinical Practice* (Accepted 17 June 2008).

V. **Bondesson Å,** Eriksson T, Kragh A, Holmdahl L, Midlöv P, Höglund P. In-hospital medication reviews reduce the numbers of unidentified drug-related problems (In manuscript).

Introduction

Although drug treatment is an important cornerstone in curing, preventing, reducing or slowing diseases or its symptomatology, it is also a cause of illness and death. In order for the drugs to have the desired effects without unacceptable adverse drug reactions they must further be selected, dosed, used and then monitored properly. However, when medicines are given, there is a risk that the patient's quality of life instead is diminished, as a result of patient idiosyncrasy, inappropriate prescribing, delivery or behaviour by the patient.

Elderly patients often use many drugs [1]. In 2007, the elderly (those ≥ 65 years of age) in Sweden constituted 18 percent of the total population [2] but accounted for 41 percent of the total drug expenditure costs [3]. The corresponding figures for elderly patients ≥ 75 years of age were; 8.7 percent of the population and 23 percent of the total drug expenditure costs. Elderly patients in nursing homes use an average of ten different drugs [4] and the corresponding figure for elderly patients admitted to wards of internal medicine is on average nine drugs [5]. The presence of multiple medical illnesses contributes to the problem of polypharmacy in the growing elderly population.

It is well established that the potential for drug-related problems and adverse drug reactions increases both with age [6, 7] and the number of medications prescribed [8-12]. Age-related alternations in pharmacokinetics and pharmacodynamics may also place the older patient at increased risk for harmful side effects from medication and drug-drug interactions. Age-related changes in pharmacokinetics principally affect drug absorption, distribution, metabolism and elimination [13]. The single most important change in pharmacokinetics in the elderly population is the decrease in renal function. Many drugs are affected by decreased renal function e.g. digoxin, metformin, which requires dosage adjustments (lowering of doses) or withdrawal of medication. The pharmacodynamic age-related alternation results in an increased sensitivity to unwanted effects of medicines. Changes in pharmacodynamics are primarily seen in the cardiovascular and CNS system [13]. Elderly patients are specifically susceptible to anticholinergic effects, having an increased risk to be mildly cognitively impaired and affected by delirium [14].

The solution to avoiding drug toxicity when prescribing medications for elderly patients requires an understanding of the ageing process, a familiarity with the medications prescribed, a restraint in prescriptions and a high index of suspicion for drug side effects [15]. Experts suggest that substantial morbidity and health care expenses could be avoided by improving prescribing practices [16]. Inappropriate medication prescription is common in nursing home patients [16, 17], elderly ambulatory care patients [18] and elderly patients presented to the emergency department [19]. Based on a consensus expert opinion and literature review Beers *et al* [20], in 1991 created a list of explicit criteria for inappropriate prescribing in older patients, latest up-dated in 2003 [21]. A similar list of inappropriate medication for elderly patients, adapted to suit Swedish conditions has been produced by the Swedish National Board of Health and Welfare [22]. Identifying inappropriate medication use have the potential to decrease drug-related costs and overall health care costs, reducing the adverse drug event-related admissions and improving care for the elderly.

Pharmaceutical Care and Clinical Pharmacy

Pharmaceutical care was defined by Hepler and Strand [23] as *the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life*. The process of pharmaceutical care involve pharmacists or health care practitioners cooperation with the patient and other health care professionals in order to design, implement and monitor a therapeutic plan that will produce specific therapeutic outcomes for the individual patient. Pharmaceutical care involves three major functions on behalf of the patient; identification of potential and actual drug-related problems and then solution of the actual ones and prevention of the potential ones. Pharmaceutical care is provided for the direct benefit of the patient and the health care practitioner that practice pharmaceutical care are responsible for the patient's quality of care. The practitioner has the responsibility to make sure that the patient's goals of therapy are met and that optimal outcomes are realized. Integration with other elements of health care is essential to guarantee the patients' outcome.

There is no consensus on the definition of **clinical pharmacy**, although all proposed definitions refer to the contribution that clinical pharmacists can make to the realization of high-quality and rational drug therapy for the individual patient or a specific patient population [24, 25]. The practice of clinical pharmacy embraces the philosophy of pharmaceutical care; blending a caring orientation with specialised therapeutic knowledge, experience and judgement for the purpose of ensuring optimal patient outcomes [25]. The aim is to provide the best treatment alternative for the individual patients, and then maximise the clinical effect and minimise the risk of treatment induced adverse events for the selected medicine. Clinical pharmacy may be practiced in any setting where medicines are prescribed and used, including hospital wards, clinics, general practitioners practices, nursing homes and even community pharmacies.

The concept pharmaceutical care and clinical pharmacy are closely related and have similar goals, but differs in philosophical base. Clinical pharmacy is a process carried out by clinical pharmacists without reference to affect patient specific therapeutic outcomes or quality of life. Pharmaceutical care, on the other hand, is a practice involving patient specific outcomes and a responsibility towards the patient; improving the patients' quality of life. Further more, according to the definition, pharmaceutical care is not explicitly carried out by a clinical pharmacist, but may be practiced by other professions that provide care. Pharmaceutical care has a larger scope, describing a cooperative system providing drug therapy for the individual patient. Pharmaceutical care and clinical pharmacy may be seen as two complementary approaches, both contributing to safer and more effective drug therapy.

Drug-related problems

The identification, prevention and solution of drug related problems, is the core process of pharmaceutical care, aiming to improve patient outcomes. A drug-related problem is defined by Strand et al [26] as *an undesirable patient experience that involves drug therapy and that actually or potentially interferes with the desired patient outcome*. A drug-related problem always has two primary components: the patient must be experiencing an undesirable condition (or incurs a risk) and some relationship must exist (or be suspected to exist) between the undesirable condition and the drug therapy. Sometimes the term drug-therapy problem [27] is used instead of drug-related problem, to emphasize that the concept refers to a

system approach, including problems in the whole drug therapy chain, including untreated indications.

Classification of drug-related problems is essential to the development of the pharmaceutical care practice as well important for pharmaceutical care research [28]. Several drug-related problem classification systems can be found in the literature, however, it is generally agreed that a comprehensive, well constructed and validated system is currently lacking [28]. In a review article, van Mill *et al* [28] identified 14 classifications systems for drug-related problems. None of these classification systems meet the authors' ideal classification system of being clearly defined, validated, easy to use, having an opened, hierarchical structure and focusing on the drug use process and outcome and being able to separate the problem itself from the cause. According to our knowledge, Strand *et al* [26] 1990 constructed the first sub-group classification system of drug-related problems (**Table 1**). Many of the latter published classification systems have been developed from this classification system, and have made modifications and/or adaptations to suit their purposes. Even Strand has modified the initial classification system in the Cipolle, Strand and Morley classification system [27] (**Table 1**). The initial Strand *et al* category *interaction* is classified as the Cipolle, Strand and Morley categories *dosage too low, dosage to high* or *adverse drug reaction,* according to the result of the interaction. In both classification systems each of the types of drug-related problems may be further classified as *actual* problems that requires interventions or *potential* problems that requires care, intervention and/or monitoring to ensure that the problem is prevented.

Table 1 Categories of drug-related problems.

Strand *et al*	**Cipolle, Strand and Morley**
Medical indication for drug therapy	Need for additional therapy
No valid medical indication	Unnecessary drug therapy
Wrong drug	Wrong drug
Too little of the correct drug	Dosage too low*
Adverse drug reaction	Adverse drug reaction*
Too much of the correct drug	Dose to high*
Patient not receiving the prescribes drug	Non-compliance
Drug-drug, Food-drug, Drug-Laboratory interaction*	-

* The category interaction (Strand *et al*) is divided into the three categories *dosage too low, dosage to high* or *adverse drug reaction* (Cipolle, Strand and Morley), according to the result of the interaction.

Compliance

Effective pharmacotherapy requires the medication to be consumed in a particular dosage, at a specified time and for a specific period of time. Non-compliance to drug therapy therefore represents one type of drug-related problem, related to the patients' drug taking behaviour. Compliance is often defined as *to which extent a persons behaviour (in terms of taking medications, following diets, or executing lifestyles changes) coincides with medical or health advice* [29]. The clinical outcome or the result of the treatment is another way to define compliance [30]. The purpose of improving the compliance is not to achieve a perfect agreement between 'what the patient do' and the prescription of the physician, but to increase compliance only to the level where the outcome of the treatment improves [31]. However, this specific level is seldom known in clinical practice.

Poor compliance with drug therapy can jeopardize treatment and have shown to increase morbidity [32], mortality [33-35], admission to hospital [17, 36] as well as costs [36] and the

problem is very common. In a review article [30] the compliance rate for long term medication used for prevention, treatment or cure ranged between 33% and 94%. The compliance rates in long-term therapy tend to reach at the most 50%, regardless of the illness or setting [37-39]. Because of the potential negative consequences of non-compliance it is very important to identify non-compliant patients and motivate them to become and stay adherent.

The measuring of compliance poses a methodological challenge, as no method is considered to be the golden standard [31]. The methods available for measuring compliance can be broken down into direct methods of measurement (for example directly observed therapy and measurement of the level of medicine in the blood) and indirect methods of measurement (for example patient questionnaires, pill counts, prescription refills and clinical response) [40]. All methods have advantages and disadvantages, and measuring compliance has been associated with insecurity [41]. Identifying non-compliant patients can be done by using validated questionnaires, like the *Morisky four-item scale* [42]. Questionnaires are relatively inexpensive, and easy and quick to administer, but unfortunately patients' compliance tends to be overestimated [31]. Studies indicate that only 25-50% of non-compliant patients can be identified by interviews. Although, evidence support that patients reporting non-compliance are more likely to respond to compliance-improving strategies than other non-compliant patients [29].

It has been suggested that patients' motivation to take drugs depends upon their understanding of the condition and the treatment combined with their faith in the physician [43]. Patients establish the value of their treatment through a testing process, which influence decisions about how to use the medication. Based on understanding and beliefs about the medication treatment, the patients balance the perceived benefits against the perceived risks [43, 44] and decide whether they should reject, passively accept or actively modify the prescribed therapy. A correlation between beliefs about medication treatment and adherence, where negative beliefs correlated with non-adherence and positive beliefs with adherence, have been shown in previous studies [44] [45]. When working with behavioural interventions aiming to improve patients' motivation to adhere to therapy it is valuable to assess patients' beliefs about their medicines. This could be assessed by *Beliefs about Medicines Questionnaire-specific* (BMQ- specific) [46].

What is increasingly apparent, is that the role of the patient is critical in decision-making about medication, together with communication between the patient and health care professionals. This has been articulated through the concept of concordance which has been described as a therapeutic alliance between the patient and health care professionals.

Medication errors

Patients moving from one health care setting to another always face the risk of something going wrong in relation to their medicines. Incomplete or inaccurate medication lists may result in medication errors, like inadvertent discontinuation or initiation of medications and administration of too high or too low dosages. Unidentified medication errors may lead to drug-related problems, which at the worst may result in untreated disease, adverse drug reactions or adverse drug events.

A medication error is defined by Leape *et al* [47] as *any error in the process of prescribing, dispensing, or administering a drug,* whether there are any adverse consequences or not. Medication errors are much more frequent than adverse drug events and reactions. An adverse drug event is defined by Leape *et al* [47] as *an injury related to the use of a drug, although that causality of this relationship may not be proven*, and an adverse drug reaction is defined by WHO [48] as *a response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans*. The definition of adverse drug reaction excludes therapeutic failure, poisoning and drug abuse and does not include adverse events due to errors in drug administration or poor compliance.

The terms medication error, adverse drug event and adverse drug reaction overlap (**Figure 1**), but some differences exists. A medication error is present whether any adverse consequences occur or not, while adverse drug reactions and events by definition require substantial consequences to occur, related to the drug treatment. Adverse drug events and reactions are usually caused by a medication error, but there might be no error at all involved. In contrast to the WHO definition of adverse drug reaction, the definition of adverse drug events also includes errors in administration.

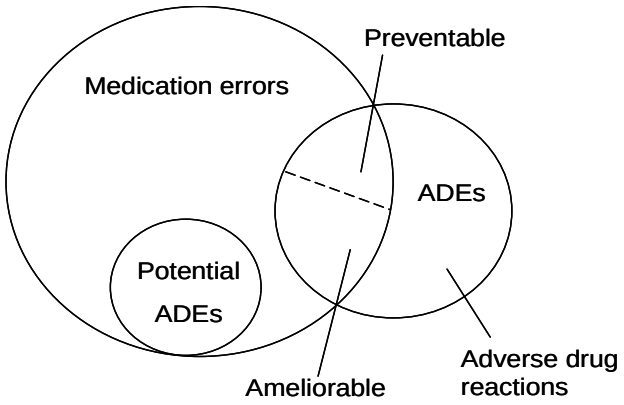

Figure 1. Relationship between adverse drug events (ADEs), potential adverse drug events, and medication errors [49]. A potential adverse drug event is a medication error with the potential to cause injury. A preventable adverse drug event is an injury that results in an injury, that is the result of an error at any stage in the medication use, in contrast to non-preventable where there is no error in the medication process, for example a new allergic reaction. An ameliorable adverse drug event is an injury of which the severity or duration could have been substantially reduced if different actions were taken.

Medication errors occur commonly at the interfaces of care. It has been estimated that 46 % of the medication errors occur on admission or discharge when new orders are written for the patient [50]. Many studies describing the problem of a correct medication list at admission are conducted on “healthy” patients, being able to give details about their medicine use before the hospitalisation. In a study by Beers *et al* [51] it was reported that 83 % of the patients at admission had at least one medication error. Other studies confirm these problems; 61 % [52] and 67 % [53]. In a study by Cochrane *et al* [54], a lack of continuity between medicines at discharge and those being taken post discharge has been shown for patients being able to give details about medicine use.

According to our knowledge, there are not many studies that describe medication errors originating from the process of transferring information between hospital and primary health

care, for patients not handling their medicines on their own e.g. nursing home patients and patients with care from the community nursing system. In a Norwegian study [55], it was shown that 19 out of 20 patients, living in nursing homes or in their own homes with care from the community nursing system, who were admitted to and discharged from a hospital had a total of 100 discrepancies in their medication information.

Consequences of non optimal drug therapy

Both drug-related problems in general [6, 8, 56-58] and specifically adverse drug reactions [7, 10, 56] have shown to cause hospital admissions. In three meta-analysis [59-61] adverse drug reactions have shown to account for approximately five percent of all hospital admissions. In a subgroup analysis, conducted by Beijer *et al* [61] the odds for elderly people to be hospitalized because of adverse drug reactions was four times higher than for younger ones, 16,6 % verses 4,1 %. Studies have further shown that the drug-related admissions often are preventable; 29 % [61], 59 % [58], 68 % [62] respectively 76 % [63] of the admissions. The meta-analysis by Beijer *et al* [61] revealed that in the elderly this figure is even higher, 88 %. A meta-analysis by Lazarou *et al* [59] showed that approximately two percent of the admitted patients were affected by serious adverse drug reactions. Adverse drug-reactions and events have further shown to increase the length of hospital stay [11, 64-67] the cost of hospital stay [65-67] as well as mortality [66].

Methods aiming to optimise drug therapy

Medication histories

Medication histories in the hospital records are often incomplete [53]. An accurate medication history, including an updated medication list is a prerequisite for the physician to make appropriate diagnostic and prescribing decisions during the hospital stay. Given the consequences of medication errors and its potential for prevention, there is a need to identify effective interventions that can reduce medication errors at admission. The medication history interview is a vital tool in identifying medication errors [51-53] and giving insight into the patient's medication taking experience, patient understanding of their medications and patient motivation for compliance. It has been shown that trained clinical pharmacists obtain more complete medication histories, compared to other health care professionals [52, 68]. In a study by Bond *et al* [69] medication histories at admission was one out of four clinical pharmacy services associated with lower mortality rates. Clinical pharmacists conducting medication histories at admission and drug information sessions with the patient at discharge have shown to reduce the numbers of readmissions to hospital [52].

Medication reviews

Medication reviews have been advocated as a method to ensure that patients gain maximum benefit from their drugs, while simultaneously reducing the potential for harm. Achieving these goals is the core of a successful medication review, defined by the National Health Services in UK [70] as *a structured critical examination of the patient medicines with the objective of reaching agreement with the patient about the continued appropriateness of the treatment, optimising the impact of medicines, minimising the number of medication-related problems and reducing waste*. Medication reviews is the base for Pharmaceutical Care, and

can be conducted in any setting where medicines are prescribed and used. It is widely acknowledged that medication reviews can be done at a number of levels [71]; ad hoc (an unstructured, opportunistic review), prescription review (a technical review of a list of patients' medicines), treatment review (a review of medicines with patient's full notes) and as a clinical medication review (a review of the patient, the illnesses and drug treatment during a consultation).

Drug-related morbidity and mortality in nursing facilities represent a serious economic problem. In a US study by Bootman *et al* [72] it was estimated that for every dollar spent on medicines, $1.33 in health care resources were consumed in the treatment of drug-related problems and that consultant pharmacist significantly reduced cost related to the treatment of drug-related problems. The Swedish National Board of Health and Welfare has concluded that the use of medicines in nursing homes can be improved by regular medication reviews with the participation of a general practitioner, a pharmacist and a nurse [73]. In a Swedish study [74] medication reviews have shown to decrease the prescribing of inappropriate drugs, e.g. psychotics, benzodiazepine hypnotics and antidepressants. Other studies conducted at nursing homes have shown to reduce surrogate outcomes like the incidence of drug-related problems [75] and the number of drugs used [76, 77], with minimal or no change in primary outcomes like morbidity or mortality [76, 77]. However, in above sited studies the benefit of medication reviews for the patient in terms of health related quality of life has not been evaluated or shown. In a review article by Pickard *et al* [78] pharmacist interventions conducted on ambulatory patients further inconsistently demonstrated positive effects on patient health-related quality of life. In order to demonstrate the positive effect of pharmaceutical services on patient health, Pickard *et al* advised future researchers to continue to incorporate health-related quality of life outcome measures.

The role of clinical pharmacists in the care of hospitalized patients has evolved over time, with increased emphasis on collaborative care and patient interaction. In the report *To err is human* [79] it was pointed out that pharmacists are an essential resource in safe medication use, that participation of pharmacists on rounds improves medication safety and that pharmacist-physician-patient collaboration is important. Clinical medication reviews in hospitals are of particular importance because most studies reporting medication errors were in hospitalized patients, and with the growth of hospital medicine, there is increased focus on interventions to improve the care of hospitalized patients. Clinical medication reviews have shown to decrease the number of used drugs [80, 81], decrease the number of drug-related problems [82], decrease costs [80, 83-87], decrease the length of stay at the hospital [83, 86, 87], decrease the number of adverse drug events [88], increase the quality of life [87] and decrease the number of readmissions to hospital [87], with no impact on mortality [85, 87].

Rationale for the studies

The emphasis in this thesis has been to describe the nature of the drug related problems in the elderly population and to evaluate methods aiming to identify, resolve and prevent drug-related problems. Elderly patients were chosen because they generally use many medicines, and are more susceptible to adverse drug reactions. Increased age and an increased number of medicines have further been associated with an increased risk of developing drug-related problems, including adverse drug reactions. As many of the adverse drug reactions are preventable and causes increased costs as well as increased mortality, it is of utmost importance to identify, resolve and prevent the drug related problems. The clinical pharmacist is a potentially valuable resource in this process, working in close liaison with other health care professionals.

Drug-related problems in the elderly

Drug-related problems are common in the elderly population and may considerably increase the risk of morbidity and mortality. It is therefore essential to identify, resolve and prevent drug-related problems. Therefore we wanted to investigate the number of and types of drug related problems identified by clinical pharmacists conducting medication reviews at nursing homes (Paper I) and at an internal medicine ward (Paper V).

Evaluation of the developed models aiming to optimise drug therapy

Medication errors are common and occur most commonly at the interfaces of care, in particularly at admission to hospital as a result of incomplete medication histories in the hospital records. An erroneous medication use history may result in failure to detect drug-related problems as the cause of hospital admission or lead to interrupted or inappropriate drug therapy during hospitalization. The medication history interview is a vital tool in identifying medication errors and we wanted to evaluate the use of the *Structured Medication Questionnaire* in identifying medication errors as well as deviations in drug handling, medication knowledge, compliance and negative beliefs about drug treatment (Paper IV).

Drug-related problems and adverse drug events have shown to cause hospital admissions, increase the length of hospital stay, cost as well as mortality. Medication reviews have been advocated as a method to ensure that patients gain maximum benefit from their drugs, while simultaneously reducing the potential for harm, minimising drug-related problems.
Studies conduced at nursing homes have shown to improve surrogate outcomes like drug therapy, with minimal or no change in measurable benefits to patients, like quality of life. In our study (Paper I) we investigated the effects of the medication review in terms of health-related quality of life, activity of daily living and confusion state.
Clinical medication reviews in hospitals are of particular importance because medication errors are common in hospitalized patients. In our study (Paper V) we investigated the effects of medication reviews and systematic medication care plans on the number of unidentified drug-related problems during the hospital stay.

Medication errors when elderly patients are transferred between different levels of care

Studies on patients being able to give details about their medicines use before hospital stay have shown that incorrect medication lists at admission are frequently present. Studies on the same type of patient population have also shown a lack of continuity between medicines at discharge and those taken post discharge. The magnitude of the problem is to our knowledge not well studied for patients not handling their medicines on their own e.g. nursing home patients and patients with care from the community nursing system. We therefore wanted to investigate the nature and frequency of errors in medication when elderly patients were transferred between hospital and primary health care (Paper III). We further investigated the nature and frequency of errors at admission, for elderly patients admitted to an internal medicine ward (Paper IV).

Health care practitioners' opinion towards the developed models

In the medication review process, there is an underlying assumption that if clinical pharmacists or multi-speciality teams provide evidence based pharmacotherapeutic recommendations, the patient responsible physicians, in turn will implement these recommendations. In both the nursing home study (Paper I) and the internal medicine ward study (Paper V) new medication review programs were started and implemented. If such programs are to be used on regular basis in clinical practice, physicians and nurses must have a positive opinion towards the programs. It is therefore essential to evaluate the opinions of the health care providers.

Aims of the thesis

The general aim of this thesis was to optimise drug therapy in the elderly by identifying, resolving and preventing drug-related problems.

More specifically, the aims of the studies were to:

- Describe the frequency and types of drug-related problems identified in elderly patients at nursing homes (Paper I) and at hospital (Paper V)

- Evaluate the frequency and nature of medication errors identified when elderly patients are transferred between hospital and primary care (Paper III and Paper IV)

- Develop and evaluate the models aiming to optimise drug therapy by resolving and preventing drug-related problems in the elderly at nursing homes (Paper I) at admission to hospital (Paper IV) and during the hospital stay (Paper V)

- Assess health care practitioners opinions towards the developed models (Paper II and Paper V)

Material and methods

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

Paper I

Letters were sent to the directors of the nursing homes in the county of Skåne in Sweden, offering participation to patients with anti-epileptic or anti-parkinsonian medication in this study. After obtaining informed consent, pharmacists visited the included patients at the nursing home. Patients' medication use, specific disease problems, health related quality of life (SF-36) [89], behavioural symptoms (the Behaviour Pathology in Alzeimer's Disease Rating Scale, Behave-AD) [90] and activity of daily living (the Schwab and England capacity for daily living scale, ADL) [91] were collected and documented during this visit. Based on the judgement of problems derived from all these sources the pharmacist then identified and classified drug-related problems. The use of inappropriate drugs for the geriatric nursing homes patients, according to Beers criteria [20], was specifically studied. The drug-related problems were grouped according to an application of previously described principles [23]. A multi-speciality group consisting of pharmacists, a primary care physician, a neurologist, a neuro-psychiatrist and a clinical pharmacologist evaluated the patients' medication and, when appropriate suggested drug changes. For intervention patients, the drug-related problems together with the suggested drug changes were sent to the physician involved in the care of the patient. All measurements were repeated after approximately 6 months.

Paper II

A questionnaire was sent to all participants, general practitioners and nurses, of our previous pharmacotherapeutic intervention study (Paper I), about 6 months after completion. The questionnaire assessed opinions towards the pharmacotherapeutic intervention and opinions on alternative or complementary future methods, potentially improving the patients' drug treatment. Answers were obtained using six-point ordinal scales, from 1 (no use) to 6 (great use) and 0 (don't know).

Paper III

Nurses in primary care identified primary health care patients (> 65 years) living in nursing homes or in their own homes with care provided by the community nursing system, after discharge from hospital. All written information of the included patients' medication was collected, including referral forms, admission records, discharge summaries and medication lists from the hospitals and from the community. Medication errors identified in the information transfer of drugs between the hospital and the primary care were then studied. A medication error was defined as any error in the process of prescribing, dispensing or the administration of a drug, and whether there were adverse consequences or not [47]. Discrepancies in the medication list after a transfer were considered as a medication error, if the changes were not mentioned in the medication notes.

Paper IV

A *Structured Medication Questionnaire* was developed with the purpose of being used to identify an accurate medication list and assess patients' drug handling at home, knowledge about indication for, compliance to and beliefs about their drug treatment. Clinical pharmacists used this questionnaire when patients were newly admitted to the hospital.
Discrepancies in the medication list at hospital were identified by comparing it to the medications taken at home, according to the patient. The documented discrepancies within the medication list were classified into four groups; medication erroneously added, medication erroneously not ordered, ordered dose to high and ordered dose to low.
Compliance was measured using the Morisky four-item scale [42] and patients' beliefs about their drug treatment were measured using the BMQ-specific [46].

Paper V

For intervention patients a pharmacist identified drug-related problems, using a *Structured Medication Review* sheet and proposed changes in drug therapy. In order to increase the detection of drug-related problems the *Structured Medication Review* sheet included a checklist of seven specific factors, risk factors, assumed to increase the risk of drug-related problems. These risk factors were compiled by one pharmacist and one geriatrician. Decisions concerning changes in drug therapy were discussed in multidisciplinary teams, with the physician as the leader and co-ordinator. The drug-related problems identified by the clinical pharmacist during the intervention period were first classified as actual or potential drug-related problems [27], and further according to a modified version of Cipolle, Strand and Morley [27]. Control patients received conventional care.
After the end of the study, a clinical pharmacist identified drug-related problems and drug changes, using blinded records, for both intervention and control patients. Two pairs of evaluators then independently evaluated and classified the drug-related problems, from the blinded patient records, as identified/unidentified during the hospital stay and according to type and severity of the drug-related problems. The type of drug-related problem was classified according to a modified version of Cipolle, Strand and Morley [27], and the severity of the drug-related problems was classified according to Hatoum [84].

Using a questionnaire, the health care practitioners' satisfaction about the intervention was assessed shortly after the inclusion of the last patient. Answers were obtained using six-point ordinal scales, from 1 (no use) to 6 (great use).

Results

Identification and classification of drug-related problems (Paper I and Paper V)

Many in the studied geriatric population used inappropriate medications. According to Beer's criteria 32 (43%) epilepsy patients and 31 (37%) Parkinson's disease patients used at least one inappropriate medication (Paper I). Of the studied hospitalized patients (Paper V) 78 (53%) used less appropriate drug therapy (criteria according to the Swedish National Board of Health and Welfare). The control group more frequently used less appropriate medicines during the hospital stay, compared to the intervention group (**Table 2**)

Table 2 Risk factors for drug related problems identified during the hospital stay in the intervention and the control groups. Results are presented as number of patients (%) with at least one risk factor within each risk factor category.

	Intervention group (n=70)	Control group (n=71)
Changes of interchangeable drugs^	56 (80.0)	48 (67.6)
Drug-drug interactions	50 (71.4)	53 (74.7)
Less appropriate drug therapy*	29 (41.4)	49 (69.0)
Anti-cholinergic drugs	6 (8.8)	14 (19.7)
Long-acting benzodiazepines	13 (18.6)	30 (42.3)
Polypharmacy	14 (12.0)	11 (15.5)
Not possible to calculate creatinin clearance	7 (10.0)	45 (63.4)
Drugs that require therapeutic monitoring	36 (51.4)	42 (59.2)
Digoxin	26 (37.1)	25 (35.2)
Warfarin	17 (24.3)	15 (21.1)
Theofyllin	2 (2.9)	9 (12.7)
Problems with swallowing	8 (11.4)	6 (8.5)
Problems with allergy or similar	14 (20.0)	12 (16.9)

^ Generic and analogous substitution according to regional inter changeable list

* The National Board of Health and Welfare, Sweden. [Indikatorer för utvärdering av kvaliteten i äldres läkemedelsterapi, SoS, 2003]

For epilepsy patients, on average 6.7 drug-related problems were identified. For Parkinson's disease patients fewer drug-related problems were identified, on average 5.0 problems. The hospitalized patients had the highest number of drug-related problems, on average 9.9 problems. The most common types of drug-related problems for epilepsy patients were *adverse drug reaction* and *wrong drug*, whereas for Parkinson's patients' *unnecessary drug treatment, drug for on-demand use without specification* and *adverse drug reaction* were most common (**Table 3**). The most common types of drug-related problems for hospitalized patients were *wrong drug*, *adverse drug reaction* and *need for additional therapy*.

Table 3 Frequency of drug-related problems for patients at nursing homes (epilepsy and Parkinson's disease patients) (Paper I) and for patients admitted to a ward for internal medicine (Paper V).
Results presented as number of patients (%).

	Epilepsy patients	Parkinson's disease patients	Hospitalized patients
Need for additional drug therapy	13 (21)	9 (16)	50 (71)
Wrong drug	30 (48)	22 (39)	62 (89)
Dosage too low	2 (3)	15 (26)	41 (59)
Non-compliance	0 (0)	1 (2)	2 (3)
Dosage too high	5 (8)	3 (5)	49 (70)
Adverse drug reaction	35 (56)	26 (46)	53 (76)
Drug-drug interaction	28 (44)	20 (35)	- *
Unnecessary drug therapy	28 (44)	27 (47)	53 (76)
Medication has not the intended effect	13 (21)	13 (23)	- *
Dosage interval	8 (13)	7 (12)	- *
Drug intake in connection with food	0 (0)	1 (2)	- *
Drug for on-demand use without specification	25 (40)	27 (47)	- *
Other	5 (8)	9 (16)	19 (27)

* This types of drug-related problems were not present (Paper V)

Evaluation of frequency and nature of medication errors (Paper III and Paper IV)

Medication errors when patients were transferred from primary care to hospital and vice versa were common in the studied geriatric population. When transferred from primary health care to hospital (Paper III), 29 out of 34 patients (85%, 95% CI 69-95%) had at least one medication error compared with 19 out of 35 patients (54%, 95% CI 37-71%) for the transfer from hospital to primary health care. Using the *Structured Medication Questionnaire* (Paper IV), at admission, the pharmacist identified medication errors in 24 of 39 patients (62%, 95% CI 45-77%). When patients were transferred to the hospital, the most common error was withdrawal of medications. The most common error when patients were discharged from hospital was that drugs were erroneously added. The medication error erroneous change in dosage was also present. For the primary health care patients (Paper III), an average of 19% of the medications were transferred erroneously, 21% when transferred from primary health care to hospital, compared to 17% when transferred from hospital to primary health care. Using the structured medication interview (Paper IV) 14% of the medications were considered to be erroneously transferred, at admission to hospital.

Evaluation of developed models aiming to optimise drug therapy (Paper I, Paper IV and Paper V)

Using the *Structured Medication Questionnaire* (Paper IV) at the time of admission of patients to the hospital, on average 1.2 medication errors were identified per patient. Lack of knowledge about the used drugs, non-compliance and negative attitudes were also identified.

In the study carried out in nursing homes (Paper I) there were no significant favours for intervention patients compared to controls, considering health related quality of life (SF-36), behavioural symptoms (Behave-AD) or activity of daily living. For Parkinson's disease patients, there was even a significant decrease in activity of daily living in the intervention group.

For the intervention patients, 208 changes in medication therapy were proposed by the multi-speciality team, of which 77 (37%) were carried out.

A multidisciplinary team, including a clinical pharmacist conducting medication reviews and collating systematic medication care plans (Paper V), reduced the number of unidentified drug-related problems (**Table 4**). All sub-categories of medication drug-related problems that were frequent in the control group were significantly reduced in the intervention group. This was also found for the severity of the drug-related problems.

Table 4 The number of unidentified medication drug-related problems and patient-related drug-related problems in the intervention and the control groups. Results are presented as total number of drug-related problems within each group and as median (1^{st} - 3^{rd} quartile).

	Intervention group	Control group	p-value
Medication drug-related problems	76 1 (0-2)	730 9 (6-13)	< 0.001
Patient-related drug-related problems	74 1 (0-2)	604 8 (5-11)	< 0.001

During the intervention period a total of 449 changes in medication therapy was discussed with the responsible physician, of which 31 (6.9%) was rejected. This means that 93 % of the identified and presented drug-related problems were accepted.

Assessment of health care practitioners opinions towards the developed models (Paper II and Paper V)

For the general practitioners the response rate was 62% (41 returned questionnaires), while the response rate for the nurses in the primary care was 69% (31 returned questionnaires) (Paper II). The general practitioners expressed a modest favourable opinion (median, 1^{st} -3^{rd} quartile: 3, 2-4) about the suggested drug changes sent by the multi-speciality team to the general practitioner. They further expressed favourable opinions (median ≥ 4) of the item 'suggestions are discussed in a multi-speciality team' (4, 2-5). Among the general practitioners and nurses, 35% and 86%, respectively, were positive to further cooperation with a pharmacist. All nurses that were positive to further cooperation wished to do this in a multidisciplinary team, while some of the general practitioners wished to do it in a multidisciplinary team and others in a multi-speciality group.

The hospital healthcare practitioners' response rate (Paper V) was higher, 95% for the physicians (21 returned questionnaires) and 93% for the nurses (14 returned questionnaires). All healthcare practitioners proved to be very satisfied with the model of care during the intervention (**Table 5**).

Table 5 The health care practitioner satisfaction with the model. Results are presented as median (1^{st} -3^{rd} quartile). Answers were obtained using six-point numerical scales: from 1 (no use) to 6 (great use).

	Physicians	Nurses
General opinion about the usefulness for the patient	5 (4-5)	6 (4.5-6)
General opinion about the usefulness for the health care practitioner	5 (5-5)	5 (5-6)
The usefulness of the systematic symptom checklist	3 (3-5)	4 (3-5)
The usefulness of the medication review	5 (5-6)	6 (5-6)
The advantage of physicians receiving a better decision basis to drug changes	5 (5-6)	5 (5-6)
The usefulness of a more individualised drug treatment	5 (5-6)	6 (5-6)
The usefulness of that drug-related problems, plans, actions taken are documented	4 (3-5)	6 (5-6)
The advantage of discussing drug changes during rounds	5 (5-6)	6 (5-6)
The usefulness of the pharmacist as a drug expert	5 (5-5)	5 (5-6)
The usefulness of the pharmacist as a discussion partner in drug queries	5 (5-5)	5 (5-6)
The usefulness of the pharmacist as support for drug choice, based on studies, evidence based medicine and recommendations	5 (4-5)	6 (5-6)
The usefulness of the pharmacist to identify drug-related problems	5 (4-6)	6 (5-6)

Discussion

The results from our studies show that the drug treatment of the elderly patients is not optimal. Many elderly use inappropriate drugs, drug-related problems are common both at nursing homes and at an internal medicine ward, and medication errors occurs frequently at interfaces of care. Our studies further indicate that medication histories at admission to hospital, using the *Structured Medication Questionnaire*, and medication reviews, using the *Structured Medication Review* sheet, might optimise drug therapy.

Drug-related problems

In order to prevent and resolve drug-related problems it is essential to identify the individual patients' drug-related problems. Our studies showed that a wide variety of drug-related problems were encountered in nursing home patients (Paper I) and in patients admitted to an internal medicine ward (Paper V). In fact, we found that epilepsy patients had an average of 6.7 drug-related problems, Parkinson patients 5.0 drug-related problems and hospitalized patients 9.9 drug-related problems. The number of identified drug-related problems in our study on patients admitted to an internal medicine ward (Paper V), was more than three times higher compared to other studies also conducted at medical wards; Blix *et al* [92] (2.6 drug-related problems and 2.1 clinical drug-related problems per patient) and Mannheimer *et al* [93] (2.2 clinical drug-related problem per patient). The number of identified drug-related problems in our nursing home study (Paper I) was also higher compared to other nursing homes studies; Finkers *et al* [94] (3.5 drug-related problems per patient), Ruths *et al* [95] (1.8 drug-related problems per patient) and Bellingan *et al* [75] (4.1 drug-related problems per patient).

Reasons for the higher incidence of drug-related problems might be that the patients in our studies used more drugs, had a higher disease burden or that the pharmacist in our studies detected more drug-related problems using the *Structured Medication Review* sheets, making it less likely to miss unidentified drug-related problems. A number of different classification systems for evaluating drug-related problems [28] used in different studies might also contribute to this. It is also difficult to conclude whether all identified drug-related problems or only clinically relevant drug-related problems are presented in other published studies, and if several presented drug-related problems may emerge from a single medication or not. In our study conducted at an internal medicine ward (Paper V) we therefore decided to present the results both as patient-related drug-related problems (one medicine only causing one drug-related problem) and as medication drug-related problems (one medicine may cause several drug-related problems). In our-study conducted at nursing homes (Paper I) only medication drug-related problems were presented. Patient-related drug-related problems have the advantage of being a more accurate measure, representing true problems for the patient. But, it has disadvantages in the classification into sub-group types of drug-related problems. This is because one medication may cause many types of drug-related problems which make it almost impossible to choose which category to use. However, medication drug-related problems might also be relevant. Together with the patient-related drug-related problems it gives a more detailed picture and makes it possible to specify sub-group types of drug-related problems.

In the study conducted at the internal medicine ward (Paper V) a checklist included seven specific factors, risk factors, assumed to increase the identification of drug-related problems was developed. These seven categories were compiled by one pharmacist and one geriatrician. To our knowledge, the uses of specific factors increasing the identification of drug-related problems have not previously been described. In a study by Blix *et al* [96], however ten selected clinical/pharmacological risk factors have been used to evaluate the risk of drug-related problems to occur. In this study, the risk of occurrence of drug-related problems was increased by 1.14, for each additional clinical/pharmacological risk factor. Some of the factors in our study (Paper V) was similar to the clinical/pharmacological risk factors in the study by Blix; reduced renal function, history of allergy, use of drugs with narrow therapeutic index and problems with swallowing.

The impact of the interventions on drug therapy

The Structured Medication Questionnaire

Accurate medication histories at the time of hospital admission are an important element of medication safety. First, they may uncover reasons for a patient's illness, such as adverse drug events or non-compliance to therapy. Second, medication errors may result in interrupted or inappropriate drug therapy during and following the hospital stay. In our study, a pharmacist conducting medication histories at admission, using the *Structured Medication Questionnaire*, identified on average 1.2 medication errors per patient and further identified poor knowledge about, non-compliance to and negative beliefs about prescribed medicines. The average number of identified medication errors per patient in our study is comparable to the study by Lessard *et al* [97], identifying 1.5 medication errors per patient. In two other studies the average number of identified medication errors were almost twice as high; 2.8 [98] and 2.9 [99]. Differences in the studies methodology might have contributed to this fact. Possible reasons for this difference might be that Lubowski *et al* included therapeutic substitution in the definition of medication error and that Lizer *et al* compared the pharmacist-obtained medication information with that obtained by the nurse. The result from our study (Paper III) and the study by Brookes *et al* [52], that pharmacist-acquired medication histories are more complete than those acquired by other health professionals, are confirmed by later published studies [68, 100].

In 2005 the Institute of Healthcare Improvement [101] defined medication reconciliation as *the process of creating the most accurate list possible of all medications a patient is taking- including the name, dosage, frequency and route, and comparing that list against the physicians admission, transfer, and/or discharge orders, with the goal of providing correct medications to the patient at all transition points within the hospital*. Medication reconciliation is a three step process of verifying patient medication use, identifying variances and recertifying medications at the interface of care. In Sweden, medication reconciliation is a 2008 national patient safety goal established by the Swedish Association of Local Authorities and Regions.

In UK the National Institute for Health and Clinical Excellence (NICE) has conducted a systematic review of studies aiming to prevent medication errors at admission to hospital by medicines reconciliation, and applied these studies to a cost-effectiveness analysis [102]. The

results showed that pharmacist-led reconciliation intervention is predicted to prevent most of the medication errors and is likely to be the most cost-effective intervention.
Using a multidisciplinary medication reconciliation process has shown to decreased the number of medication discrepancies occurring during admission and discharge at an inpatient family medicine unit [103] and at an surgical intensive care unit [104]. Pharmacist reconciliation at nursing homes at the time the residents return from hospital to the nursing home has further shown to decrease the risk of experiencing adverse drug events [105].

Medication reviews

The acceptance rate in the nursing home study (Paper I) was low, only 37% of the therapeutic suggestions led to actual treatment changes. Corresponding figures in other nursing homes studies are 54-58% [75, 106-108]. The acceptance rate of the suggestions concerning drug-related problems was higher in the study conducted at the internal medicine ward (Paper V); 93% (73% direct acceptance rate and 20% solving rate). This acceptance rate is comparable to Barber *et al* [109] (96%), Blix *et al* [96] (92%), Lee and McPherson [110] (84%) and Bosma *et al* [111](82 %), but higher compared to Mannheimer *et al* [93] (63%). The high acceptance rate in our study conducted at the internal medicine ward (Paper V) together with the fact that the health practitioners expressed high satisfaction with the new model of the care, indicates that the presented drug-related problems had high clinical significance. Sending a written advice to the physician, as in Mannheimer's study and in our studies conducted at nursing homes (Paper I), seems to result in lower acceptance rates. In our study conducted at the internal medicine ward and the other studies with comparable acceptance rate medication reviews were conducted in close liaison to the patient responsible physician.

One of the purposes with our study conducted at nursing homes (Paper I) was to improve the residents' pharmacotherapy and to be able to show this in terms of health-related quality of life, activity of daily living and confusion state. We failed to show an improvement in these studied variables. Many different reasons could contribute to this, but the fact that the quality of life measurement SF-36 latter was shown to be inappropriate for nursing homes patients [112] and that only 37 % of our recommendations were carried out might be strong contributors. The fact that letters with therapeutic drug recommendations were sent to the responsible physician might hindered the implementation of the recommendation. Chen and Neto [113] have concluded that a close liaison and face-to-face meetings seems to be important factors to successful outcomes in medication review. Both Holland *et al* [114] and Lenaghan *et al* [115] seems to support this opinion and stress that the most successful interventions have been delivered by small numbers of pharmacists working in close liaison with physicians. To our knowledge, no latter published study has investigated the effect of health-related quality of life in nursing home settings. Latter published studies have shown to decrease the number of drugs [94], reduced the use of inappropriate medications [116] and reduced the incidence of falls, with no significant difference in hospitalisation or death [107].

In the study conducted at the internal medicine ward (Paper V) the intervention patients benefited from a reduction of unidentified medication drug-related problems and patient-related drug-related problems. Our findings show that an increased focus on medication and drug-related problems for the multidisciplinary team including the clinical pharmacists effectively identifies drug-related problems. To our knowledge no comparative studies exists, that examines the effect of medication review and a systematic team-based approach on the

number of unidentified drug-related problems for in-patients. Lipton *et al* [82] found that drug reviews reduced the percentage of patients with drug-related problems, 92% of the control patients compared with 83% of the intervention patients. Our study further shows that all sub-categories of medication drug-related problems that were frequent in the control group were significantly reduced in the intervention group. This was also found for the severity of the drug-related problems.

Medication review is a relatively new intervention. A recent literature review found that clinical pharmacy interventions in inpatient medical care contribute to improved outcomes [117]. The review concluded that interacting with health care teams on patient rounds, interviewing patients, reconciling medications, and providing discharge counselling and follow-up all resulted in improved outcomes. Surrogate outcomes like decreased incidence of adverse drug events, reactions or medication errors, reduced costs and shortened length of stay all improved, while no effect on patient outcomes like hospital admission or mortality was shown. The review further supports the use of clinical pharmacists in the inpatient setting to improve the quality, safety and efficiency of care. These findings are supported by the large observational study by Bond *et al* [69] identifying 17 clinical pharmacy services associated with improvement in mortality, drug costs, cost of care and length of stay. The net hospital cost benefit in terms of cost avoidance and in terms of use is further confirmed, in studies evaluating the cost of incorporating clinical pharmacists into the daily work at hospitals [85, 86, 118, 119].

The composition of the multi-speciality and the multi-disciplinary teams

In Southern Sweden general practitioners normally are responsible for nursing home residents. Unfortunately, many general practitioners have little time for each individual nursing home patient and are often unaccustomed to initiating treatment of epilepsy or Parkinson's disease. In addition it often takes several months to get an appointment with a neurologist. Patients in nursing home settings usually have multiple medical illnesses and use many medications. Optimal drug treatment is an important task that requires a competent care team. In our nursing home study (Paper I) a mutli-speciality group was added to the conventional care of the nursing home patients. The multi-speciality group was composed of team members, to our opinion required; the data-collecting pharmacists, a pharmacist with special experience in neurology, a primary-care physician, a neurologist, a neuro-psychiatrist and a clinical pharmacologist. Together this team contributes with unique knowledge in neurology, neuro-psychiatry, and pharmacology, both in general pharmacology and specifically in neurology.

In Swedish inpatient settings, there are growing trends for physicians, nurses, carers and sometimes occupational therapists and physiotherapists to work in teams (in Paper V representing our control group). However, traditionally clinical pharmacists have not been part of these teams. Clinical pharmacists have unique clinical skills, e.g. knowledge in patient counselling and pharmacology, and technical skills, e.g. supply and product knowledge, making the clinical pharmacist an expert in drugs and drug therapeutics. In many Swedish inpatient settings, the clinical pharmacist is a scarcely used resource. In our study conducted at the internal medicine ward (Paper V) the clinical pharmacist was added to the conventional care of inpatients.

The opinions of the health care practitioners

The opinions of the health care practitioners towards the multi-speciality team model indicated that this or similar methods may successfully be used in clinical practice for improving drug therapy (Paper II). The health care practitioners participating in the multidisciplinary team model (Paper V) were even more positive toward this new model of care. If such working models are to be used on regular basis in clinical practice, physicians and nurses must have a positive opinion. In an overview article by Chen and Neto [113] it was concluded that for the medication review to be successfully implemented a collaborative environment must exist in the healthcare setting, cultural barriers must be overcome and face-to-face meetings are especially important for effective team work and to create a trusting environment. Applied to our studies, working in multidisciplinary teams or in close liaison with the patient responsible physician (Paper V) seems to be the most optimal way.

The transfer of drug information

Our studies demonstrated that medication histories at admission often are incomplete, resulting in medication errors. When patients were transferred from primary health care to the hospital 85% of the patients were identified with at least one medication error. When using the structured medication questionnaire, the corresponding number of patients with at least one medication error was 62%. The results from our study were comparable with the results of a review article by Tam *et al* [120]. Studies in this review reported that 10-67% of the patients had at least one medication error at admission.

Our study further showed that the transfer of medicine information at discharge, results in medication errors. When the patients where transferred back from the hospital to primary health care at least one medication error was identified in 41% of the patients. In a study by Coleman *et al* [121] 14% of the elderly, community-dwelling patients experienced one or more medication discrepancies. Another study by McMillan *et al* [122] further addressed the problem, as an average of 1.4 medicine errors were found per medical discharge summary.

The fact that the frequency of patients with at least one medication error is higher for patients not handling drugs on their own, compared to patients being able to give details about their drug use before admission, is alarming and remarkable. Poor communication between the hospital and primary care and inadequate record-keeping both at the hospital and at primary health care may possibly contribute to the higher frequency. One possible explanation for this finding might also be that more information was available, as all medical notes used for information transfer were collected, yielding a higher frequency of patients with medication errors. Our studies have not dealt with the clinical outcomes caused by medication errors. In a study by Cornish *et al* [123] almost 40 % of the medication errors had the potential to cause moderate to severe discomfort or clinical deterioration.

The Lund-model; recent ongoing and future studies

In order to optimise drug therapy in the elderly, a systematic approach is necessary, involving pharmaceutical care in primary care, at admission to hospital, during the hospital stay and at discharge from hospital.

In this thesis methodologies aiming to optimise drug therapy in the elderly have been developed and evaluated separately at nursing homes (Paper I and Paper II; distance medication reviews, using the *inventory questionnaire*), at admission to hospital (Paper IV; medication histories, using the *Structured Medication Questionnaire*) and during the hospital stay (Paper V; medication reviews, using the *Structured Medication Review* sheet). Beyond the scope of this thesis, our research group has developed the *Structured Medication Report* [124], aiming to improve medication errors at discharge. This *Structured Medication Report* provides the patient and the general practitioner with information regarding changes in patients' drug therapy during the hospital stay and a structured updated list of the patients' current medications at discharge. This discharge summary has also been evaluated separately and has shown to decrease the number of medication errors at discharge [124] and reduce the need for further medical care due to medication errors [125].

The three separate methodologies, the *Structured Medication Questionnaire, Review* and *Report*, have further been used and evaluated together as an integrated medicine management methodology, the *Lund-model*. Our research group has evaluated the *Lund-model* in two integrated management projects; the LIMM-study (Landskrona Integrated Medicines Management) and in a study conducted at the University Hospital of Lund. Result from the LIMM-study has shown that using the *Lund-model* increases the appropriateness of drug therapy in the elderly [126]. The results from our study conduced at the University Hospital of Lund confirmed these results [127]. Other results from our LIMM-study indicated that using the *Lund-model* improved the quality of the *Structured Medication Report*, further reducing the incidence of medication errors at discharge [128]. Further evaluations of our study conducted at the University Hospital of Lund, have shown that using the *Lund-model* identified and resolved medication errors at admission [129] and drug-related problems during the hospital stay [130].

The developed and evaluated methodologies described above are at present implemented, in separate parts or as the model as a whole, into the daily practice in several hospitals in Sweden. The methodologies are further used in the education of clinical pharmacists in Sweden.

In the future our research group will evaluate the impact of the *Lund-model* on patient outcomes, such as incidence of hospital readmission, and if possible incidence of mortality. Future studies may evaluate cost-effectiveness and patient-specific factors associated with improvements, for example quality of life. Randomised controlled multicenter studies may further be conducted to prove the external validity across institutions and to quantify the value to the health care system.

Conclusions

The general aim with this thesis was to optimise drug therapy in the elderly by identifying, resolving and preventing drug-related problems.

In conclusion:

- Drug-related problems were frequently present in the elderly population, both for nursing home patients (Paper I) and for patients admitted to hospital (Paper V). Common identified drug-related problems were adverse drug reactions, wrong drug and unnecessary drug treatment.

- Medication errors were common when elderly are transferred between hospital and primary care (Paper III and Paper IV). At admission to hospital the most common medication error was withdrawal of drugs, while at discharge from hospital the most common medication error was erroneously addition of medications.

- Models were developed aiming to optimise drug therapy in the elderly. A multidisciplinary team, including a clinical pharmacist, conducting medication reviews and collating systematic medication care plans, proved very effective in reducing the number of un-identified drug-related problems for elderly in-patients (Paper V), and thereby optimised drug therapy. At admission the *Structured Medication Questionnaire* may be used as a tool to identify medication errors, and thereby contribute to an optimised drug therapy (Paper IV). Using a multi-speciality team sending suggestions, considering optimisation of drug therapy, to the physician involved in the care of the patient failed to demonstrate any positive effects in nursing home patients (Paper I).

- The opinions of the health care practitioners towards the multi-speciality team model indicated that this or similar methods may successfully be used in clinical practice for improving drug therapy (Paper II). The opinions of the hospital health care practitioners towards the multidisciplinary team model and the clinical pharmacist further confirmed this statement (Paper V).

Swedish summary (Svensk sammanfattning)

Aspekter på optimeringen av äldre patienters läkemedelsterapi

Avsikten med en läkemedelsbehandling är att förebygga, lindra eller bota sjukdom eller symtom på sjukdom. När läkemedel skrivs ut finns det dock alltid en risk att läkemedelsbehandlingen utfaller negativt, ett läkemedelsrelaterat problem uppstår. Ett läkemedelsrelaterat problem definieras som *ett problem som patienten verkligen upplever eller har potential att uppleva, och som kan relateras till läkemedelsbehandlingen.* Äldre patienter drabbas i större utsträckning av läkemedelsrelaterade problem då de ofta har en komplicerad sjukdomsbild, använder många läkemedel samt har ändrade fysiologiska förutsättningar. Det finns dessutom ett flertal internationella studier och nationella rapporter som visar att äldre patienters läkemedelsbehandling är olämplig.

Läkemedelsrelaterade problem leder till ökade kostnader genom ett ökat utnyttjande av sjukvårdsresurser (ex akutbesök, inläggning på sjukhus), ett ökat lidande för patienten (ex biverkningar) samt en ökad risk för död. Stora studier har visat att ca 5 % av alla patienter som läggs in på sjukhus, läggs in pga biverkningar orsakade av läkemedel. Motsvarande siffra för äldre patienter är ännu högre, 15-20%. Dessutom rapporteras det att majoriteten av dessa biverkningar kan förebyggas. Det är därför av stort värde att identifiera, lösa och förebygga dessa läkemedelsrelaterade problem. Läkemedelsgenomgångar, som genomförs av kliniska apotekare, har förespråkats som en metod för att optimera läkemedelsbehandlingen.

Det finns andra studier som visat att det är en stor risk att informationen kring en patients läkemedel överförs felaktigt i samband med in- och utskrivning från sjukhus. Ofullständiga och/eller felaktiga läkemedelslistor kan leda till att läkemedelsbehandlingar felaktigt sätts ut eller in, eller att läkemedlen ges i fel dos. Läkemedelsavstämning vid inkomst till sjukhus anses vara en värdefull metod för att identifiera felaktiga läkemedelslistor.

Syftet med denna avhandling var att optimera äldre patienters läkemedelsterapi genom att identifiera, förebygga och lösa läkemedelsrelaterade problem.

I den första studien utvärderades effekten av läkemedelsgenomgångar på patienter boende på särskilda boenden, med Parkinsons sjukdom eller epilepsi. Läkemedelsgenomgångarna genomfördes på distans av ett multispecialist team (neurolog, klinisk farmakolog, primärvårdsläkare, apotekare). De läkemedelsrelaterade problem som identifierades vid genomgångarna samt eventuella åtgärdsförslag för att förebygga eller lösa dessa, skickades sedan till ansvarig läkare. Effekten av läkemedelsgenomgångarna utvärderades vidare med avseende på patienternas livskvalitet.
I denna studie identifierades många läkemedelsrelaterade problem, i genomsnitt 6.7 för patienterna med epilepsi samt 5.0 för patienterna med Parkinsons sjukdom. Endast 37 % av multispecialist teamets åtgärdsförslag genomfördes. Denna studie visade vidare inga positiva effekter på livskvalitet.

I den andra studien utvärderades deltagande läkares och sjuksköterskors attityder till distansläkemedelsgenomgångarna som genomfördes av multispecialist teamen i den första studien, via enkäter. Alla sjuksköterskor som var intresserade av ett fortsatt samarbete ville

arbeta multidisciplinärt, medan en del av läkarna ville arbeta multidisciplinärt och andra med multispecialist team.

I den tredje studien så kartlade vi omfattningen av felaktiga läkemedelsordinationer orsakade av brister i överföringen av information, mellan sjukhus och kommunal hemsjukvård eller sjukhem. I genomsnitt överfördes 19 % av läkemedelsordinationerna felaktigt, samt 85 % av patienterna hade minst ett fel i läkemedelsordinationen vid inskrivning samt 54 % vid utskrivning.

I den fjärde studien utvärderades effekten av en läkemedelsavstämning genomförd av kliniska apotekare vid inskrivning på sjukhus, med det strukturerade formuläret *Läkemedelsintervju*. Syftet med *Läkemedelsintervjun*, var att ta fram en aktuell läkemedelslista samt identifiera brister i patientens hantering av, kunskap om, följsamhet samt attityder till sin läkemedelsbehandling.
Genom att använda *Läkemedelsintervjun,* identifierade den kliniska apotekaren minst ett fel i läkemedelsordinationen vid inskrivning på sjukhus, hos 62 % av patienterna. Kunskapsbrister, dålig följsamhet samt negativa attityder identifierades också.

I den femte studien utvärderades effekten av läkemedelsgenomgångar i multidisciplinära team, inkluderande klinisk apotekare, för patienter som ligger inne på sjukhus. Retrospektiva journalgenomgångar genomfördes för att studera om antalet oidentifierade läkemedelsrelaterade problem under sjukhusvistelsen var färre för patienter, för vilka läkemedelsgenomgångar hade genomförts. Deltagande läkares och sjuksköterskors attityder till detta arbetssätt utvärderades med enkät.
För patienter där läkemedelsgenomgångar genomfördes identifierades signifikant färre oidentifierade läkemedelsrelaterade problem under sjukhusvistelsen, i genomsnitt åtta färre. Läkare och sjuksköterskor var mycket positiva till det nya arbetssättet.

Resultaten från dessa studier visar att äldre patienters läkemedelsbehandling inte är optimal. Många äldre använder olämpliga läkemedel och läkemedelsrelaterade problem samt överföringsfel är vanligt förekommande. Dessa studier visar vidare att läkemedelsavstämning vid inskrivning på sjukhus, genom att använda *Läkemedelsintervjun,* samt läkemedelsgenomgångar, genom att använda strukturerade formulär, kan optimera äldre patienters läkemedelsterapi.

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Appendix (I-V)