Effects of Clinical Pharmacists' Interventions

on Drug-Related Hospitalisation and Appropriateness of Prescribing in Elderly Patients

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Dissertation presented at Uppsala University to be publicly examined in B:41, BMC, Husargatan 3, Uppsala. Friday, March 9, 2012 at 09:00 for the degree of Doctor of Philosophy (Faculty of Pharmacy). The examination will be conducted in English.

Abstract

The overall aim of this thesis was to evaluate clinical pharmacist interventions with the focus on methods aiming to improve the quality of drug therapy and increase patient safety. Adverse drug events caused by medication errors, suboptimal dosages and inappropriate prescribing are common causes of drug-related morbidity and mortality. Clinical pharmacists integrated in multi-professional health-care teams are increasingly addressing these issues. A randomised controlled trial (RCT) was conducted to investigate the effectiveness of clinical pharmacists’ interventions in reducing morbidity and use of hospital care for patients 80 years or older. The results showed that the intervention group had fewer visits to hospital and that the intervention was cost-effective. In a subsequent study based on the population in the RCT, the appropriateness of prescribing was assessed using three validated tools. The results indicated improved appropriateness of prescribing for the intervention group as a result of the intervention. The tools and the number of drugs at discharge were then tested for validity in terms of causal links between the scores at discharge and hospitalisation. No clear correlations between high scores for the tools or a high number of drugs and increased risk of hospitalisation could be detected. During the inclusion period of the RCT a survey based study was conducted where the perceived value of ward-based clinical pharmacists, from the perspective of hospital-based physicians and nurses as well as from general practitioners (GPs) was evaluated. The respondents were positive to the new collaboration to a high degree and stated increased patient safety and improvements in patients’ drug therapy as the main advantages. In the last study the frequency and severity of prescription and transcription errors, when patients enrolled in the multidose-dispensed medications (MDD) system are discharged from hospital, was investigated. The results showed that errors frequently occur when MDD patients are hospitalised.

Keywords: Drug-related problems, medication review, appropriateness of prescribing, quality of prescribing, hospitalisation, pharmacist, clinical pharmacy, inter-professional relationships, collaboration, medication error, medication reconciliation, multidose-dispensed medications, prescription errors, transition of care

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ISSN 1651-6192
ISBN 978-91-554-8262-6
urn:nbn:se:uu:diva-167343 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-167343)
To the patients
Cover: Old Lady
Water colour (19x16.5cm)
Olle Christoffersson 2012
www.ollec.se
List of Papers

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


II Gillespie, U., Alassaad, A., Melhus, H., Mörlin, C., Henrohn, D., Bertilsson, M., Hammarlund-Udenaes, M. Effects of pharmacists’ interventions on appropriateness of prescribing for elderly and exploration of a possible correlation between scores for appropriateness and clinical outcomes – analyses from a randomized controlled trial. In manuscript.


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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
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<td>DRP</td>
<td>Drug related problem</td>
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<td>MAI</td>
<td>Medication appropriateness index</td>
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<tr>
<td>STOPP</td>
<td>Screening Tool of Older Persons' Prescriptions</td>
</tr>
<tr>
<td>START</td>
<td>Screening Tool to Alert doctors to Right Treatment</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse drug event</td>
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<tr>
<td>MDD</td>
<td>Multidose dispensed drugs</td>
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<tr>
<td>PCI</td>
<td>Pharmaceutical care issue</td>
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<tr>
<td>MAR</td>
<td>Medication administration record</td>
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<tr>
<td>ESCP</td>
<td>European Society of Clinical Pharmacy</td>
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<tr>
<td>PCNE</td>
<td>Pharmaceutical Care Network Europe</td>
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<tr>
<td>PIM</td>
<td>Potentially inappropriate medicines</td>
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<td>PPO</td>
<td>Potential prescription omissions</td>
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<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
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<tr>
<td>OTC</td>
<td>Over-the-counter</td>
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<tr>
<td>ED</td>
<td>Emergency department</td>
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<td>GP</td>
<td>General practitioner</td>
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Introduction

The elderly population

Demographics

In Sweden, there are nearly half a million people aged 80 years or older (5.3% of the population). Sixty-two percent of these are women. It has been estimated that in 2050 this population will be around 900 000 (1). The numbers of elderly people who are fit and healthy are increasing but, in parallel, the numbers who are vulnerable and frail are also increasing, and these require healthcare (2). Approximately 200 000 people in Sweden over the age of 65 years receive home help regularly and 94 000 live in residential homes (1). Most people in residential homes require a lot of help from the nursing staff to be able to move around, eat, take medication and participate in social activities. Many also have cognitive conditions such as dementia and therefore need even more attention.

Drug therapy in the very old

Effects of ageing on drug treatment

Increasing age confers natural changes in body composition and physiology and consequently also in the pharmacokinetics and pharmacodynamics associated with administered drugs. The ability to absorb, distribute, metabolise and eliminate drugs differs vastly between young healthy individuals and the very old, especially in the presence of certain chronic disease states. Changes in absorption can result from reductions in blood flow, gastric motility and acidity as well as from other physiological changes associated with ageing (3).

Reductions in hepatic mass and blood flow in older people can result in higher bioavailabilities of drugs that undergo first-pass metabolic effects in the liver (e.g. beta-blockers, tricyclic anti-depressants and nitrates), with subsequent requirement for prescription of lower doses. Cytochrome P450 oxidation, an important step in the metabolism of many drugs, also declines with ageing, with similar consequences (4).

Ageing often also implies a relative increase in body fat and decrease in lean body mass, changes that affect the distribution of drugs in the body (3).
It is also important to take age-related changes in the responsiveness to drugs at receptor level into consideration. For example, sensitivity to beta-blockers and beta-agonists is generally decreased while sensitivity to drugs such as opiates is increased (5).

However, perhaps the most important change associated with ageing is related to the excretion of drugs. Decreases in the glomerular filtration rate mean that drugs that are mainly eliminated by the renal route require dose adjustment (3).

Polypharmacy

Polypharmacy has been defined in many different ways, with the definition differing according to the patient population and study setting (6).

Twenty-one observational studies examining the epidemiology of polypharmacy were included in a review article in 2007 (7). The studies used various definitions of polypharmacy, which makes it difficult to compare them; some defined it as “using more than [...] drugs irrespective of the appropriateness of drug use”, others defined it as “the presence of unnecessary drugs or drug use without clinical indication”. This review highlights the confusion around the concept of polypharmacy.

It is well known that the use of larger numbers of drugs is associated with an increased likelihood of inappropriate prescribing, reduced adherence to drug regimens, and adverse drug events (ADEs) (8). As older patients seek treatment for various ailments from a variety of physicians, they are at increased risk of accumulating layers of drug therapy. Drug-induced symptoms can also produce prescribing cascades that develop when an adverse effect is misinterpreted as a new medical problem, leading to the prescription of additional drugs (9).

Selecting an arbitrary limit for the number of medications taken as a definition of polypharmacy can be counterproductive in populations with multiple co-morbidities, especially since under use of beneficial medicines that are clinically indicated but not prescribed is as common in patients using 15 prescribed drugs as in patients using 5 (10).

In this thesis, the definition of polypharmacy used is “the use of more drugs than is clinically warranted.”

Multidose Drug Dispensing (MDD)

MDD systems are commonly used in Scandinavia. Over 175 000 people (2% of the population) are enrolled in the Swedish system, with the highest rate in Uppsala (11).

The typical MDD user is elderly, with extensive drug therapy regimens, receiving an average of 10 prescribed drugs (12). Almost all nursing home residents in Sweden are enrolled in the MDD system.
The MDD system used in Sweden is called ApoDos®. This is a computer-based, automated medication dispensing system run by Apoteket AB (the state-owned pharmacy company). All drugs to be taken at a specific time are packaged in a plastic pouch, and labelled with patient data, date, time and contents (brand names, dosage and number of tablets). All the drugs prescribed for an individual patient are recorded on the MDD list, which thus provides a comprehensive overview of his/her drug therapy. The MDD prescription is checked by a pharmacist at the dispensing pharmacy to identify any interactions, duplicate prescriptions or irrational dosage details.

It has been proposed that the use of an MDD system will increase patient safety by reducing medication errors, aid drug adherence, and reduce wastage of unused drugs (13-16). This has not been proved in scientific studies, however, and discussions have recently begun in Sweden about whether the MDD system actually results in more perfunctory and extensive prescribing, without sufficient follow up and re-evaluation (17).

MDD – routines in hospital

When patients enrolled in the MDD system are admitted to hospital in Sweden, pre-dispensed drugs are generally discarded. At the University Hospital of Uppsala, traditional drug administration is used for all patients. The information on the MDD list is transcribed to the hospital Medication Administration Record (MAR) by a physician on admission of MDD patients. The drugs are then redispensed and administered from ward stocks by nurses on the ward. Individual hospital wards keep the MAR as part of their electronic medical records or on paper; either way, it is updated continuously by physicians for the duration of the patient's stay as changes in drug treatment are made. On discharge, the details are transcribed back from the MAR to the MDD list either electronically or manually, as preferred by the physician.

The hospital pharmacy provides discharged MDD patients with an extended distribution service. This service, which aims to provide patients with a seamless supply of medications, is highly appreciated by both patients and health professionals. Patients receive pre-packed medications to last for two weeks from the day of discharge. To achieve this, the up-dated MDD list acts as an order form and is collected from the hospital ward (a service provided each weekday morning) by a pharmacist from the hospital pharmacy for automated dispensing, allowing the MDD pouches to be delivered to the respective ward later the same day. The MDD prescription is checked by a pharmacist for potential problems but the list is not checked for conformity with the patient's MAR (i.e. the drugs taken by the patient in the ward on the day of discharge), and a study from 2010 has shown that discrepancies are frequent (Paper IV)(18).
Drug-related problems (DRPs)

Clinical DRPs

In 1990, Linda Strand wrote: “A Drug Related Problem (DRP) exists when a patient experiences or is likely to experience either a disease or symptom having an actual or suspected relationship with drug therapy”(19). Strand also categorised DRPs in a list that has been extensively used worldwide, especially among pharmacists. The eight categories are:

1. The patient has a medical condition that requires drug therapy (a drug indication) but is not receiving a drug for that indication. This category addresses underprescribing.
2. The patient has a medical condition for which the wrong drug is being taken. Here, the notion of “wrong drug” includes drugs that are contraindicated, unnecessarily expensive or ineffective.
3. The patient has a medical condition for which too little of the correct drug is being taken.
4. The patient has a medical condition for which too much of the correct drug is being taken. Here, a typical example would be that the dose is not appropriately adjusted for renal failure.
5. The patient has a medical condition resulting from an adverse drug reaction (ADR).
6. The patient has a medical condition resulting from a drug-drug, drug-food or drug-laboratory interaction.
7. The patient has a medical condition that is the result of not receiving the prescribed drug. There can be a number of reasons for this problem – within or outside of patients’ control – such as noncompliance, poverty or administration failure.
8. The patient has a medical condition that is the result of taking a drug for which there is no valid medical indication. Unnecessary drug use tends to be far too often overlooked as a DRP category, according to the author (19).

Categorisation of DRPs can serve as a focus for developing a systematic process for pharmacists to contribute significantly to positive patient outcomes. Several research groups and organisations have developed their own systems for the classification of DRPs; The Pharmaceutical Care Network Europe (PCNE)(20), The American Society of Health-System Pharmacists (21) and Krska et al (22) are perhaps the most well-known and used among pharmacists. In 2004, van Mil et al published an overview and critical appraisal of existing DRP classification systems (23). During the randomised controlled trial (RCT) in Uppsala, on which the main part of this thesis is
based, identified DRPs were categorised using an adapted version of the list developed by Strand et al (19).

Technical DRPs

*Medication errors in transition of care*

Unintentional discrepancies in drug charts (prescription and transcription errors) are common when patients are transferred between different health care establishments (18, 24-31). These types of preventable medication errors are frequent causes of harm in healthcare and can lead to ADEs, prolonged hospital stays, and drug-related morbidity and mortality (30, 32-38). Medication errors can occur during four processes: prescribing/ordering, transcribing, dispensing, and administering a drug (39). Errors involving the prescribing/ordering of drugs include a technical component and/or a decision-making component (40). The other three types of medication errors are mainly of a technical nature.

The majority of serious medication errors and ADEs seem to occur during the discharge process (18, 26, 28, 30-32, 36). These medication errors are generally preventable (29, 33, 34, 39, 41).

The clinical consequences of medication errors can be anything from minor (no harm to the patient) to catastrophic (resulting in death or severe loss of bodily function. Several methods can be used to determine the importance of medication errors. In one study, a list of drugs known to be associated with a higher-than-normal risk of patient harm was used. When a medication error occurred that involved one of the drugs on the list it was automatically classified as being clinically important (42). In the study by Vira et al., an experienced internist assessed all medication errors for clinical importance (29). The method developed by the Veteran’s Affairs group for assessing safety uses four severity categories based on potential ADEs and their consequences (43). It does not focus on drug therapy specifically but can be used, in a modified version, to classify the clinical importance of medication errors. This was the method used in paper IV.

The term 'potential ADE' is defined as a medication error with potential for causing an ADE; this term is commonly used as a way of measuring medication safety (28, 30, 33, 35, 39, 41). Bates et al. showed that reductions in potential ADEs following intervention can be linked to reductions in actual ADEs (44).

It is important to perform system analyses of when, where, how and why the medication errors occurred in order to successfully correct system errors and prevent future errors from happening (45, 46). A systematic approach also has a greater and longer lasting effect on reducing medication errors than interventions where errors are just corrected randomly (44).
Inappropriate prescribing

'Inappropriate prescribing' is a term that is used frequently. Numerous studies have tried to assess its prevalence and the resulting clinical consequences (10, 47-84). It is well known that inappropriate prescribing can cause substantial morbidity and it is recognised as an important public-health issue, especially among the elderly (85-87). Inappropriate prescribing can be divided into three types (85, 86):

1. Underprescribing: failure to prescribe drugs that are needed;
2. Overprescribing: prescribing more drugs than are clinically needed;
3. Misprescribing: incorrectly prescribing a drug that is needed.

Underprescribing can be the result of doctors lacking adequate training in geriatric pharmacotherapy (56, 88) or due to a phenomenon called ageism; i.e. refusal to prescribe a drug or increase a dose solely because the patient is old (89, 90).

Overprescribing is often caused by drug therapy not being adequately re-evaluated over time with the consequence that drugs continue to be prescribed even though the indication for their use is no longer present.

Misprescribing can occur when a patient with a recognised medical indication is prescribed a drug that is harmful or ineffective, or a suboptimal dose, formulation or dosage interval.

Inappropriate prescribing can also arise from the absence of communication between doctors practising in different settings (89, 91).
Drug-related hospitalisation

Ten to thirty percent of all acute hospital admissions are thought to be caused by DRPs (92-95) and 50-70% of these are considered to be preventable (96, 97). Although DRPs can involve untreated indications, provision of drugs without a matching indication, administration problems and suboptimal dosage, most studies investigating the causes of DRP-related hospitalisation focus on ADRs.

The World Health Organisation defines an ADR as: “a noxious, unintended and undesired effect of a drug, which occurs at doses used in humans for prophylactics, diagnosis or therapy”. ADRs differ from ADEs in that ADRs are directly caused by normal dosages of the drug whereas the causal connection is less clear with ADEs, which may be the result of ADRs, overdosage, discontinuing medication, etc.

Beijer et al performed a meta-analysis of 68 studies exploring the effect of ADRs on hospitalisation (98). An average of 5% of nearly 124 000 admissions were considered to be the direct result of an ADR. The percentage of patients hospitalised due to an ADR varied in the studies from 0.2% to 41.3%. A sub-group analysis revealed that hospital admissions were ADR-related for an average 4.1% of nonelderly and 16.6% (four times higher) of elderly patients. Data in the literature indicate that 24.0% of the ADR-related hospital admissions of non-elderly and 87.9% of those of elderly people could have been prevented (98).

Mjörndal et al. assessed the probability that an ADR could have caused or contributed to the hospital admission of 681 randomly selected patients who were acutely admitted to an internal medicine clinic at a Swedish university hospital. Ninety-four patients (13.8%) had symptoms and signs that were judged as drug-related and that had caused or contributed to the admission. The ADRs responsible for the admissions were dominated by type A reactions, i.e. reactions in principle predictable and preventable (99).

A survey performed at the University Hospital of Uppsala in 2004 (unpublished data) aimed to establish the cause of hospitalisation for 214 patients who were 80 years of age or older (100). A multi-professional group decided that the admissions were certainly or probably caused by a DRP for 20 patients (9.4%). The DRPs most commonly resulting in admissions were ADRs, followed by inadequate dose (too low) and non-compliance.
Clinical pharmacy and pharmaceutical care

Clinical pharmacy and pharmaceutical care are two concepts that are closely related and yet distinctly different from one another. Various definitions of the terms have been suggested by research groups and healthcare organisations and authorities over the years (101-107). The different definitions and interpretations confuse practitioners and researchers alike, especially when crossing professional and national borders (108).

Clinical pharmacy

The term clinical pharmacy was used as early as the 1960s in the US when pharmacists started to provide ward-based, and later clinical-based services (109).

The latest definition from the European Society of Clinical Pharmacy (ESCP) website is: “clinical pharmacy includes all the services performed by pharmacists practising in hospitals, community pharmacies, nursing homes, home-based care services, clinics and any other setting where medicines are prescribed and used”(110). It should be emphasised that clinical pharmacy is not synonymous with hospital pharmacy, a term that is widely used on the European continent. Hospital pharmacy differs in that it also includes activities such as drug manufacturing and quality control, supply and procurement of drugs, and systems management, activities that are not within the concept of clinical pharmacy, according to the ESCP.

Clinical pharmacy first emerged as a hospital-based practice; however, over the last twenty years, clinical pharmacy is also increasingly being practised in primary and community care establishments. This transition has led to increased continuity of clinical pharmacy services as patients are referred around the whole healthcare system.

The definition of clinical pharmacy by ESCP is rather broad as it includes all services performed by pharmacists practising in a healthcare setting. In contrast, the US Department of Health and Human Services defines clinical pharmacy as:

“Functions performed by pharmacists on behalf of the patient to identify, resolve and prevent drug-related problems”(107). This definition focuses more on optimising the drug therapy of individual patients but is nonspecific as to where and in what context the pharmacist should practise.

In the Clinical Pharmacist’s Survival Guide, the term clinical pharmacy is used to describe a series of patient-related services, including prescription monitoring, therapeutic drug monitoring and patient counselling (111).

Clinical pharmacy in Sweden has developed slowly over the last twenty years, typically starting as small projects initiated by pharmacists employed by Apoteket AB. Positive results from these projects and the good relationships developing between individual healthcare professionals and pharma-
cists (as well as between their organisations) led to new initiatives and sometimes continuation of clinical pharmacy services at the end of the project period.

In the mid-nineties, Apoteket AB and the Swedish National Board of Health and Welfare jointly initiated a large project involving pharmacist-led, multi-professional medication reviews in nursing homes across the country that introduced the service model still widely used today. Clinical pharmacy in a hospital setting was initially established in the county of Jönköping and later in Skåne and Uppsala.

There are very few scientific publications from the early years of clinical pharmacy in Sweden, despite numerous projects having been undertaken. This fact has probably halted the development of clinical pharmacy in this country considerably, as decision makers in healthcare, on a local, regional and national level, increasingly request evidence from Swedish studies that clinical pharmacy has beneficial effects and is cost-effective in order to provide funding for the practice.

In countries such as the US and the UK, where clinical pharmacy has been well established for decades, pharmacists are often specialists in clinical areas such as oncology, intensive care, infectious diseases, etc. In Sweden, clinical pharmacy is more homogeneous and most pharmacists are involved in caring for elderly patients with multiple conditions and extensive drug treatment.

Pharmaceutical care

Hepler has recently stated that “pharmaceutical care can be said to describe the original purpose of clinical pharmacy” and that the concept can be used to guide clinical pharmacy into working in a more coordinated and effective manner (112).

Earlier, Hepler and Strand defined pharmaceutical care as “the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient’s quality of life” (104). Thus, pharmaceutical care is not about what the pharmacist does but about what the patient should receive. Pharmaceutical care can therefore be delivered in many different clinical settings by different teams of pharmacists, technicians, doctors and nurses and can be viewed as a quality assurance system for drug treatment based on multi-professional teamwork (113).

Pharmacists delivering pharmaceutical care must strive to develop their own personal practice as well as improve the systems that enable cooperation with other professions (101). To improve their own personal level of practice, pharmacists need to have good problem solving and communication skills added to a sound knowledge of drugs and drug therapy. Pharmacists should also be prepared to take greater responsibility in ensuring that patients are getting the best from their medicines (113).
Pharmaceutical care is a concept that is relevant to patient populations and is becoming an accepted term at policy-making levels in some EU countries because it has clear public health implications (105).

Education and training

Hudson et al propose that “the lack of clinical orientation is a continuing barrier to professional advancement in Europe, where in many countries pharmacy education remains dominated by a traditional emphasis on molecular science that is often poorly linked to clinical application” (113). Dramatic changes in a pharmacist's responsibilities and tasks in the health-care environs have forced most colleges of pharmacy to perform a critical review of the traditional educational methods used (114). Clinical pharmacists need to be able to solve therapeutic problems and make clinical judgments, skills that are better gained in a clinical environment than with a teacher-centred, subject-based approach in a class room (114).

In many countries, pharmaceutical education has changed accordingly, with increased teaching in therapeutics, partly in hospital wards, giving students an insight into diseases, lab-tests and investigations as well as the organisation of the healthcare system. This form of teaching also improves their confidence in communicating with patients and clinicians (115).

Joint therapeutics teaching sessions with pharmacy and medical students is another method that should also be encouraged according to Greene et al (115). These sessions allow the students to gain a better understanding of the other profession’s knowledge and scope of practice, something that is likely to be beneficial for future collaborations.

Franke et al. found that, to be able to practice on a satisfactory level, contemporary clinical pharmacists need to be:
1. Educated to become the main authority on drug products and efficacious drug therapy;
2. Educated to be skilful communicators of pharmaceutical knowledge to both patients and other healthcare professionals;
3. Knowledgeable of and sensitive to the physical, socioeconomic, cultural and psychological factors that contribute to illness and health, and the management of associated problems;
4. Taught skills of analysis and problem solving, decision making, and synthesis of new and old data in the day-to-day practice of their profession; and
5. Taught that the patient’s welfare transcends all other considerations and that their management skills should be directed toward this end (116).

In the US, the extension of clinical training of pharmacists became formalised through the Doctor of Pharmacy (PharmD) programmes, emerging first in California in the late eighties, and subsequently in Kentucky and Michigan, both early adopters of clinical pharmacy. The PharmD programmes
now include a planned clinical placement rotation built into the final voca-
tionally orientated degree (113).

In the UK, postgraduate clinical pharmacy programmes (MSc in clinical
pharmacy) offer a combination of taught elements such as workshops in
clinical topics, clinical skills, clinical pharmacokinetics, problem solving and
critical appraisal skills with experiential or task-based learning and a re-
search project (117). There are now MSc courses in clinical pharmacy, in-
spired by the UK programmes, in Denmark, Greece, Ireland, Malta and
Turkey and in Sweden (118). The Swedish MSc course at Uppsala Univer-
sity started in 2006 and comprises a one-year full-time course or two years
of part-time study.

The increased demand for clinical pharmacy services has increased the
need for practice-based research. Universities adapting to a patient-centred
pharmacist philosophy face the challenge to build strength in the field
through research. In the UK, professors of pharmacy practice have been
appointed in all Schools of Pharmacy (113).

Clinical pharmacy tools

Medication reconciliation

Medication reconciliation is “the process of identifying the most accurate list
of a patient’s current drugs and comparing that with the current list in use,
recognising any discrepancies, and documenting any changes. Reconciliation
should be undertaken at every transition in care in which new drugs are or-
dered or existing orders are rewritten” (119).

In 2009, Karnon et al. performed a model-based cost-effectiveness
analysis that provided reasonably strong evidence that some form of inter-
vention to improve medication reconciliation is a cost-effective use of
healthcare resources. The results also indicated that pharmacist-led medica-
tion reconciliation was likely to be the most cost-effective intervention
(120). In Sweden, the Board of Health and Welfare has listed it as one of
three tools for improving the safe use of medicines (121).

Medication reconciliation as a process can be divided into three steps:

- Verification (collection of the patient's medication history);
- Clarification (ensuring that the medications and dosages are appro-
  priate); and
- Reconciliation (documentation of changes in the orders)(122).

Researchers in southern Sweden have developed the LIMM (Lund Integrated
Medicines Management) model, which includes a comprehensive package of
tools for improving patients’ drug therapy, and which can be used in all
healthcare settings. LIMM tools used in the medication reconciliation proc-
ess include a structured patient interview on admission and a structured medication report on discharge (123-125).

Medication review

Lowe et al. define the concept of medication review as: “the process where a health professional reviews the patient, the illnesses and the drug treatment during a consultation. It involves evaluating the therapeutic efficacy of each drug, unmet therapeutic needs and the progress of the conditions being treated. Other issues, such as compliance, actual and potential adverse effects, interactions and the patient’s understanding of the condition and its treatment are considered where appropriate. The outcome of a clinical review will be a decision about the continuation (or otherwise) of the treatment” (126).

While this definition covers most of the relevant aspects that should be considered in a thorough medication review, it does not specify whether the drug treatment also includes over-the-counter (OTC) drugs and natural remedies or only prescribed drugs. It does not mention the qualifications needed to perform a medication review or practical or economic issues. It does, however, state that the medication review should be performed during a consultation with the patient (or caregiver/next of kin) and not, as sometimes occurs, on a more theoretical level without input from the patient, which would identify potential rather than actual, clinically relevant DRPs. Krska et al. found that the medical notes and/or the patient was the source of information, rather than only the list of medications taken by the patient, for 50% of the relevant pharmaceutical care issues that were identified (127).

The definition by Lowe et al. does not mention the important aspects of evaluating drug changes, monitoring clinical outcomes and follow-up contact with the patients. These omissions are important, as many tend to look at a medication review as a “quick fix” rather than an ongoing process.

Tools that assess appropriateness of prescribing

The appropriateness of prescribing can be assessed using tools that are explicit and/or implicit. Explicit tools are criterion-based, usually drug oriented and/or disease oriented, and can be applied with little or no clinical judgment. These tools have usually been developed from a literature review using expert opinion and consensus techniques. As evidence-based aspects of drug treatment in a geriatric population are frequently absent, expert opinion is usually needed. Explicit tools have the disadvantage of requiring regular and frequent updating and being overly nation-specific. Beer’s criteria (57, 128, 129) and STOPP/START (52, 67, 130, 131) are explicit tools that have been clearly described in the literature. Another explicit tool, ACOVE (83,
Beer’s criteria comprise lists of drugs that should generally be avoided by elderly people because the risks of use are judged to outweigh the benefits. The lists also include dosages that should not be exceeded and drugs to avoid in patients with specific disorders. These criteria have been frequently applied to aggregated data in large databases. The most common application has been to detect overprescribing of neuroleptic drugs for patients in nursing homes (133, 134).

The STOPP/START (Screening Tool of Older Persons’ Prescriptions/Screening Tool to Alert doctors to Right Treatment) criteria consist of two complementary parts. STOPP comprises 65 criteria for potentially inappropriate prescribing in elderly patients, allowing the identification of PIMs (Potentially Inappropriate Medicines). START, on the other hand, consists of 22 prescribing indicators for commonly encountered diseases in older people and identifies PPOs (Potential Prescription Omissions) (131). The use of STOPP and START as screening tools in everyday clinical practice significantly improved prescribing appropriateness in a recent RCT (68).

Implicit (judgment-based) tools require extensive information about the patient and knowledge about pharmacotherapy in the elderly to allow the user to make qualified judgments about the appropriateness of each drug. The focus is usually on the patient rather than on the drugs or the diseases.

The Medication Appropriateness Index (MAI) has been used extensively worldwide since it was developed in 1991 (59, 70, 72, 73, 135-138). To our knowledge, it is the only validated implicit tool available. The MAI includes assessment of ten aspects of appropriateness of prescribing: indication, effectiveness, dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration, and cost. Clinical judgment is needed to assess the criteria. The MAI has operational definitions and clear instructions, which standardize the rating process (available on request from Hanlon et al.). The ratings generate a weighted score that summarises the appropriateness of a patient’s pharmacotherapy. Three questions from the MAI (indication, effectiveness, and duplication) can be used independently to detect unnecessary polypharmacy.

The MAI has the advantage of not having to be frequently up-dated or adjusted to different countries’ drug formularies as the criteria are general in their nature. The main disadvantage is that using the tool is very time-consuming.

Pharmacists in healthcare teams
Pharmacists are being seen as natural members of healthcare teams in many countries, especially in Anglo-Saxon countries where pharmaceutical care
and clinical pharmacy have been established concepts for the last 30-40 years. In Sweden, as in many other European countries, the concept of clinical pharmacy is being increasingly recognised. Many studies have shown that multi-professional collaborations including pharmacists result in beneficial effects. These studies have focused on the effects on patient safety (reduction in medication errors and ADRs) (123, 139-142), pharmacoeconomics (reduction in drug costs and healthcare utilisation) (125, 143-147) appropriateness of prescribing (124, 125, 138, 145, 148). It is evident that there is a strong case for preventing drug-related morbidity, for clinical, humanitarian, and economic reasons, and that pharmacy has much to offer (112).

Chronic disease management, increasingly complex in its nature, increasingly requires a team approach (149).

The introduction of clinical pharmacy means that professionals who are traditionally part of healthcare teams, primarily physicians and nurses, will start to interact with a new professional – the pharmacist – in their daily routines. The implications of the interactions between physicians and pharmacists have been studied extensively (144, 150-159). The implications for nurses have been explored less extensively (144, 158, 159). A descriptive study from Australia using interviews showed that pharmacists and physicians often have limited understanding of and confidence in the breadth of knowledge of each other. This study also found that their expectations of one another and perceptions of patient needs differed (154).

Holland et al. found that collaborations between pharmacists and physicians in close liaison with each other were most commonly linked with positive patient outcomes (157). This was thought to be due to the development of professional relationships, mutual trust and recognition of each other’s competences and skills. Importantly, the team members also felt that they shared a common focus – the patient.

McPherson et al. also mention good communication, appropriate training and access to the required resources as important factors for successful collaboration (153). When a successful inter-professional team is formed, it can improve patient outcomes and the cost effectiveness of care in all healthcare settings, according to the researchers (153).
Aims of the thesis

The main aim of the thesis was to evaluate clinical pharmacist interventions with the focus on methods of improving drug therapy and patient safety.

The specific aims were:

I To investigate the effectiveness of interventions carried out by ward-based pharmacists in reducing morbidity and usage of hospital care for elderly patients.

II To investigate the effect of pharmacist interventions on appropriateness of prescribing, as assessed by STOPP, START and MAI, and to explore the relationship between these results and clinical health outcomes defined as re-visits to hospital.

III To evaluate the perceived value of ward-based clinical pharmacy, from the perspective of hospital-based physicians and nurses, and to capture the perceived advantages/disadvantages related to the new inter-professional collaboration for the practitioners themselves and for the patients under their care.

IV To investigate the frequency, type and occurrence of prescription/transcription errors for patients receiving drugs using the Multidose Drug Dispensing system (ApoDos®) when discharged from hospital and to assess the severity of the identified errors.
Materials and methods

Detailed descriptions of the various methods used in the presented papers are provided in each publication or manuscript (Appendices I-IV).

Paper I

This study was an RCT comparing hospitalised patients receiving standard (non-pharmacist) care with those receiving an enhanced, more comprehensive service performed by a pharmacist integrated into the healthcare team.

The trial was carried out at Uppsala University Hospital between October 2005 and June 2006; 400 patients aged 80 years or older were recruited from two acute internal medicine wards. Patients from both wards were randomly assigned to the intervention or control groups.

Clinical pharmacists provided the intervention group patients with an enhanced service:

1. A comprehensive list of current medication was compiled on admission, to complement that obtained in the emergency department (ED), ensuring that the medication list received by the ward was correct.
2. A drug review was performed and advice was given to the physician on drug selection, dosages and monitoring needs, with the final decision made by the physician in charge.
3. Patients were educated and monitored throughout the admission process.
4. Patients received discharge counselling.
5. Information on discharge medications (e.g. rationale for changes and therapeutic goals and monitoring needs for newly commenced drugs) was communicated to primary care representatives.
6. A follow-up call to patients was made two months after discharge.

The standard care received by the patients in the control group was provided by physicians and nurses.

The pharmacists compiled a comprehensive list of current medication from various information sources including interviews with the patients, prescriptions and medicine lists from primary care centres and medical notes. Identified transcription errors were corrected.
All intervention group patients received a comprehensive medication review carried out by the pharmacists. The review followed the well-defined procedure developed by Strand et al (19) and addressed issues of indication, effectiveness, safety and adherence. Information was collated using information from admission, clinical chemistry, urinalyses, haematology results, and the patient’s medical notes. All relevant DRPs were discussed within the healthcare team during ward rounds and adjustments to the drug treatment were subsequently carried out by the physician. The patient’s response to drug treatment was monitored throughout the hospital stay. The DRPs identified by the pharmacist were recorded in a database together with suggested actions and outcomes (i.e. whether or not the action was carried out).

The general practitioners (GPs) of the intervention group patients received a written summary from the pharmacist, giving a comprehensive account of all changes in drug therapy during the hospital stay, including the rationale behind medication decisions, the monitoring needs and the expected therapeutic goals of the intervention group patients. DRPs not yet dealt with were also listed, along with suggested actions.

Two months after discharge, the pharmacist contacted the individual intervention group patients by telephone to ensure adequate home management of medications.

The study was closed twelve months after the discharge of the last included patient. Patients in the intervention group who were re-admitted to the study wards received the enhanced service again. After the closure of the study all patients’ national identification numbers were entered into the hospital’s patient administrative system to explore secondary care utilisation during the follow-up year. Data regarding re-admissions and visits to the ED were recorded along with the costs associated with each visit/admission.

The electronic medical notes were used to establish the reasons for re-admission. For a re-admission to be counted as drug-related it had to have been coded as such by a physician who was unaware of the patient’s study status.

Paper II

The data used in this study originated from the previously reported RCT (Paper I) and included data on drug therapy (on admission and at discharge) as well as data on re-hospitalisation.

Three tools commonly used to evaluate appropriateness of prescribing; STOPP, START and MAI, were applied to the drug lists of 368 study patients (27 of the 400 originally included patients died during the index admission and 5 wished to be excluded – the drug lists of these patients were not assessed in this study). The researcher applying the tools was an experienced clinical pharmacist, blinded to the patients’ study allocation (i.e. con-
The electronic case notes gave access to the information needed to assess the appropriateness through each criterion.

The patients’ total drug therapy was assessed twice: on the first day of admission and on the day of discharge from hospital. As recommendations from the pharmacists had not yet been presented to the physician on the first day of admission these were regarded as baseline data. All prescribed drugs with pharmacologically active ingredients were included in the analyses and renal function, estimated using the Cockroft and Gault equation, was recorded for all patients.

STOPP and START were used according to detailed instructions published by the developers of the instruments. The MAI (updated version from 2004) comes with comprehensive instructions using examples to illustrate the rationale for judgments and scoring. The instructions were carefully followed during the assessments. Data about hospital care consumption had been obtained previously from the hospital administrative records.

Scores for appropriateness of prescribing (using MAI, STOPP and START), from the dates of admission and discharge, were registered for all patients to detect a difference over time and between the groups. Further analysis of the scores at the time of discharge and data on hospitalisation from the follow-up year was undertaken to detect any correlations. Data on the number of drugs on admission and discharge for each patient were also included and the same analyses were performed as for the tools.

**Paper III**

The data collection for this study was undertaken during the inclusion period of the RCT. The study subjects were hospital-based physicians and nurses, and GPs. This descriptive study was based on questionnaires and interviews.

Questionnaires were distributed to the physicians (n=29) on the study wards who had been involved with at least one patient in the intervention group. After they had completed the questionnaires they posted them to the researcher responsible for the data collection. The day-time nurses (n=44) working on the study wards also received a questionnaire. All GPs (n=21) who had received two or more medication reports regarding their patients were identified and sent a questionnaire at the end of the study period.

Data were collected using study-specific questionnaires, containing both closed- and open-ended questions. The questionnaires were designed to capture the perceived advantages and disadvantages of integrating clinical pharmacists in the healthcare team, for the practitioners themselves and for the patients under their care. For most of the closed-ended questions, the answers were to be given on a four-grade verbal scale, ranging from “yes, very much so” to “no, not at all”. One question was answered with a dichotomised response alternative, “yes” or “no”. The aim of the open-ended
questions was to investigate aspects of the advantages and disadvantages that had not been covered in the closed-ended questions, and to give the respondents the opportunity to emphasise matters they considered particularly important.

MH, who was responsible for the data collection in this study, worked independently of the pharmacists and the questionnaires were analysed before the outcome of the RCT was known.

Answers to the closed-ended questions were analysed descriptively. Answers to the open-ended questions were analysed by content analysis.

**Paper IV**

The survey in Paper IV was a prospective, longitudinal, descriptive, experimental cohort study conducted at the University Hospital of Uppsala. The study subjects were patients enrolled in the MDD (ApoDos®) scheme who had been admitted to hospital. Twenty hospital wards use the extended discharge service for MDD patients and they were all included in the survey.

The data collection was performed by two pharmacy students at Masters level, supervised by experienced clinical pharmacists.

Data were collected between February and April 2010. The data collectors visited each ward every weekday morning prior to the visit from the hospital pharmacist who came to collect the MDD orders that were to be prepared that day.

All MDD orders were reconciled (i.e. they were compared with the patient’s current MAR on the ward) and relevant information about the patients was collected from the MDD orders and recorded. All identified discrepancies were recorded with respect to the medication involved and the type of discrepancy. Only unintentional discrepancies were included and the outcome (whether or not the error was corrected) was recorded. Since the aim of this study was to evaluate the MDD ordering process at discharge, only the errors relating to this were subject to further analysis and safety assessment.

The medication discharge errors were categorised into the following types: A. omission of drug (drug on the MAR missing from the MDD order); B. extra drug (drug discontinued during the hospital stay but present on the MDD order); C. wrong drug; D. wrong dose/formulation/dosage regimen; E. wrong dosage time; and F. double prescribing.

All medication discharge errors were classified into one of four severity categories (Table 1).
Table 1. Severity categories and potential consequences.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Potential Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catastrophic</td>
<td>Death or major permanent loss of function not related to the natural course of the patient's illness or underlying condition</td>
</tr>
<tr>
<td>Major</td>
<td>Permanent loss of bodily functioning. New acute hospital admission or visit to the Emergency Department.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Increased length of stay or increased level of care. Need for new health-care contact; therapeutic failure</td>
</tr>
<tr>
<td>Minor</td>
<td>Adverse drug reactions (mild). Reduced effect of drug treatment on medical condition.</td>
</tr>
</tbody>
</table>

Each error was classified collectively by the two data collectors and two experienced clinical pharmacists. The pharmacists’ assessments were then reviewed by an experienced physician, a specialist in internal medicine. The assessment was carried out systematically. The patient’s age, the type of error and the nature of the drug involved were factors taken into account. Errors involving drugs with a direct, serious effect or with a narrow therapeutic window were judged to be potentially more serious. Each error was classified individually, i.e. the occurrence of several errors in one MDD order did not influence the scoring of each error.

The occurrence of one or more medication errors in the orders and the rate of error correction were modelled as multiple logistic regressions.
Results and Discussion

Paper I

This study is, to our knowledge, the only randomized controlled study of the effectiveness of pharmacist interventions, in a hospital setting, on drug-related morbidity and hospitalisation in patients, 80 years or older.

Of the 400 patients originally included, 368 were followed for the predefined 12-months period. The typical study subject was an 86 year old female with multiple chronic conditions and 8 prescribed drugs. The patients in the study were frequently admitted to hospital and after the follow-up year, only 22% were still alive and had not been admitted to hospital and/or visited the ED. The fact that the study only included very old, often frail elderly persons was challenging as many factors caused deteriorating health and need of secondary care and the role of sub-optimal drug therapy, which was the focus of the study, was probably only contributing to a certain degree.

The medication review performed by the pharmacists resulted in 476 identified DRPs of which the most common was adverse drug reaction (119), commonly caused by a dose that was too high and not adjusted to the patient’s physical status and elimination capacity. The second most common DRP was need for additional drug therapy (90) and unnecessary drug therapy (86).

A total of 75% of the pharmacists’ recommendations were implemented which was considered satisfactory. Data on acceptance-rate is interesting, especially when a new practice model is introduced, as it gives an indication on how well the team functions. Studies have shown that when the recommendations are discussed face-to-face rather than presented in writing and when the inter-professional team is well established and builds on mutual trust, then the acceptance rate is increased (157, 160, 161).

When the primary outcome measure; all visits to hospital, was investigated a difference of 16% percent was detected between the groups in favour of the intervention group. Further, there was a 47% decrease in visits to the ED. The researchers are of the opinion that the follow-up phone calls, made by the pharmacist, probably contributed substantially to this result as it gave the patients a chance to air their concerns and ask relevant questions regarding their drug therapy. Readmissions by itself did not differ between the groups, possibly due to insufficient power, as the morbidity and mortality in the study population was so high (Table 2.).
Table 2. Summary of outcomes at 12 months’ follow-up.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention (n=182)</th>
<th>Control (n=186)</th>
<th>Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits to hospital* - No. (Incidence)</td>
<td>266</td>
<td>316</td>
<td>0.84 (0.72, 0.99)</td>
</tr>
<tr>
<td>Patients re-admitted* - No. (%)</td>
<td>106</td>
<td>110</td>
<td>0.96 (0.64, 1.46)</td>
</tr>
<tr>
<td>Re-admissions* - No. (Incidence)</td>
<td>217</td>
<td>223</td>
<td>0.97 (0.01, 1.17)</td>
</tr>
<tr>
<td>Drug-related re-admissions* - No. (Incidence)</td>
<td>9</td>
<td>45</td>
<td>0.2 (0.1, 0.41)</td>
</tr>
<tr>
<td>Visits to emergency department* - No. (Incidence)</td>
<td>49</td>
<td>93</td>
<td>0.53 (0.37, 0.75)</td>
</tr>
<tr>
<td>Overall survival 2)</td>
<td>0.69</td>
<td>0.67</td>
<td>0.94 (0.65, 1.34)</td>
</tr>
</tbody>
</table>

*a* Comparison using Odds ratio, *b* Comparison using quotient, *c* Comparison using hazard ratio

Drug-related readmissions, however, were substantially reduced in the intervention group (Table 3).

Table 3. Drug-related readmissions

<table>
<thead>
<tr>
<th>Drug-related causes for re-admission</th>
<th>Intervention (n=9)</th>
<th>Control (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin intoxication</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Over-prescribing of antihypertensive agents</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Sub-optimal drug therapy – heart failure</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Sub-optimal drug therapy – ischaemic heart disease</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dehydration due to over-prescribing of diuretics</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Anaemia due to aspirin or NSAIDs</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Confusion and or fall due to sedatives, opioids or anticholinergics drugs</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Sub-optimal drug therapy – diabetes mellitus</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Diarrhoea due to antibiotic treatment</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hyponatraemia due to diuretics and SSRI therapy</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Lack of drug treatment – atrial fibrillation (embolism)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Bleed (haematoma) due to warfarin</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Out of 54 readmissions classified as drug-related only 9 were in the intervention group. Interestingly, 4 of these could possibly have been avoided, as the pharmacist had suggested alterations in drug therapy that had not been acted
upon (reduction in doses of digoxin, frusemide and two antihypertensive agents).

Holland et al performed a meta-analysis of 32 studies evaluating effects of pharmacist led medication reviews (162). They could not detect a beneficial effect on re-hospitalisations although positive effects on other end-points such as knowledge, adherence and appropriateness of prescribing were seen. However, none of the included studies had a similar design to our study; most were based in community and did not involve a direct contact between the pharmacist and the physician.

To further strengthen the theory that the physician/pharmacist cooperation is more fruitful for the patients if there is a closer liaison between the professions a hospital-based study from Northern Ireland showed a significantly lowered re-admission rate and a reduction in the duration of stay with pharmacist intervention (144).

The time for the pharmacist intervention in the study was estimated to 2 hours and 20 minutes per patient. Since the conditions were regulated by the RCT this time estimate is vastly exaggerated compared to if the same intervention would have been performed in regular care. Never the less, cost savings balanced against the cost of intervention was 1800 SEK ($230) per patient. If this was to be extrapolated over a year, the cost savings on hospital based care in the county council of Uppsala would be 9 million SEK ($1 200 000).

**Paper II**

When the criteria of three instruments were applied to the drug lists of the patients in the RCT (Paper I), it was obvious that the pharmacist intervention had a substantial effect on the appropriateness of prescribing. For the MAI, the summed score per patient was similar for both groups on admission but nearly two-fold different at discharge, as the mean score was 5.0 for the intervention group and 10.0 for the control group. The same pattern was seen for the STOPP and START tools (Table 4.).
Table 4. Changes in scores and number of drugs, between the groups and over time

<table>
<thead>
<tr>
<th></th>
<th>Intervetion group (n=182)</th>
<th>Control group (n=186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Summated score per patient, mean (SD)</td>
<td>8.5 (6.8)</td>
<td>5.0 (4.23)</td>
</tr>
<tr>
<td>START</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of PPOs per patient, mean (SD)</td>
<td>0.36 (0.67)</td>
<td>0.09 (0.32)</td>
</tr>
<tr>
<td>STOPP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of PIMs per patient, mean (SD)</td>
<td>1.42 (1.46)</td>
<td>0.93 (1.02)</td>
</tr>
<tr>
<td>Number of drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of drugs per patient, mean (SD)</td>
<td>8.84 (4.43)</td>
<td>9.10 (3.75)</td>
</tr>
</tbody>
</table>

Scores for MAI, STOPP and START generally improved for patients in the intervention group during the period of admission and deteriorated for patients in the control group (Figure 1a-b).

Figure 1a. Percentage of patients with improved scores
It is possible that this was because the focus of a traditional healthcare team on an acute medical ward is on treating the current cause of admission, and hence drugs are often added without a thorough review of previous, ongoing prescriptions.

The number of drugs remained unchanged for the intervention group but was increased in the control group. It is noteworthy that even though the control group patients in general were prescribed more drugs at discharge than they were on admission, they were still missing clinically indicated medicines as assessed by START. Polypharmacy has repeatedly been shown to be a predictor of negative clinical outcomes. However, since polypharmacy does not provide a quality assessment it should not be treated as an independent determinant of inappropriate prescribing.

The scores for MAI, STOPP and START, either unadjusted or adjusted, did not correlate with the primary outcome measure: visits to hospital. However, there was a correlation between the unadjusted number of drugs and the number of visits to hospital, with a rate ratio (RR) of 1.04, implying that for each added drug the risk of hospitalisation increased by 4% (Table 5).
When the secondary outcome measures (re-admissions, ED visits and drug-related admissions) were added, improvements in MAI showed a stronger correlation with the outcomes than improvements in STOPP and START. It is possible that this was because the components in the pharmacist intervention were more similar to the components of MAI than to those in STOPP or START. Alternatively it could be because, for a drug review to result in a quality improvement that can be reflected in positive health outcomes such as hospital visits, it needs to be done in a specific and individualised manner, and the MAI instrument, unlike STOPP and START, is used in a similar way.

Although several other screening tools are available, we chose to use STOPP and START because they are recently developed and validated instruments that despite not yet being extensively tested appear promising in many aspects: they are organised according to therapeutic areas and can be quickly and easily applied. When used together, they cover most of the pharmacological aspects of inappropriate prescribing, including omission of drugs.

Although STOPP and START were developed to complement each other, the creators of the tools have not to our knowledge used and analysed the
combined scores. Although it is tempting to try to combine all aspects of appropriate prescribing into one score, we chose not to present the results in this manner because the representation of each tool was not well balanced. In our study, the vast majority (84%) of points for inappropriateness (combining PIMs and PPOs) were represented by scores from the STOPP criteria.

The use of MAI is associated with some practical obstacles. Firstly, it is time consuming; each drug is scrutinised using ten different aspects of appropriateness. Secondly, since MAI is an implicit judgment-based tool, the researcher needs to be clinically experienced and to have access to all the relevant patient data. Therefore, in our view, the MAI can be an excellent tool for training and education purposes and for evaluating the quality of prescribing retrospectively, but it is not practically feasible in everyday practice.

The ability of a tool to predict hospitalisation is important, but other aspects such as user friendliness and comprehensiveness need to be considered in order for the tool to be useful in clinical practice. STOPP and START are quick and easy to use but they need to be adjusted to the pharmacotherapy traditions in the country in which they are used and they require frequent updating. Further, it was not evident in our study that they could predict rehospitalisation.

In our opinion, the key elements of the RCT that made it possible to improve the appropriateness of prescribing included the focus on and knowledge of prescribing for the elderly that was brought into the care team by the clinical pharmacists, the close working relationship between doctors, nurses and pharmacists, and the extensive communication with the patients. Since the clinical pharmacist intervention in the RCT consisted of a number of elements and the screening tools only evaluate the drug review part of the intervention, the reduction in hospital visits that was observed cannot be assumed to be directly due to changes in MAI, STOPP, START or the number of drugs, since the effects of the interventions that aimed to increase the patients’ knowledge of and adherence to drug treatment and the reduction in medication errors would not therefore be taken into consideration. In order to increase the overall quality of drug use, it is necessary not only to focus on pharmacological appropriateness but also to consider what the individual patient wants and needs.

There is currently no one validated tool that covers all the relevant aspects of appropriate prescribing. The three tools used in this study all focus on different aspects but none of them take the patients’ views, wishes or adherence to treatment into consideration. However, when used together, the three tools present a multidimensional assessment and aspects of underprescribing, overprescribing and misprescribing are evaluated.

Improvements in the appropriateness of prescribing by introducing a pharmacist intervention have been demonstrated in several previous studies.
In this study, a more in-depth investigation of the correlation between results of process measures and important clinical outcomes is presented.

Paper III

The response rate for this descriptive study was high: 76% of the hospital-based physicians, 81% of the nurses and 81% of the GPs completed the questionnaires. Ninety-five percent of the hospital-based physicians and 97% of the nurses wanted the collaboration with the pharmacists to continue in the same or in a similar way. In general, all respondents considered the pharmacists’ suggestions for patients’ drug therapy to be relevant and the collaboration not to be too time-consuming. The majority thought that both drug-related patient safety and their own knowledge of drug therapy for elderly patients had improved as a result of the collaboration. The nurses also mentioned that they had received much information and support from the pharmacists in their daily work (Table 6.).

Table 6. Experiences and perceptions of hospital-based physicians (n=22) and nurses (n=29) on the addition of clinical pharmacists to the health-care teams.

<table>
<thead>
<tr>
<th></th>
<th>Yes, very much so</th>
<th>Yes, to a certain extent</th>
<th>No, not really</th>
<th>No, not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Are you satisfied with the collaboration with the pharmacists on the ward?</em></td>
<td>95/93</td>
<td>5/7</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td><em>Has the collaboration been time consuming?</em></td>
<td>0/3</td>
<td>18* /17</td>
<td>59* /38</td>
<td>18* /41</td>
</tr>
<tr>
<td><em>Have the pharmacists made relevant suggestions to the patients’ drug therapy?</em></td>
<td>50* /79b</td>
<td>45* /17b</td>
<td>0* /3b</td>
<td>0* /9b</td>
</tr>
<tr>
<td><em>Has your knowledge about drug therapy for elderly patients increased as a result of the collaboration with the pharmacists?</em></td>
<td>23/14</td>
<td>68/59</td>
<td>9/17</td>
<td>0/10</td>
</tr>
<tr>
<td><em>Do you think that the collaboration with the pharmacists has enhanced drug related patient safety?</em></td>
<td>45/62b</td>
<td>50/31b</td>
<td>5/3b</td>
<td>0/0b</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Would you like to continue to work with pharmacists in the same or a similar way in the future?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Would you like to continue to work with pharmacists in the same or a similar way in the future?</em></td>
<td>95/97</td>
<td>5/3</td>
</tr>
</tbody>
</table>

Negative aspects that were mentioned in the section containing open-ended questions were that two hospital-based physicians felt somewhat questioned in their professional role by the pharmacists. This highlights the need to clarify the role of the pharmacist for all team members. The nurses raised practi-
cal concerns regarding increased time spent on ward rounds and limited space on the wards.

The majority of GPs (71%) wanted to continue to receive medication reports in the same or a similar way in the future. The majority thought that the medication reports could improve drug-related patient safety and the quality of prescribing in primary care. Negative aspects raised were that some GPs felt they had to spend more time dealing with their patients' drug therapy after they had received a medication report than they otherwise would have done. Some also thought that the medication reports did not include enough information and that they could cause confusion for both themselves and the patients.

As the results indicate, the GPs were positive about the new service but not as positive as the hospital physicians and nurses. This is in line with the finding that a close, trusting relationship is favourable for inter-professional collaboration. Since the pharmacists did not communicate with the GPs other than by fax and an occasional phone call, the relationships were not as direct.

The formation of an inter-professional team on the study wards was challenging as nearly 30 physicians worked on the wards during the nine-month inclusion period, some for very short periods of time. The residence time for the nurses and nursing staff was more stable and they played an important role in introducing new physicians to the team model. Another important factor was that the few more permanent, senior physicians on the wards acted as role models for the new physicians.

One limitation of the study was that the characteristics of the pharmacists that may have influenced the attitude of the physicians and nurses, such as age, gender, experience, level of friendliness and prestige, were not analysed. These factors may have affected both the replies, in terms of satisfaction and willingness to continue with the collaboration, and the response rate.

Paper IV

Suggested advantages of the MDD system are that it offers increased protection against medication errors, it aids adherence to drug therapy regimens and it reduces wastage of unused drugs (11, 12). For elderly patients with multiple prescriptions who are unable to manage their drugs independently, the system has been proven to be of great benefit. For nursing home residents it is almost obligatory to be enrolled in the system, mainly due to the staffing situation.

However, when patients are admitted to hospital, the MDD system is not in use and the transfer of information to the hospital MAR on admission and back at discharge often fails, as this study shows.
Of the 290 reviewed MDD orders at discharge, 72 (25%) contained at least one verified discharge error. A total of 120 discharge errors were subjected to further analysis. The number of errors ranged from 1 to 14 per order. There was no correlation between patient age or gender and the error rate. However, orders with at least one discharge error contained a significantly higher number of drugs than orders without discharge errors.

The most common types of error were omission of drug and wrong dose/frequency/formulation (44% and 31%, respectively). The majority of the discharge errors (57%) were considered to be of minor clinical importance but forty-nine (41%) were classified as being of moderate clinical importance. Three errors in three patients were scored as being of major importance; i.e. had they not been identified and rectified, a new admission would very likely have occurred. These three patients – had they been admitted to hospital – would have generated a cost of approximately 100 000 SEK ($14 000), based on data from paper I.

There were no significant correlations between electronic ordering and error rates, even when adjusted for the number of drugs. The errors classified as of moderate or major importance were equally divided between the electronic and hand-written orders.

The number of drugs prescribed was a predictor of more errors at discharge in our study. The fact that a high number of medications is associated with a higher risk of medication errors is not surprising and has been shown previously (38). It emphasises the importance of alertness when treating people with extensive pharmacotherapy and it also highlights the importance of avoiding unnecessary prescribing of drugs.

Sixty-nine (58%) of the discharge errors were corrected by the physician in charge of the patient when they were pointed out by the pharmacists. However, errors categorised as being of moderate or major severity were more likely to be corrected (90% and 100%, respectively) than errors categorised as minor (32%). The severity of the errors was the only factor identified that could be linked to the correction rate (OR: severity 2 or 3 vs. severity 1 = 20.80; p<0.001). All wards followed the same pattern in this respect. This indicates that the intervention was effective in that it managed to identify and correct serious errors that could have resulted in new healthcare visits. The intervention also reduced the risk of less severe medication errors that could potentially have generated ADEs, confusion about current drug treatment for the patient and for the next caregiver, and other undesired effects.

A communicating, electronic link between the MDD lists and the hospital MARs would probably reduce these errors substantially. The technical possibility of creating this link is presently under investigation by the company that provides the MDDs. Using the patient’s own pre-packed MDDs while he/she is in hospital would also lead to a seamless supply of drugs and take
away the element of transcribing one list to another. This model is currently being piloted in some hospitals in Sweden.
Conclusions

- Patients who had received the comprehensive pharmacist intervention in the randomised controlled trial had fewer visits to hospital during the follow-up year and the intervention was cost-effective.

- The intervention significantly improved the appropriateness of prescribing for patients in the intervention group as evaluated by all three instruments used; STOPP, START and MAI. There were no clear correlations between high scores for the tools or a high number of drugs and increased risk of hospitalisation.

- Hospital-based physicians and nurses as well as GPs were generally positive to the new collaboration with clinical pharmacists to a high degree and wanted to continue working in the same or in a similar way.

- Prescription and transcription errors frequently occur when patients enrolled in the Swedish MDD system are discharged from hospital. The majority of errors identified in the study were of minor clinical importance, some were of moderate importance and a few of major importance.
Future perspectives

Controversies are common when a new profession is introduced to and included in traditional healthcare. Physiotherapists, occupational therapists and dieticians can all verify this fact. The first question asked by the management is often: “How much added value, in terms of increased quality and safety and reduced costs, can be gained?” And “Does this added value justify the additional costs?” It is then up to the profession to prove that their contribution to healthcare is of high value and cost-effective. Pharmacists, world-wide, have over the years tried to prove this in numerous studies. However, achieving positive results on hard clinical endpoints such as morbidity and mortality is challenging when the interventions are only targeting one aspect of patient care, i.e. drug therapy. Thus, many researchers choose to study the effects of their interventions on process outcomes such as reductions in medication errors and identification of drug-related problems instead. The randomised controlled trial, previously reported by our research group, provides reasonably strong evidence that the inclusion of a clinical pharmacist into the healthcare team, who will provide a comprehensive service to patients and physicians, is a cost-effective use of healthcare resources. As a result of this, clinical pharmacy has received funding from the county council of Uppsala to develop multi-professional collaborations aiming to improve drug therapy for elderly patients.

As many pharmacists world-wide feel; now is the time when we should stop trying to prove professional value and instead focus on value for the patients and for society. Drug therapy today is so complex in its nature that multi-professional models are necessary. Contemporary pharmaceutical care research should not be divided into sub-specialties but include interventions performed by all relevant healthcare professionals, focusing on improving important clinical outcomes.

Medication related patient safety needs to be ensured so that efforts can instead be used on achieving treatment goals, increasing the evidence base for pharmacotherapy in elderly patients and promoting active patient participation. To increase patient safety, more resources should be used on developing safe and effective processes which can be naturally incorporated in the healthcare system, to prevent errors from occurring rather than on correcting them. Pharmacists can, and should, take on a big responsibility for this.
Pharmacists working in healthcare settings need additional education research and training. The pharmacy curriculum in Sweden today does not provide newly graduated pharmacists with enough skills to make clinical judgments regarding individual patients’ drug therapy or prepare them for the multi-professional environment within healthcare teams. The clinical pharmacy masters program at Uppsala University is unique in Sweden and provides post-graduate students with much needed clinical experience and in-depth knowledge. As the need for clinical pharmacists is likely to increase substantially in Sweden in the future, the number of students on this program is likely to rise.

Another aspect on education and training is that there should be joint therapeutics teaching sessions, based on problem solving and with a patient focus, with pharmacy and medical students to allow the students to gain a better understanding of the other profession’s knowledge and scope of practice. This would most likely be beneficial for future collaborations.

Today there are several instruments available that can be used to assess the appropriateness of prescribing for elderly people. Neither the ones used in our study (STOPP, START and MAI) nor others have shown links to hard clinical endpoints, such as hospitalisations, in scientific studies. In order to properly evaluate drug therapy and to detect improvements in appropriateness over time a validated tool is required. The tool should be correlated to important clinical outcomes, be user-friendly and cover all aspects of appropriate prescribing. Further research to develop a tool that fills these expectations is warranted.
Förskrivningsfel, över/underdosering, förskrivning av olämpliga läkemedel och dålig följsamhet leder ofta till läkemedelsorskad sjuklighet. Förutom att patienter blir lidande medför denna sjuklighet även stora kostnader för samhället i form av vårdkonsumtion. Särskilt utsatta är äldre, multisjuka personer med en komplex och omfattande läkemedelsanvändning.

Upp till 30% av äldre patienters sjukhusinläggningar tros vara direkt kopplade till läkemedelsrelaterade problem (LRP) och majoriteten av dessa problem hade kunnat förhindras. Vanliga LRP som ger upphov till besök i sjukvården är biverkningar och att patienten inte tagit läkemedlet som ordnat.


Apotekarnas insatser för patienterna i interventionsgruppen bestod av:

- läkemedelsavstämning vid inskrivning och vid utskrivning
- en grundlig läkemedelsgenomgång där identifierade LRP och förslag på lösningar diskuterades med den patientansvarige läkaren på avdelningen
- uppföljning av de genomförda läkemedelsförändringarna
- patientinformation vid utskrivning, samt
- kommunikation med patienternas läkare i primärvården.

Kontrollgruppen fick sedvanlig vård utan apotekarmedverkan.

I det första delarbetet undersöktes behovet av sjukhusbaserad vård under en 12 månader lång uppföljningsperiod för interventions- och kontrollgruppen. Huvudeffektmåttet var den totala frekvensen av sjukhusbesök (besök på akutmottagningen och återinläggningar [totalt -och läkemedelsrelaterade]).
Resultatet blev att interventionsgrupp-patienterna hade 16% färre sjukhusbesök jämfört med kontrollgruppen, 47% färre besök på akutmottagningen och 80% färre läkemedelsrelaterade återinläggningar. Kostnaderna för sjukhusbaserad vård var 1 800 kronor lägre sett per patient i interventionsgruppen jämfört med kontrollgruppen efter att kostnaderna för apotekarnas arbete hade medräknats, detta trots att patienterna var över 80 år och att flertalet var multisjuka. Vid en uppskalning av dessa resultat till samtliga patienter, 80 år eller äldre, som besökte Akademiska sjukhuset under det aktuella året, skulle kostnadsreduktionen bli 9 miljoner SEK.

I det andra delarbetet var kvaliteten på patienternas läkemedelsförskrivning i fokus. Tre internationellt välkända instrument för bedömning av lämpligheten av äldres läkemedelsförskrivning användes; STOPP, START och MAI. STOPP och MAI identifierar olämpliga läkemedelsförskrivningar och START identifierar utebliven läkemedelsförskrivning. Då instrumenten appliceras på en patienters sammanlagda förskrivning erhålls en total poängsumma. Denna ska vara så låg som möjligt.


Det tredje delarbetet var en enkät och intervju-baserad studie riktad till läkare och sjuksköterskor på de två studieavdelningarna samt till de läkare i primärvården vars patienter ingått i interventionsgruppen. Det som undersöktes var det upplevda värdet av det nya multiprofessionella samarbetet med kliniska apotekare, ur läkarnas och sjuksköterskornas perspektiv, samt om de såg några för- och nackdelar med samarbetet för dem själva eller för deras patienter.

Majoriteten av de svarande var nöjda eller mycket nöjda med samarbetet och ville fortsätta med samma eller en liknande modell. Ökad patientsäkerhet och kvalitet på läkemedelsbehandling var de fördelar som nämndes oftast.

Det är välkänt att läkemedelsfel ofta uppstår då patienter byter vårdfорм och information om behandlingen ska överföras mellan olika system. I det sista, fristående, delarbetet undersökt hur vanligt förekommandet var att det blev fel i läkemedelsförskrivningen då patienter med ApoDos skrevs ut från

Under 8 veckor kontrollerades ApoDoslistorna för 290 patienter samma dag som de skulle skrivas ut. Det visade sig att för 72 patienter (25%) innehöll listan minst ett oavsiktligt överföringsfel. En patient hade hela 14 fel på sin lista och det totala antalet fel uppgick till 120. Det vanligaste felet var att läkemedel som borde funnits med saknades, att doserna blivit fel eller att ett läkemedel som blivit borttaget under vårdtiden ändå fanns med. Majoriteten av de identifierade felet (57%) bedömdes vara av mindre klinisk betydelse. Tre av felet bedömdes vara av stor allvarlighetsgrad, dvs om de inte hade åtgärdat hade risken för en ny akutinläggning varit hög. De återstående felen klassificerades till at vara av måttlig klinisk betydelse.

Det faktum att förskrivnings- och överföringsfelen var så vanligt förekommande är oroande och pekar på ett behov av att utveckla och införa säkrare rutiner och processer kring hanteringen av ApoDospatienters läkemedel på sjukhus.

Det är ofta en svår uppgift för läkaren att förskriva läkemedel till äldre personer med flera diagnoser. Behandlingen av en diagnos får inte negativt påverka någon annan diagnos och äldre har dessutom ofta en nedsatt organfunktion till följd av det naturliga åldrandet. I anglosaxiska länder har apotekare sedan drygt 30 år arbetat kliniskt i hälso- och sjukvården med huvudsaklig uppgift att vara ett kunskapsstöd för läkare och sjuksköterskor samt att hjälpa patienterna att använda läkemedlen rätt.

Idag är läkemedelsbehandling ett så omfattande och komplext område att ett multiprofessionellt samarbete är nödvändigt för att åstadkomma en säker, ändamålsenlig och kostnadseffektiv läkemedelsförskrivning. I Sverige finns det multiprofessionella team med apotekare och läkare både inom den öppna- och slutna vården, men än så länge inte i någon stor skala och med stor variation inom landet.
Acknowledgements

This work was performed at the Department of Pharmaceutical Biosciences, Division of Pharmacokinetics and Drug Therapy, Uppsala University. The interventional parts were carried out at the University Hospital of Uppsala.

I would like to thank all of you who have contributed to this thesis. Especially I would like to thank:

The Swedish Academy of Pharmaceutical Sciences for extensive financial support. This support has been crucial in these early days of pharmacy practice research in Sweden.

The County Council of Uppsala for financing the randomised controlled trial. A special thank to Agneta Eklund and Kerstin Hulter-Åsberg whose strong support made it possible.

The hospital pharmacy at the University Hospital of Uppsala and Apoteket Farmaci AB, for giving us the opportunity to perform the RCT and providing us with a stable base to work from.

The wards 30E and former 30C, with all patients and staff, for making it so easy for us to work there and for making us feel so welcome in your team. A special thank to Fiffi, we miss you.

Margareta Hammarlund-Udenaes, my main supervisor. I have always felt so fortunate to work with you; my PhD is just the last of many projects that we have been involved in together! You are so insightful and grounded and I always enjoy our discussions.

Claes Mörlin, my co-supervisor. Where do I begin? When we stormed into your office in 2001? Thank you for all help and support, for all great trips we have been on together, for all your stories and for always cheering me up when I need it. You have no idea of how much I have enjoyed working with you!
Håkan Melhus, my co-supervisor. Your sharp, scientific brain in combination with you being an extremely friendly and helpful person makes you the perfect supervisor. If it is up to me we will be working together on many more projects in the future!

Astrid Forsström, my “super-boss”, who I have been working closely together with for over 10 years. It has been fun! (Vi är inte besatta vi är besjälade…)

Anna Alassaad, my colleague, co-author and friend. I don’t think it is possible to have a better working relationship than we had during the years of the RCT. We completed each-other, were so productive and had so much fun. I look forward to working with you again, you are a wonderful person.

My co-authors: Dan Henrohn, Mariann Hedström, Henrik Toss, Åsa Kettis, Hans Garmo and Maria Bertilsson. It has been a privilege to work with you and I am very grateful for your contribution and help – especially towards the end when things got a bit stressful.!

Our pharmacy students who contributed greatly to Paper IV: Sara Käck and Sandra Creutz.

Olle Christoffersson, for the beautiful, hard-headed old lady on the cover of my thesis.

Antona Wagstaff and Magnus Jansson for help with the thesis, (proof-reading and helping me with lay-out respectively.)

All clinical pharmacists in Uppsala, former and present, that I have been lucky enough to work with: Malin D, Malin K, Anna E, Sara C, Erika W, Lotta G, Anna S, Jonatan D, Ulrika T, Anna A, Catherine DM, Kridden, Frida M, Mia K, Jonna L, Laila S, Maria S, Matts B, Anna-Lena H-L and Celina S. I can’t believe how many we are now.!

All Swedish pharmacists in the informal network of pharmacists working within health-care settings. Thank you for support, advice and great discussions!

All friends that I usually meet at ESCP conferences: Cecilia, Lina, Rannveig, Foppe, Tommy (x2), Anne S, John, Anne L, Frank, Catherine, Louise, Martin, Tobias and many more… Thanks for the inspiration and ideas for all the fun times in your company.
Steve Hudson. I am incredibly sad that you are not here today. Ever since you welcomed me at the MSc course in Scotland 1998 you have been a very significant person in my life as a teacher, role-model and friend. Thank you.

Our friends from our visits in Canada and Northern Ireland: Martin, Kelly, Barb, Janet, Mike, Anita, Peter and more. It has been invaluable for us to learn from you. Thank you for your hospitality and generosity!

Ann-Marie, Niclas, Emma, Jonas, Emma, Fredrik and families—our first close Uppsala friends. Now when the “baby-years” and PhD years are over, I really want to see more of you again!

”Valsättragänget” – Sara, Jocke, Maria, Kaj, Anna, Johan, Jukka, Mia, Fred, Hatixhe and families (and hamsters). The last couple of years would have been much harder and much less fun without you!

University friends: Karin J, Malin, Sara, Karin N, Eva C, and Jenny –your friendship makes me so happy. We are spread out in Sweden now and have families and busy lives but still it feels like in the old days!

All other friends and family-members near and far; in Uppsala, Lidköping, Lotorp, Eskilstuna, Göteborg, Sigtuna, Skåne, Köge, Kalmar, Borås, Stockholm, Hudiksvall, Skellefteå, Edinburgh, Stirling, Falkirk and Denny – I know how lucky I am to have you all in my life!

The fun-loving, supportive great bunch of people that work (and have worked) at the Division of Pharmacokinetics and Drug Therapy – you are too many to mention but I will miss you all very much once my PhD period is over and I clear out my desk. Thank you for 10 fantastic years and for always making me feel like I belong in the group.

My Scottish family; John, Isabel, Christine, Keith, Jan and John. Thank you for being there for us, always, and caring so much about us all.

Jenny, my cousin who is more like my sister, for helping me see things clearer and for your love.

My brother Anders (with family Ute, Albert and Hilda) for all great times together and for also being a close friend.

My mum and dad, Inger and Bengt. Thank you for all your support and love throughout my whole life. You are the best parents anyone could have!

My wonderful daughters Elsa and Maia who make me so happy!
Carrick, you are the love of my life and my best friend – thank you for keeping up with me for the last 13 years, especially the last months…
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Acta Universitatis Upsaliensis

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Editor: The Dean of the Faculty of Pharmacy

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