OPTIMIZING DRUG THERAPY AMONG OLD PEOPLE WITH DEMENTIA

THE ROLE OF CLINICAL PHARMACISTS

MARIA GUSTAFSSON
To my family
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ABSTRACT

BACKGROUND: Drugs are one of the cornerstones in the management of many diseases. In general, drugs are used for diagnosis, prevention, mitigation of symptoms, and, sometimes, to cure disease. However, drug treatment in elderly people, especially those with dementia and cognitive impairments, may involve significant risk of adverse drug events. The aim of this thesis was to identify the extent of potentially inappropriate drug treatment among people with dementia and cognitive impairment and to assess the occurrence and character of drug-related problems that lead to acute hospital admissions. Another aim was to assess the potential impact of a comprehensive medication review conducted by clinical pharmacists as part of a health care team on quality of patients’ drug therapy and drug-related hospital readmission rates.

METHOD: Long-term use of antipsychotic/psychotropic drugs and associated factors were investigated among 344 and 278 people respectively with dementia living in specialized care units. Trends in the prescribing of potentially inappropriate drugs between 2007 and 2013, comprising 2772 and 1902 people, living in nursing homes in the county of Västerbotten, were assessed using six national quality indicators. Data on drug use, function in the activities of daily living, cognitive function and behavioral and psychological symptoms were collected using the Multi-Dimensional Dementia Assessment Scale. Further, an investigation of a separate corresponding population from 2012 was done, where potentially inappropriate drug use was measured before and after a total of 895 medication reviews. Finally, a randomized, controlled trial was carried out among people 65 years or older with dementia or cognitive impairment in internal medicine and orthopedic wards at two hospitals in northern Sweden. The proportion of hospital admissions that were drug-related were estimated, and also whether comprehensive medication reviews conducted by clinical pharmacists as part of a health care team could affect the risk of drug-related hospital readmissions.

RESULTS: Antipsychotic and other psychotropic drugs were frequently prescribed to people with dementia living in specialized care units for prolonged periods. Associations were found between behavioral and psychological symptoms and different psychotropic drugs. The extent of potentially inappropriate drug use declined between 2007 and 2013. In the separate corresponding population from 2012, the frequency of potentially inappropriate drug use was significantly reduced among people who underwent medication reviews. Hospitalizations due to drug-related
problems among old people with dementia or cognitive impairment were prevalent. We found that inclusion of a clinical pharmacist in the health care team significantly reduced the risk of drug-related 30-day and 180-day readmissions. However, in a subset of patients with concomitant heart failure no effect was seen.

CONCLUSION: Among patients with dementia or cognitive impairment long-term treatment with antipsychotic and other psychotropic drugs is common. The results indicate that these drugs are prescribed to treat behavioral and psychological symptoms among cognitively impaired individuals, despite limited evidence of their efficacy and the high risk of adverse effects. Drug-related problems, such as adverse drug reactions, constituted a major cause of hospital admissions. By reducing potentially inappropriate drug use and optimizing overall drug therapy, inclusion of clinical pharmacists in a health care team might improve the quality of patient care and reduce the risk of hospital readmissions among people with dementia.
This thesis is based on the following papers:


In the frame of this thesis the original papers will be referred to by Roman numerals.

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# Abbreviations and Definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>5-HT</td>
<td>5-Hydroxy tryptamine (Serotonin)</td>
</tr>
<tr>
<td>AC</td>
<td>Västerbotten County, Sweden</td>
</tr>
<tr>
<td>AC2007</td>
<td>The survey “Äldre vårdade på institution i Västerbotten år 2007”</td>
</tr>
<tr>
<td>AC2013</td>
<td>The survey “Äldre i Västerbotten vårdade i särskilda boenden 2013”</td>
</tr>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>Ach</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>AchE</td>
<td>Acetylcholine-esterase</td>
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<tr>
<td>ADE</td>
<td>Adverse drug event</td>
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<tr>
<td>ADL</td>
<td>Activities of daily living</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
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<td>AP</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>ASHP</td>
<td>American Society of Health-System Pharmacists</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutical Chemical Classification</td>
</tr>
<tr>
<td>BEHAVE-AD</td>
<td>Behavioral pathology in Alzheimer’s disease</td>
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<tr>
<td>BPSPD</td>
<td>Behavioral and Psychological Symptoms of Dementia</td>
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<tr>
<td>BuChE</td>
<td>Butyrylcholinesterase</td>
</tr>
<tr>
<td>BZ</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>CKD-EPI</td>
<td>Chronic Kidney Disease Epidemiology Collaboration</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>D2</td>
<td>Dopamine subtype 2</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>DRP</td>
<td>Drug-related problem</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EPS</td>
<td>Extrapyramidal symptoms</td>
</tr>
<tr>
<td>ESCP</td>
<td>European Society of Clinical Pharmacy</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>GABA</td>
<td>γ-amino butyric acid</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>H₁</td>
<td>Histamine subtype 1</td>
</tr>
<tr>
<td>MAI</td>
<td>Medication Appropriateness Index</td>
</tr>
<tr>
<td>MDDAS</td>
<td>Multi-Dimensional Dementia Assessment Scale</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NO5A</td>
<td>ATC-code for antipsychotic drugs</td>
</tr>
<tr>
<td>NO5B</td>
<td>ATC-code for anxiolytic drugs</td>
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<tr>
<td>NO5C</td>
<td>ATC-code for hypnotic and sedative drugs</td>
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<tr>
<td>NO6A</td>
<td>ATC-code for antidepressant drugs</td>
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No6D  ATC-code for anti-dementia drugs  
NPI  Neuropsychiatric Inventory  
NPI-NH  Neuropsychiatric Inventory-Nursing Home Edition  
NSAID  Non-Steroidal Anti-Inflammatory Drug  
OTC  Over the Counter  
PCNE  Pharmaceutical Care Network Europe  
PHASE 20  PHArmacotherapeutical Symptom Evaluation, 20 questions  
PRN  Pro Re Nata, as needed  
RCT  Randomized controlled trial  
SNRI  Serotonin and norepinephrine reuptake inhibitors  
SSRI  Selective serotonin reuptake inhibitors  
STOPP  Screening Tool of Older Persons’ Prescriptions  
START  Screening Tool to Alert doctors to Right Treatment  
TCA  Tricyclic antidepressants  
Vd  Volume of distribution  
WHO  World Health Organization

Delarbete 1 till 3 fokuserade på kvaliteten av läkemedelsförskrivningen. Det första delarbetet visade att användningen av antipsykotika hos äldre personer på demensboende var vanligt förekommande, 38% använde minst ett antipsykotiskt preparat vid studiens start. Studien visade även att långtidsanvändningen av antipsykotika var frekvent, 72% behandlades fortfarande med antipsykotika efter sex månader. Delarbete två visade att även andra psykofarmaka som till exempel sömnmedel användes under lång tid. I första och andra delarbetet undersöktES även vilka faktorer som är relaterade till förskrivning av dessa läkemedel till äldre med demenssjukdom. Analyserna visade att flera beteendemässiga och psykiska symptom vid demens har samband med användning av antipsykotika och andra psykofarmaka. Detta indikerar att psykofarmaka används för att behandla sådana symptom hos patienter med demens trots kända risker och begränsat vetenskapligt stöd för läkemedels effektivitet.

olämpliga läkemedel minskade efter läkemedels genomgång med apotekare. Arbetet indikerar att läkemedels genomgångar som involverar kliniska apotekare kan vara en viktig faktor för att minska olämplig läkemedelsanvändning och förbättra läkemedelsbehandlingen bland äldre.


I det femte och sista delarbetet undersökt om läkemedelsrelaterade återinläggningar bland personerna minskade när en klinisk apotekare deltog i vårdsammanhang. Interventionen bestod i att kontrollera att patientens läkemedelslista på sjukhuset var korrekt och komplett, göra en fördjupad läkemedels genomgång, d.v.s. grundligt gå igenom alla patientens läkemedel samt framföra eventuella förslag på förbättringar till ansvarig läkare och diskutera detta i vårdsammanhang. Delarbetet visade att interventionen halverade risken för läkemedelsrelaterade återinläggningar under den 180 dagar långa uppslagstiden. Hos patienter med samtidig hjärtsvikt sågs dock ingen effekt av interventionen. För hela gruppen minskade interventionen även risken för tidiga läkemedelsrelaterade återinläggningar på sjukhus (inom 30 dagar).

Sammantaget visar avhandlingen att problematiken kring äldres läkemedelsbehandling är stor. Insatser behövs från flera håll för att förbättra kvaliteten och säkerheten kring läkemedels användning till äldre personer med demens. Avhandlingen visar att kliniska apotekares deltagande i vårdsammanhang kan bidra till förbättrad läkemedelsbehandling och minskad risk för läkemedelsrelaterade återinläggningar.
INTRODUCTION

Drugs are an essential component of the care of older people. Organic dysfunctions are, however, common among the elderly, and older individuals are in general more susceptible to side effects and drugs often exhibit narrower therapeutic ranges. The number of drugs prescribed per elderly person has increased over the years, and, today, people living in nursing homes are prescribed an average of 8-10 different medications [1]. This extensive drug treatment in old people poses significant risk of drug-drug interactions, medication errors, and adverse drug events (ADEs). Appropriate prescribing among old people is a considerable challenge, and optimizing drug therapy for old people with dementia is even more complex due to for example the generally increased sensitivity to drug effects among this population. Except for prescription rates being high among old people with dementia, the choice of drugs is often inappropriate [2].

Potentially inappropriate drugs have been associated with increased risk of adverse drug events and hospitalization [3-5], and people with dementia show even higher rates of hospitalization [6]. Among old people, up to 30% of admissions have been deemed drug-related [7]. Consequently, there is a strong need to improve older people’s drug treatment in general, and in old people with dementia in specific. Since a high proportion of drug-related admissions are potentially preventable [8], it is reasonable to believe that optimizing drug therapy will impact the quality of patient care among old people. Research is needed to find strategies to improve drug management in this population.

OLD PEOPLE

In 2013, the population in Sweden was 9,644,864, of whom 1,872,207 (19.4%) were aged 65 years or older [9]. Correspondingly, in the county of Västerbotten the population was 261,112 in 2013, of whom 52,577 (20.1%) were aged 65 years or older [9]. The number of individuals living in nursing homes in the county was 3,210, corresponding to 6.1% of the 65+ population. In this thesis, people aged 65 or more are termed old people, according to Swedish practice [10]. One of the main reasons why this age limit is used is that usually, individuals must be 65 years old to be eligible to live in a nursing home in Sweden.
OLD PEOPLE WITH DEMENTIA

Dementia disorders are age-related, progressive, neurodegenerative disorders that affect cognitive, emotional, behavioral, and neurological functions. The Diagnostic and Statistical Manual of Mental Disorders (DSM) provides diagnostic criteria for mental disorders. Unlike the old criteria in DSM IV, central memory dysfunction is no longer a necessary condition in the new DSM-5 criteria. In DSM-5, all six areas are given equal weight in the criteria for dementia. These criteria for dementia (called major neurocognitive disorder in DSM-5) include evidence from the patient history and clinical assessment indicating significant cognitive impairment in at least one of the cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor function and social cognition. The impairment must be acquired and represent a significant decline from a previous level of functioning. These cognitive deficits must interfere with independence in everyday activities. Also, in the case of neurodegenerative dementias such as Alzheimer’s disease, disturbances are of insidious onset, progressive, and based on evidence from the medical history or serial mental-status examinations. Disturbances do not occur exclusively during the course of delirium and are not accounted for by another mental disorder [11, 12].

Approximately 25,000 people are diagnosed with dementia each year in Sweden, and the risk of developing dementia increases with age. Eight percent of all people aged 65 or older and nearly half of people aged 90 years or older suffer from dementia, and the total number of people with dementia in Sweden is estimated to be 160,000, a figure that will rise as the elderly population increases in number [13]. Alzheimer’s disease is the most common of the neurodegenerative diseases and represents approximately 60% of all dementias. The second most common type is vascular dementia, accounting for about 10-25%. Other types are Lewy body dementia, frontotemporal dementia, and Parkinson’s disease with dementia. In addition to this, there are several less common forms such as Creutzfeldt-Jacob disease [11, 14].

Alzheimer’s disease comprises a wide range of symptoms with memory dysfunction as a hallmark. Initially, the patient has difficulty recalling things that happened recently and learning new information. As Alzheimer’s disease progresses, the changes become more marked, and the memory loss worsens to include remote memory. Early in Alzheimer’s disease, the language is relatively preserved, but at later stages many patients become more recognizably aphasic. Symptoms such as getting lost and having
difficulty drawing complex figures (visuospatial impairment) are other problems that occur during the course of Alzheimer’s disease. Further, apraxia and agnosia are disturbances that occur as the disease progresses. Apraxia may impair earlier obvious activities and practical tasks, and agnosia includes features such as failing to recognize family members [14]. Behavioral and psychological symptoms of dementia (BPSD) occur frequently in Alzheimer’s disease [14], which is of particular relevance for drug treatment among this patient group.

**BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS AMONG PEOPLE WITH DEMENTIA**

BPSD represent a group of non-cognitive symptoms and behaviors that often occur in people with dementia [15]. Prevalence rates up to 90% have been reported [16, 17]. The symptoms, including hallucinations, depression, agitation, aggression, and wandering can be difficult for relatives and care staff to manage, and the patient’s quality of life might be severely affected [18]. It has been shown that the presence of BPSD is associated with faster cognitive and functional decline [19], and symptoms such as disruptive behavior (e.g. agitation and wandering), hallucinations, and aggression are associated with increased risk of institutionalization [19-21]. The term BPSD is designated by the International Psychogeriatric Association [22], but the term “neuropsychiatric symptoms” is also used, particularly in the United States [17]. Rating scales for BPSD are for example the BEHAVE-AD (Behavioral pathology in Alzheimer's disease) scale [23] and the NPI (Neuropsychiatric Inventory) scale [24].

Today, non-pharmacological approaches are considered most appropriate for reducing BPSD in patients with dementia, and are recommended before pharmacological treatment [25, 26]. It is also important to review current pharmacological treatment and consider discontinuation of drugs with potential negative impacts on the central nervous system, including cognitive function [26]. When it comes to pharmacological treatment of BPSD, selective serotonin reuptake inhibitors (SSRIs), memantine, and cholinesterase inhibitors have shown positive effects on BPSD in various studies [27-38]. Also antipsychotic drugs have shown positive effects and are considered second line treatments for severe aggression and psychotic symptoms [26].
SPECIALIZED CARE UNITS AND NURSING HOMES

In this thesis, the term nursing home is used synonymously with the term geriatric care unit used in paper III. The term nursing home corresponds to the Swedish term särskilt boende, a collective name for the Swedish terms äldreboende, sjukhem, omsorgsboende, demensboende, and gruppboende, which are used differently in different municipalities. The term nursing home includes specialized care units for people with dementia, a term used in papers I and II. These specialized care units are designed to provide care for about six to twelve persons with dementia in homelike environments.

DRUG USE AMONG OLD PEOPLE WITH AND WITHOUT DEMENTIA

Old people

Age-associated physiological changes among old people are important to consider when prescribing a drug, since these changes lead to an increased vulnerability to adverse drug reactions (ADRs) and published data are sparse as elderly are often excluded from clinical studies [39]. The age-related changes are progressive and effects increase gradually with advancing age. The effects on drug response can be classified according to age-related changes in pharmacokinetics and pharmacodynamics [40].

Pharmacokinetic changes concern drug absorption, distribution, metabolism, and elimination, of which the most important is the decrease in elimination rate due to gradual decline in renal function. The glomerular filtration rate (GFR), a measure of renal function, decreases by approximately 8 mL/min per decade of life after the age of 40, or about 1% per year [41]. As renal drug elimination declines, the risk of drug accumulation increases, which is especially important for drugs with unchanged renal excretion or drugs with active metabolites, such as morphine and glibenclamide. Of special concern are drugs with narrow therapeutic indices, such as digoxin and lithium. Age-related changes in renal function can be evaluated by calculating creatinine clearance based on serum creatinine values. The creatinine clearance is an estimate of GFR, and can for example be calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, alternatively by the Cockcroft Gault equation.
Age-related reduction in hepatic clearance and increased distribution of lipid soluble drugs are also seen [42]. Age-related decrease in liver metabolism is due to decreased hepatic mass, blood flow, and altered enzymatic capacity [42]. Drugs such as nitrates, barbiturates, and propranolol may have reduced hepatic metabolism in older adults. Changed body composition during aging can affect the distribution of drugs. The volume of distribution (Vd) of lipophilic drugs such as diazepam may be increased, leading to accumulation during continuous use [42].

Age-related pharmacodynamic changes involve altered sensitivity to several classes of drugs, although the effect varies with the drug studied and generalizations are difficult [40]. Homeostatic regulation mechanisms decline with age and the therapeutic width of many drugs is reduced. This makes older people more sensitive to drug interactions, including drug-induced orthostatism. The central nervous system (CNS) in old people is also particularly sensitive when it comes to drug effects. Age-related reduction in dopamine and acetylcholine content predisposes individuals for increased risk of adverse drug reactions when exposed to antidopaminergic and anticholinergic drugs [43]. In addition, an increased sensitivity to benzodiazepines is observed, due to changes in the GABA (γ-aminobutyric acid) - benzodiazepine receptor complex [43].

Old people with dementia

In people with dementia more pronounced changes in endogenous neurotransmitter concentrations such as acetylcholine and dopamine in the CNS are observed and this makes this group of people extremely sensitive to adverse drug reactions [44]. Alzheimer’s disease has in addition been associated with serotonergic deficit [45]. Moreover, alterations in the blood-brain barrier have been reported in people with Alzheimer’s disease, potentially impacting the ability of drugs to reach the CNS [46].

There are additional specific problems challenging drug treatment among people with dementia. Weight loss is very common in patients suffering from early stage dementia [47], and malnutrition may alter drug-metabolizing enzyme activity [48]. Further, even minor cognitive decline may have major negative impact on drug compliance among otherwise healthy elderly [49]. Problems with understanding instructions and remembering doses may lead to intake of excessively high or low doses, and this increases the risks of adverse drug effects. In combination with executive dysfunction, this might also lead to difficulties identifying, recognizing, and reporting adverse drug events.
ANTI-DEMENTIA AND PSYCHOTROPIC DRUGS

Anti-dementia drugs

Anti-dementia drugs are used in persons with Alzheimer’s disease, Lewy-body dementia, and dementia in Parkinson’s disease. Drugs in development aim to inhibit the mechanisms that lead to formation of neurofibrillary tangles and amyloid plaques, the main processes thought to be responsible for degeneration in Alzheimer’s disease. Today, there is no established medical treatment directed toward the disease mechanism of Alzheimer’s disease and other neurodegenerative disorders. Instead, the therapeutic actions aim at improving symptoms and reducing negative effects. There are currently two treatment strategies with drugs regulating levels of acetylcholine and glutamate; cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists [50].

The first cholinesterase inhibitor on the market was tacrine (Cognex), approved in 1993 by the Food and Drug Administration (FDA) but later withdrawn from the market [50]. There are currently three cholinesterase inhibitors approved for the treatment of mild to moderate dementia in Alzheimer’s disease, donepezil, galantamine, and rivastigmine. These drugs differ somewhat in their pharmacological action; donepezil and galantamine inhibits acetylcholine-esterase (AChE) selectively. Rivastigmine inhibits AChE and butyrylcholinesterase (BuChE) [51]. Use of cholinesterase inhibitors has demonstrated improvement in cognitive function, although the magnitude of effect has been debated [52, 53]. The three cholinesterase inhibitors seem to have similar efficacy [52]. Nausea, vomiting, insomnia, and diarrhea are dose-related adverse effects related to excess cholinergic stimulation [54]. Cardiac adverse effects have also been associated with these drugs, a main reason why they should be used with caution among people with a history of cardiovascular disease or who are co-medicated with negative chronotropic drugs [55].

Memantine has been approved since 2002 for treatment of moderate-to-severe Alzheimer’s disease. Memantine acts as a non-competitive antagonist of NMDA type glutamate receptors and reduces the release of glutamate in the CNS. Glutamate can cause excitotoxic reactions and cell death in Alzheimer’s disease and other neurodegenerative disorders [11, 42, 56]. Clinical benefit of memantine in reducing the symptoms of Alzheimer’s disease has been found, however, compared to cholinesterase inhibitors, the clinical evidence of effectiveness is weak [53]. Agitation, falls, and dizziness have been reported as adverse reactions to memantine [57].
Anti-dementia drugs in BPSD

Studies investigating donepezil, rivastigmine, and galantamine suggest some benefits in reducing BPSD [33, 58, 59]. However, the results are inconsistent, and one study found no benefits of donepezil over placebo [60]. In a systematic review performed in 2015 including fifteen randomized placebo-controlled trials of cholinesterase inhibitors for neuropsychiatric symptoms, small but significant improvement was found [36].

There is growing evidence that memantine reduces behavioral disturbances such as agitation, aggression, and irritability [37, 38], but the effects are small according to one review [61] and essentially non-existent according to another [36]. Today, memantine is recommended for treatment of agitation and aggression among persons with dementia [26].

Antipsychotic drugs

Antipsychotic drugs are a heterogenic group of medications that block central dopamine receptors, particularly the D2-receptor subtype [42]. The mechanisms of action are not completely understood, but interaction with 5-HT2A and additional receptors are involved, giving rise to different side effect profiles among antipsychotics (table 1 and 2) [42]. Antipsychotics have traditionally been divided into two groups, first-generation (also called typical or conventional antipsychotics) and second-generation antipsychotic drugs (also called atypical antipsychotics). First generation antipsychotic drugs can be further divided into low potency and high potency agents, based on their relative potency to block dopamine receptors [42]. Levomepromazine is, as chlorpromazine, phenothiazines belonging to low potency antipsychotics, and have similar profiles [62]. Low potency antipsychotics also affect histamine receptors and muscarinic receptors, which leads to sedation and anticholinergic side effects seen amongst these agents. High potency agents, such as haloperidol and zuclopenthixol, have extrapyramidal side effects (EPS) [42]. Of special interest among first generation antipsychotics is haloperidol, as it is a high potency agent that accounts for a large share of antipsychotic drug use in the studies of the present thesis. Normal motor function requires a balance between the cholinergic, dopaminergic, and GABAergic activity. Acute EPS side effects include parkinsonism, akinesia, acute dystonia, and akathisia. These side effects are most commonly observed with high potency agents, due to lack of anticholinergic effect among these drugs [62]. Other adverse effects associated with first generation antipsychotics are hyperprolactinemia and hormonal disruption [42].
Risperidone was the most common second generation antipsychotic drug encountered in our studies. Second generation antipsychotic drugs are generally associated with lower risk of EPS compared to first generation antipsychotics. Risperidone is associated with the highest risk of EPS in this group, and clozapine and quetiapine with the lowest risk. Different theories regarding mechanism for the lower risk of second generation antipsychotics have been suggested, including the combined blockade of 5HT2 and D2 receptors [42] or faster dissociation from D2 receptors among the second generation antipsychotic drugs [63]. Other adverse effects associated with second-generation antipsychotic drugs are metabolic side effects. However, whether this is clinically relevant for old people with dementia is debated [63].

Both first and second-generation antipsychotic drugs have been associated with increased risk of cerebrovascular events, venous thromboembolism, and higher mortality among people with dementia [63-67].

### Table 1. Relative receptor-binding affinities of antipsychotic agents for selected antipsychotics [42]

<table>
<thead>
<tr>
<th>Receptor</th>
<th>D2</th>
<th>5-HT2</th>
<th>α1</th>
<th>M1</th>
<th>H1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td><strong>Second generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Clozapine</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

D2, dopamine subtype 2; 5-HT2, serotonin subtype 2; α1, alpha-1 adrenergic; M1, muscarinic (cholinergic) subtype 1; H1, histamine subtype 1

+++ high affinity, ++ moderate affinity, + minimal affinity, - none affinity
### Table 2. Relative incidence of antipsychotic drug adverse effects for selected antipsychotics [42]

<table>
<thead>
<tr>
<th></th>
<th>Sedation</th>
<th>EPS</th>
<th>ACh</th>
<th>Orthostasis</th>
<th>Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>++++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Second generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Clozapine</td>
<td>++++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++++ c</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++ a</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++ + b</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+++ + b</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>++ +</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

a With dosages < 20 mg/d  
b Very low at dosages < 8 mg/d  
c Dose related

ACh, anticholinergic; EPS, extrapyramidal symptoms

+++++, very high effect; ++++, high effect; +++, moderate effect; ++, low effect; +, very low effect

### Antipsychotic drugs in BPSD

Traditionally, first generation antipsychotic drugs have been used to treat various non-specific symptoms of dementia such as agitation, anxiety, wandering, and shouting. Although these first generation antipsychotics have some efficacy reducing behavioral symptoms [68], they may also worsen cognitive and motor functions. For a long time, haloperidol was considered the preferable antipsychotic for people with dementia, due to low anticholinergic activity compared to other first generation antipsychotics. Haloperidol has some efficacy against behavioral problems in higher doses, but its use is limited by the high incidence of extrapyramidal side effects, even at relatively low doses of 1 to 5 mg [26, 69]. A systematic review of antipsychotics concluded that there was no clear evidence of benefit for the use of first generation antipsychotics among people with dementia [70], and occurrence of EPS and other adverse effects make first generation antipsychotics less tolerable than second generation antipsychotics [71].

The first second generation antipsychotic drug was clozapine, introduced in clinical practice in the 70s. Possibly due to strong therapeutic traditions, the switch to second-generation antipsychotic drugs was delayed and this may explain why so many old people with dementia still were treated with
haloperidol in the 2000s. Risperidol and olanzapine seem to have the best evidence for treating neuropsychiatric symptoms of dementia, although its efficacy is, at most, modest [70, 72-74]. However, according to the CATIE-AD trial, these drugs are poorly tolerated due to sedation, confusion, and EPS [75]. Today, the only antipsychotic drug approved for treatment of BPSD in Sweden is risperidol, and its indication is limited to persons with psychotic symptoms and aggressive behavior that causes suffering or potential danger for the person or others [26]. Taken together, even if second generation antipsychotics are preferable to first generation antipsychotics, the small effect size [70, 76], poor tolerability [76], and association with increased mortality [66] indicate that no antipsychotics should be used routinely. Guidelines agree that the use of antipsychotics in the treatment of BPSD in this patient group should be done carefully [77].

**Haloperidol equivalents**

Antipsychotic doses can be compared using haloperidol equivalents, i.e. converting the effective dose of a specific antipsychotic drug into the dose of haloperidol producing an equivalent effect. In the first study, we used haloperidol equivalents to compare doses of antipsychotics at baseline with doses after six months. We used a Swedish consensus document to determine haloperidol equivalents (table 3) [78].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Haloperidol equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>1 mg</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>5 mg</td>
</tr>
<tr>
<td>Dixyrazine</td>
<td>30 mg</td>
</tr>
<tr>
<td>Melperone</td>
<td>40 mg</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>4 mg</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1 mg</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3 mg</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>40 mg</td>
</tr>
<tr>
<td>Clozapine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>150 mg</td>
</tr>
</tbody>
</table>
Anxiolytic, hypnotic and sedative drugs

In the anxiolytic, hypnotic, and sedative drug group, the mechanisms of action differ. Most anxiolytics and hypnotics, e.g. clomethiazol and benzodiazepines, increase the effects of GABA through GABA transmission. Benzodiazepines potentiate GABA by binding to sites on the central GABA<sub>A</sub> receptor. There are four GABA<sub>A</sub> receptor subtypes, and currently available benzodiazepines are not selective for any of these. Binding of benzodiazepines to the four receptor subtypes gives anxiolytic, anticonvulsant, muscle relaxant, and sedative-hypnotic effects [42]. Benzodiazepines can be classified as short to intermediate acting and long acting based on their elimination half-life and their metabolism to active or inactive compounds (table 4). The use of benzodiazepines with long half-lives and active metabolites can cause drug accumulation and prolonged clinical effects, which may be detrimental for old people. Adverse effects associated with benzodiazepines are increased agitation, confusion, risk of falling and fractures [79, 80], impaired cognition [81, 82], and sedation [42]. The association between benzodiazepines and falls might be the consequence of psychomotor effects such as problems with balance, coordination, and muscle relaxation in combination with sedation [42].

**Table 4. Pharmacokinetic comparison of benzodiazepines and Z-hypnotics acting at benzodiazepine receptors [42, 83, 84]**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination Half-Life (hours)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Active metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short to intermediate half-life</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazepam</td>
<td>5-14</td>
<td>None</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>12-15</td>
<td>Insignificant</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10-20</td>
<td>None</td>
</tr>
<tr>
<td><strong>Long half-life&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>16-35</td>
<td>Yes</td>
</tr>
<tr>
<td>Diazepam</td>
<td>20-50</td>
<td>Yes</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>24-29</td>
<td>None</td>
</tr>
<tr>
<td><strong>Z-hypnotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolpidem</td>
<td>2.5</td>
<td>None</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>3.5-6.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>1.1</td>
<td>None</td>
</tr>
</tbody>
</table>

<sup>a</sup> Parent drug  <sup>b</sup> Classification according to the National Board of Health and Welfare
Other hypnotics and sedatives that act through the benzodiazepines binding sites associated with $\text{GABA}_A$ receptors are the new generation hypnotic drugs, zolpidem, zopiclone and zaleplon (Z-hypnotics). These drugs show some differences from benzodiazepines in pharmacological effects and mechanisms of action and have varying degrees of selectivity for the $\text{GABA}_A$ receptors. This selectivity entails that the hypnotic effect remains, but theoretically, there are no significant anxiolytic, anticonvulsant or muscle relaxant effects among Z-hypnotics [42, 85].

Propiomazine is a phenothiazine derivative traditionally used in Sweden for treatment of insomnia. The substance is a sedating antihistamine, but it also has anticholinergic effects [86]. Propiomazine has a half-life of nine to 13 hours [87] and is not recommended for use in old people due to residual daytime sedation and extrapyramidal symptoms, including restless legs [1]. Other sedating antihistamines that are not recommended for use among old people are hydroxyzine, alimemazine, and promethazine due to the anticholinergic effects [1].

Clomethiazole increases the transmission of GABA in the CNS, but the exact mechanism of action is not known. Clomethiazole has sedative, muscle relaxant, and anticonvulsant properties [88]. Reported side effects are hypotension, sleep apnea, and nasal irritation [83].

**Anxiolytic, hypnotic and sedative drugs in BPSD**

Benzodiazepines have limited value treating non-cognitive symptoms in dementia and are not recommended. However, benzodiazepines may be used (short-term) for acute agitation or agitation based on anxiety [77]. Clomethiazole may be used short-term when urgent sedation is needed and if the patient is adequately monitored [26].
Antidepressant drugs

Most antidepressant drugs act by interfering with the metabolism of monoamine neurotransmitters and their receptors, particularly norepinephrine and serotonin. In the studies in this thesis, SSRIs and α2-antagonists accounted for the largest share of antidepressant prescriptions, but serotonin and norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) were also used by the study population. Table 5 lists adverse effects for selected antidepressants especially important to consider when treating old people. Of special concern among old people with dementia is the use of TCAs. Many of the substances in this group exert effects on muscarinic acetylcholine receptors and histamine receptors, which are responsible for the occurrence of important side effects [56]. In particular the anticholinergic side effects like dry mouth, constipation and confusion are important to consider. In addition, increased risk of orthostatism [42] and seizures [89] make TCAs inappropriate for old people. Most SSRIs and SNRIs do not exert anticholinergic effects. However, they are associated with other side effects such as nausea, diarrhea, and sleep disturbances [42]. SSRIs are also associated with increased risk of hyponatremia [90] and gastrointestinal (GI) hemorrhage, particularly when combined with warfarin [91] or low-dose aspirin [92]. The combination between SSRI and low-dose aspirin was shown to increase risk for upper GI bleeding 5.2-fold [93]. SNRIs, particularly venlafaxine, are associated with an increased risk of adverse effects related to norepinephrine such as tachycardia and hypertension [42]. Mirtazapine and mianserine are α2-antagonists. The most common adverse effects associated with this group are weight gain and sedation [42]. However, for old people with diminished appetite and insomnia, these could be positive effects.

Antidepressant drugs in BPSD

Studies have shown correlation between aggression and a generally decreased serotonergic neurotransmission among people with dementia [94-96]. This might explain the effect of SSRIs on certain behavioral problems [97]. In one study, the addition of citalopram in patients with probable Alzheimer’s disease who were receiving psychosocial intervention, agitation and caregiver distress was significant reduced [28]. A review from 2011 showed mixed results, but two studies investigating the SSRIs sertraline and citalopram showed a reduction in agitation compared to placebo [35]. In Swedish guidelines, SSRIs are recommended as first line treatment for irritability, agitation, and anxiety [26].
## Table 5. Adverse Effects of Selected Antidepressants [42]

<table>
<thead>
<tr>
<th>Medication</th>
<th>Sedation</th>
<th>Agitation/Insomnia</th>
<th>Anti-cholinergic Effects</th>
<th>Orthostasis</th>
<th>GI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective Serotonin Reuptake Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>+</td>
<td>+++</td>
<td>o/+</td>
<td>o/+</td>
<td>+++</td>
</tr>
<tr>
<td>Sertraline</td>
<td>+</td>
<td>+++</td>
<td>o/+</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>+++</td>
<td>+</td>
<td>o/+</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Citalopram</td>
<td>++</td>
<td>+</td>
<td>o/+</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>+</td>
<td>++</td>
<td>o/+</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Serotonin Norepinephrine Reuptake Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>++</td>
<td>+</td>
<td>o/+</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>++</td>
<td>+</td>
<td>o/+</td>
<td>0</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Norepinephrine Reuptake Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>o</td>
<td>+++</td>
<td>+</td>
<td>o</td>
<td>+</td>
</tr>
<tr>
<td><strong>Tricyclic Antidepressants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>o/+</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>++++</td>
<td>o/+</td>
<td>+++</td>
<td>++++</td>
<td>o/+</td>
</tr>
<tr>
<td><strong>Presynaptic α2-antagonists</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>++++</td>
<td>0</td>
<td>++/+</td>
<td>o/+</td>
<td>+</td>
</tr>
</tbody>
</table>

GI, Nausea/Diarrhea
++++, high ++++, moderate ++, low +, very low, 0, negligible

*According to [98]*
The terms potentially inappropriate medications or potentially inappropriate drugs refer to drugs in which the risks outweigh the benefit [99]. Among the drug classes studied in this thesis, antipsychotic drugs, long-acting benzodiazepines, and propiomazine are classified as potentially inappropriate, since use of these drugs in old people is associated with high risk of severe adverse reactions (discussed above) [1]. The other drug classes and drugs designated as inappropriate according to the quality indicators used in this thesis, are anticholinergic drugs, non-steroidal anti-inflammatory drugs (NSAIDs), and tramadol.

**Anticholinergic drugs**

Anticholinergic drugs are a heterogeneous group. Some drugs are used therapeutically to block muscarinic receptors, used for the treatment of disorders such as urinary incontinence and Parkinson’s disease. Other classes of drugs have anticholinergic effects not necessarily important for their therapeutic effects, such as antipsychotic drugs, antihistamines, or antidepressants. Anticholinergic drugs increase the risk of both peripheral and central side effects. Typical peripheral symptoms include dry mouth, constipation, urinary retention, and decreased sweating. Central side effects due to anticholinergic drugs include impaired concentration, confusion, and memory impairment [100]. In older people with dementia, these adverse effects may be more pronounced due to the cholinergic deficit [101]. Anticholinergic drugs may also antagonize the potential benefits of cholinesterase inhibitors [102].

**Non steroidal anti-inflammatory drugs**

NSAIDs are a group of drugs that exert analgesic and anti-inflammatory effects through inhibition of the enzyme cyclooxygenase. Old people are at high risk of developing side effects of NSAIDs, such as gastrointestinal bleeding. NSAIDs also increase the risk of nephrotoxicity, hypertension and heart failure [103-105].
Tramadol

Tramadol is a centrally acting opioid analgesic. Tramadol and its active metabolite bind to µ-opiate receptors in the CNS causing inhibition of ascending pain pathways. The substance has also been shown to inhibit the uptake of norepinephrine and serotonin, neurotransmitters involved in the descending inhibitory pain pathway [84]. Tramadol should be avoided in old people due to side effects such as nausea and confusion [1]. Other adverse drug reactions seen among old people are constipation, fatigue, weakness and dyspepsia [84]. Due to increased risk of serotonin syndrome, tramadol should not be combined with other drugs that increase serotonin levels [1].

Instruments to assess appropriateness

To improve a patient’s drug therapy, tools to assess the appropriateness of prescriptions have been developed. These tools can be divided into implicit or explicit criteria. Implicit criteria include measures based on clinical assessment of the individual patient. Explicit criteria are criterion-based [106]. A recent review summarizes 46 existing tools available for assessment of inappropriate prescribing [107]. Explicit criteria do not take the individual into account, i.e. the drugs are considered inappropriate regardless of effects on the individual patient. The tools are mostly drug-oriented and/or disease-oriented [106]. The advantage of explicit criteria is that these can be used with little or no clinical judgment. However, explicit criteria require continuous updating. They may also be country-specific and may need to be adjusted to country-specific therapeutic traditions [107]. A European list of potentially inappropriate drugs has recently been developed [108].

Beers’ criterion is one of the most commonly used and studied criterion-based instruments for the evaluation of inappropriate medication among old people [109-112]. Examples of other criterion-based instruments are the Screening Tool of Older Persons’ Prescriptions/Screening Tool to Alert doctors to Right Treatment (STOPP/START) [113-116] and the quality indicators developed by the Swedish National Board of Health and Welfare, used in this thesis [1]. The quality indicators include a list of drugs to be avoided, as well as inappropriate drug dosage and combinations. They also include diagnosis-specific indicators.

Implicit tools are patient-specific, and take the individual patient’s entire medication treatment including the patient’s experience of the drug therapy
into consideration, which makes these approaches time consuming [106, 117]. The Medication Appropriateness Index (MAI) is based on implicit criteria [118, 119], which focus on the individual patient and requires more information about the patient, since several aspects are taken account for including indication, effectiveness, dosage, correct directions, practical directions, drug-drug interactions, drug-disease interactions, duplication, duration, and expense [119].

**Use of inappropriate drugs**

Extensive prescription of potentially inappropriate and psychotropic drugs among old people is a well-known and worldwide problem, and numerous studies have documented high prevalence [2, 77, 120, 121].

The use of inappropriate and psychotropic drugs appears to have declined during recent years. One study demonstrated a decrease of antipsychotic drugs from 31.3% in 2000 to 20.4% in 2012 [122]. This is in line with another study investigating drug use from 2006 to 2013 [123]. The use of long-acting benzodiazepines, propiomazine and tramadol decreased significantly while the use of drugs with anticholinergic effects decreased only marginally.

The use of inappropriate and psychotropic drugs has been associated with various behavioral and psychological symptoms in a number of studies [121, 124, 125]. Other factors associated with inappropriate and psychotropic drugs are staff distress at patient’s agitation [126] and severity of the caregiver’s burden [127].

**MEDICATION ERRORS, ADVERSE DRUG EVENTS AND ADVERSE DRUG REACTIONS**

Medication errors have been defined as “any error in the process of prescribing, dispensing, or administering a drug, whether there are any adverse consequences or not” [128]. The definition of a medication error is broad, and these errors occur considerably more frequently than ADEs and ADRs. One study indicated that only 0.9% of all medication errors resulted in an ADE [129]. An ADE is defined by Leape as “an injury related to the use of a drug, although that causality of this relationship may not be proven” [128], similar to the definition by the World Health Organization (WHO), “any untoward medical occurrence that may present during treatment with a
medicine but which does not necessarily have a causal relationship with this treatment” [130]. ADRs are defined by the WHO as “a response to a medicine which is noxious and unintended, and which occurs at doses normally used in man” [130]. Consequently, ADEs describe a broader scenario compared to ADRs and include events caused by suboptimal use of drugs, such as inappropriate prescribing or poor compliance [131]. The relationship between medication error, ADE and ADR is shown in figure 1.

Fig 1. Relationship between medication error, adverse drug event and adverse drug reaction. The size of the circles is intended to indicate a measure of prevalence and the definitions of “adverse drug reaction”, “adverse drug event” and “medication error” do not completely overlap.
A drug-related problem (DRP) has been defined by Strand et al as “an undesirable patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome” [132]. This definition, however, does not include potential DRPs. In the randomized clinical trial (RCT) included in this thesis, both actual and potential DRPs were considered as DRPs. However, only clinically relevant drug-related problems (potential and actual) were explicitly mentioned to the physicians and discussed in ward rounds. The relationships between DRPs and the former mentioned medication errors, ADEs and ADRs - according to the definition used in the present thesis - are illustrated in figure 2. Strand classified DRPs into eight categories, but several other research groups and organizations have developed their own systems how to classify subgroups of DRPs [133]. According to van Mil, few of these criteria have been validated, and none of these classification systems met the authors' standards of an optimal system [133]. The classification system used during the RCT in Umeå/Skellefteå was adopted from Cipolle et al [134]. The seven subgroups applied by Cipolle et al for classification of DRPs are: 1. unnecessary drug therapy, 2. needs additional drug therapy, 3. ineffective drug, 4. dosage too low, 5. ADR, 6. dosage too high, and 7. noncompliance. In paper IV, an extra category, interactions, was added. In paper V, the subgroup ADR also included interactions and transmission errors. In papers IV and V the group ineffective drugs also included use of inappropriate drugs.
Fig 2. The relationship between drug-related problems and medication error, adverse drug event and adverse drug reaction.

**DRUG-RELATED HOSPITALIZATIONS**

Problems associated with drug treatment such as medication errors and adverse drug events are common, particularly among old people. Adverse drug events can result in drug-related morbidity and mortality, and are the cause of a large proportion of hospital admissions among old people [7, 8, 131, 135, 136]. Studies show that from 7% up to approximately 30% of hospital admissions are directly related to drug treatment problems. A high proportion of drug-related hospital admissions have been assessed as preventable [7, 8].

According to one review, reported prevalence's of hospital admissions caused by drug-related problems ranged between 0.1% and 56%, depending on study characteristics [137]. These considerable variations in prevalence
exemplify the caveats when comparing results between different studies. In this particular review, differences were due to the different study populations, definitions of DRPs, methods of data collection, and geographic area. Higher prevalence was found in studies examining ADEs than in studies examining only ADRs. Also, higher prevalences were found among older people compared to children [137]. Earlier studies found polypharmacy to be associated with higher probability of adverse drug reactions leading to hospitalization [7, 138] and potentially inappropriate drugs have been associated with increased risk of admission to hospital [3, 5]. Women appear to be more associated with adverse drug reactions leading to hospitalization, compared to men [139].

Adverse drug reactions caused by cardiovascular drugs were responsible for 36% of drug-related admissions in one study [140]. Diuretic drugs seem to be one of the most involved drugs in this class, causing syncope, hypotension, electrolyte disturbances, and dehydration. In addition, drugs that are active in the CNS accounted for a large share in different studies, 3.6-20.5% according to one review [131]. Confusion and falls are examples of clinical manifestations that may cause hospitalization due to this drug class. Analgesic drugs and endocrine and hematological agents are other drug classes frequently involved in drug-related hospitalizations according to the review [131].
CLINICAL PHARMACY

Pharmacists’ roles have traditionally been to compound, produce, and dispense pharmaceutics. Over time, these roles have drifted away from the products towards the patient receiving the drugs, to ensure the best possible drug therapy and patient safety with collaborative care and patient interaction in focus [141-143]. Clinical pharmacy is defined as “a health specialty, which describes the activities and services of the clinical pharmacist to develop and promote the rational and appropriate use of medical products and devices” [143]. According to the same organization, the European Society of Clinical Pharmacy (ESCP), clinical pharmacy is not limited to an activity implemented in a hospital setting, but also includes all the services performed by pharmacists where medicines are prescribed and used, for example in nursing homes [143]. Medication reconciliation, medication reviews and education are common services in clinical pharmacy, but clinical pharmacy service is a wide concept and not limited to these activities [141, 144].

Recent systematic reviews suggest that clinical pharmacist interventions can improve patient outcomes in both inpatient and outpatient care settings [145-148], and in many countries, for example in the US, the clinical pharmacist’s role has been established for several years [144]. In Sweden, studies concerning the impact of clinical pharmacy services on clinical outcome parameters have been few so far, and this has probably contributed to slower progress. Clinical pharmacy services are not routinely implemented in hospital and community settings, and the debate over who is best suited to perform clinical pharmacy services is still going on. However, during recent years, the number of clinical pharmacists working as part of health care teams in both inpatient and outpatient care has increased also in Sweden.

In principle, there are no formal requirements for a pharmacist to work with clinical pharmacy in Sweden except for a Bachelor or Master of Science degree in Pharmacy. However, for improved patient safety and benefit, enhanced training in clinical pharmacy skills is desirable and will help meet the demands of complex and advanced hospital care. One way to achieve this is to enroll in the Master Program in Clinical Pharmacy, a postgraduate education opportunity offered by Uppsala University. In addition, a certification model in clinical pharmacy has been developed in Sweden, recently. The certification is a guarantee of quality for extensive knowledge and experience in the field of patient-oriented clinical pharmacy.
In Västerbotten County Council, clinical pharmacy services started in 2002 as a collaboration project between the County Council and the hospital pharmacy located at the Umeå University Hospital. The project lasted for five months and the positive response from the health care team led to the continuation and later progression of the service. Today, six clinical pharmacists are active in inpatient and outpatient care in Västerbotten.

Medication reconciliation/medication reviews

According to American Society of Health-System Pharmacists (ASHP), the aims and objectives of medication reconciliation are to “obtain and maintain accurate and complete medication information for a patient and use the information within and across the continuum of care to ensure safe and effective medication use” [149]. Medication reconciliation is defined as “the process of comparing the medications a patient is taking (and should be taking) with newly ordered medications” in order to identify and resolve discrepancies or potential problems [149].

Discrepancies in the medication list might occur when a patient is moved between different care units, when new drugs are ordered, or when the transfer of the patient’s existing drug list is done. Incorrect medication administration records at the hospital may lead to ADEs [150], and if errors are not discovered, incorrect medication lists may follow the patient when moving between wards, or when patients leave the hospital, potentially rendering great risks for the patients.

To reduce the problems, the Swedish National Board of Health and Welfare has since 2012 required health care providers to conduct medication reconciliation for all patients aged 75 years and older and with five or more medications, at every transition between different care setting, or at least once a year. A brief medication review is also required for these patients.

A medication review is a systematic evaluation of an individual patient’s medicine treatment. According to the Pharmaceutical Care Network Europe (PCNE), a medication review is "an evaluation of a patient’s medicines with the aim of optimizing the outcomes of medicine therapy. This entails identifying the risks, detecting medication-related problems and suggesting solutions” [151]. Drug interactions, unusual dosages, adherence issues, drug-food interactions, effectiveness issues, side effects, problems with over-the-counter drugs (OTC), indication without a drug and drugs without indication, and dosage issues are revealed in a medication review [151]. When comparing the results of research studies on medication reviews, the
fact that medication reviews are performed in different settings, by different health care personnel, and with access to various clinical/patient information must be taken into consideration.
AIM

The overall aim of this thesis was to identify drug-related problems that might contribute to non-optimized drug treatment among old people with dementia and cognitive impairment and to assess whether interventions by clinical pharmacists might contribute to more optimized drug treatment for this group of people. In papers I-IV, the aim was to identify the extent of psychotropic and other inappropriate drugs among people with dementia living in nursing homes and assess the proportion of hospital admissions that were drug-related. In papers III and V the aim was to investigate whether interventions (medication reviews, medication reconciliation, and participation in ward rounds) performed by a clinical pharmacist as part of a ward team could reduce inappropriate drug use and drug-related readmissions.

SPECIFIC AIMS

I - to describe the prevalence, associated factors, and long-term use of antipsychotic drugs among people with dementia living in specialized care units.

II - to describe the prevalence, associated factors, and long-term use of psychotropic drugs among people with dementia living in specialized care units.

III - to assess trends in the prevalence of potentially inappropriate drug use among old people living in nursing homes and the impact of medication reviews on potentially inappropriate drug use.

IV - to assess the occurrence and type of drug-related problems that lead to acute hospital admissions in old people with dementia or cognitive impairment.

V - to investigate the impact of interventions conducted by clinical pharmacists as part of a ward team on drug-related readmissions of old people with dementia or cognitive impairment.
METHODS

This thesis is based on five data collections (tables 6 and 7). Tvång i vården av äldre – en interventionsstudie (Physical restraint use intervention study) from years 2005-2006 [152], AC2007 - Äldre vårdade på institution i Västerbotten år 2007 ("Old people cared for in institutions in the county of Västerbotten in 2007") from 2007, and AC2013 - Äldre i Västerbotten vårdade i särskilda boenden 2013 ("Institutional care of the elderly in the county of Västerbotten in 2013") from 2013. Medication review data were constructed from 895 medication reviews performed in Västerbotten 2012 and the clinical pharmacist intervention study was conducted between 2012 and 2015.

**Table 6. An overview of the data collections used in this thesis**

<table>
<thead>
<tr>
<th>Data collection</th>
<th>Paper</th>
<th>Study-period</th>
<th>n</th>
<th>Design</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restraint use study</td>
<td>I, II</td>
<td>2005-2006</td>
<td>344/278</td>
<td>Cohort</td>
<td>MDDAS</td>
</tr>
<tr>
<td>AC2007</td>
<td>III</td>
<td>2007</td>
<td>2772</td>
<td>Cross-sectional</td>
<td>MDDAS</td>
</tr>
<tr>
<td>AC2013</td>
<td>III</td>
<td>2013</td>
<td>1902</td>
<td>Cross-sectional</td>
<td>MDDAS</td>
</tr>
<tr>
<td>Medication reviews 2012</td>
<td>III</td>
<td>2012</td>
<td>895</td>
<td>Cross-sectional</td>
<td>Assessment of inappropriate drug use</td>
</tr>
<tr>
<td>Clinical pharmacist intervention collection</td>
<td>IV</td>
<td>2012-2014</td>
<td>458</td>
<td>Cross-sectional</td>
<td>Assessment of drug-related admissions</td>
</tr>
<tr>
<td>Clinical pharmacist intervention collection</td>
<td>V</td>
<td>2012-2015</td>
<td>429</td>
<td>RCT</td>
<td>Clinical pharmacist intervention</td>
</tr>
</tbody>
</table>

MDDAS, Multi-Dimensional Dementia Assessment Scale; RCT, Randomized controlled trial
<table>
<thead>
<tr>
<th>Paper</th>
<th>Participants selection</th>
<th>Drug class studied</th>
<th>Primary outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>People with dementia living in specialized care units</td>
<td>Antipsychotic drugs (N05A)</td>
<td>Long-term use of antipsychotic drugs</td>
</tr>
<tr>
<td>II</td>
<td>People with dementia living in specialized care units</td>
<td>Antidepressants (N06A), Anxiolytics (N05B) and Hypnotics and sedatives (N05C)</td>
<td>Long-term use of psychotropic drugs</td>
</tr>
<tr>
<td>III</td>
<td>People ≥65 years living in nursing homes</td>
<td>Inappropriate drugs*</td>
<td>Prevalence of inappropriate drugs in 2007 and 2013. Comparison of inappropriate drugs with and without medical review performed</td>
</tr>
<tr>
<td>IV</td>
<td>People with dementia or cognitive impairment** and ≥65 years admitted to hospital</td>
<td>All drugs</td>
<td>Occurrence and character of drug-related problems leading to hospitalization</td>
</tr>
<tr>
<td>V</td>
<td>People with dementia or cognitive impairment** and ≥65 years admitted to hospital</td>
<td>All drugs</td>
<td>Risk of drug-related readmissions</td>
</tr>
</tbody>
</table>

*Described in section “Procedures” in Methods **Described in section “Participants” in Methods.
PARTICIPANTS

Physical restraint use study

The study population in papers I and II, was used in a research study conducted in 2005-2006 concerning use of physical restraint [152]. The study included 40 specialized care units in nine communities (Umeå, Skellefteå, Örnsköldsvik, Robertsfors, Vindeln, Bjurholm, Nordmaling, Vännäs, and Lycksele) in northern Sweden. All specialized care units in these communities were inventoried, 99 units were contacted, and units with the highest prevalence of physical restraint use (≥20%) were selected. Twenty units were cluster randomized to an intervention group and 20 units to a control group. In paper I, this population was used as one sample comprising 353 people with dementia (40 specialized care units). In the final population, 9 persons were excluded due to incomplete data, leaving 344 persons. In paper II, 278 people with dementia were included in the final population, after exclusion of those with incomplete data (16), death (47), or dropout (12) at follow-up.

AC2007 and AC2013 questionnaires

Every six or seven years since 1975, questionnaires have been sent out to all nursing homes in the county of Västerbotten in the northern part of Sweden. In paper III, the collections from 2007 (AC2007) and 2013 (AC2013) were used. The response rate to the AC2007 data collection was 85.8%, or 3070 responses. The response rate to the AC2013 data collection was 70.5%, or 2262 responses. In the 2007 collection, geriatric and psychogeriatric hospital wards were included. In 2013, no hospital wards were included. People in hospital wards in 2007 were therefore excluded (99 persons). People less than 65 years old or for whom no age was registered were excluded from analyses. Also, only those who had a complete medical list were selected. The final study populations comprised 2772 people (AC2007) and 1902 people (2013).

Medication reviews from 2012

In paper III, material from medication reviews was used. In 2012, clinical pharmacists performed 895 medication reviews in the county of Västerbotten in northern Sweden. Medication reviews were a service
provided to municipalities in Västerbotten county, and such reviews were carried out in nursing homes that actively requested them. Occasionally, doctors or nurses also requested pharmacist-guided medication reviews for individual patients at nursing homes.

**Intervention study**

Data from the clinical pharmacist intervention study was used in papers IV and V. Patients from acute internal medicine wards and from the orthopedic ward at the University hospital in Umeå, and patients from internal medicine wards in Skellefteå Hospital from January 09, 2012, to December 02, 2014 were included. Eligible patients were aged 65 years or older and suffering from dementia or cognitive impairment. In total, 460 patients were included. Dementia diagnoses were collected from the medical record. People were considered to have cognitive impairment if sufficient information in medical records related to memory, orientation, or executive function was noted before the present hospitalization. This procedure was chosen to avoid the risk of including persons without dementia who had developed a delirious or confused state during the hospital stay and therefore would score low on a Mini-Mental State Examination (MMSE). In addition, patients in whom dementia was suspected and medical investigation had commenced or would be initialized were included. In ambiguous or uncertain cases, patients were excluded.

The populations studied in papers IV and V constituted basically the same individuals. However, in paper V patients were randomized into a control and intervention group, while in paper IV the study population was treated as a whole. Individuals who withdrew from the intervention study before hospital discharge (1 person) and planned admissions for elective procedures (1 person) were excluded in paper IV. The final sample thus comprised 458 persons. In paper V, 460 patients were randomized to an intervention and a control group. Out of 460 randomized patients (230 in the intervention and 230 in the control group), one individual in the control group withdrew before discharge. In addition, 31 patients (18 intervention and 13 control) died during the index admission. These 31 individuals were excluded from the analyses, leaving a final sample of 429 patients.

**Randomization and masking**

In paper V, patients were randomly assigned to one of two groups: intervention and control. Randomization sequences were prepared before
the start of the study using a coin toss method by an independent person who was not engaged in the trial in any other way. The sequence was performed in blocks of 6–36 (each block contained between 3–18 intervention allocations and control allocations each). Each ward used its own blocks, consecutively starting a new block when the previous was filled. Different block sizes were used in order to reduce predictability. The clinical pharmacist enrolled participants in the ward. Permission was sought and approved for research without consent. Information was given to both patients and relatives in an appropriate way (written and oral information), and people who did not want to participate were able to refuse. When a patient formally entered the trial, an employee of the Department of Pharmacology and Clinical Neurosciences at Umeå University not involved in the interventions provided the randomization scheme and treatment allocation to the clinical pharmacist. Patients and clinical pharmacists were not masked to treatment assignment.

PROCEDURES

Papers I, II and III - MDDAS

Assessments in paper I-III were made using the Multi-Dimensional Dementia Assessment Scale (MDDAS) [153]. The scale includes BPSD, assessments of functioning in activities of daily living (ADL), cognition, and a registration of current drug prescriptions. The scale includes other measurements, for example pain, vision, and hearing, but these data were not used in the paper included in this thesis.

The study form was sent out to the nursing homes and the staff members who knew the resident best was asked to fill in the individual assessment scales. Written instructions about how to carry out the assessments were included. The staffs were informed that their assessments should be based on observations of the resident’s condition during the preceding week.

Behavioral and psychological symptoms

The MDDAS contains 25 behavioral items and 14 psychological symptom items [153]. The scale is presented in Appendix 1. Each item is rated on a three-point scale indicating that the symptom was present at least once a day, once a week, or never during the observation period of one week. These
variables are dichotomized between at least once a week and less than once a week when used in papers I and II.

Activities of daily living

An ADL score was calculated based on the resident’s ability to cope with dressing, hygiene, eating and bladder and bowel control [153]. The scale is presented in Appendix 2. All ADL categories score 1 to 5, except that for bladder control, which scores 0 to 4. Hence the ADL score ranges from 4 to 24, where a higher score indicates greater ADL independence. ADL scores are presented in papers I, II and III.

Cognitive function

Cognitive impairment was measured using a scale developed by Gottfries and Gottfries [154, 155], presented in Appendix 3. The scale consists of 27 items that measure a person’s level of cognitive function. A score of less than 24 indicates cognitive impairment, which correlates with a sensitivity of 90% and a specificity of 91% [153] to the usual 24/30 MMSE cut-off [156]. Cognitive function using the Gottfries’ scale is presented in paper I, II and III. In papers I and II, the scale is subdivided into three groups, mild cognitive impairment (16-23), moderate cognitive impairment (8-15), and severe cognitive impairment (0-7), with reference category severe cognitive impairment when used in the regression analyses. In papers IV and V, data concerning cognitive impairment was collected as MMSE [156] when it was stated in the medical record.

Papers III and V - Clinical pharmacist interventions

In papers III and V, clinical pharmacists performed interventions. In paper III, these interventions consisted of medication reviews conducted for patients in nursing homes. A symptom rating scale, PHASE-20 (PHArmacotherapeutical Symptom Evaluation, 20 questions) [157] was used as a tool, and the clinical pharmacist participated in ward rounds and discussed drug-related problems with the health care team. In paper V, interventions consisted of medication reconciliation and medication reviews conducted for hospitalized patients. The clinical pharmacist participated in ward rounds and discussed drug-related problems with the health care team.
Medication reconciliation

Medication reconciliation is a check of individual patient’s drug list to make sure that the list is updated, correct, and complete. Information was gathered from drug lists at the primary care center and from hospital medical records, with occasional inputs from patients or relatives of patients. The total collected information was then compared with the patient’s current medication administration record at the hospital.

Medication review

Based on information taken from the patient’s medication list, medical record notes, laboratory values, results from PHASE-20 when used, medication reconciliation and other relevant data, the clinical pharmacists identified relevant DRPs, with respect to impaired body function (renal function, liver function, cardiac function, contraindications, allergies, swallowing problems), certain drugs (toxic drugs, drugs prone to produce side-effect, potentially inappropriate drugs), interactions (between different drugs and food), symptoms (adverse drug reactions), and overall view (proper drug selection, dosage, duration of treatment, polypharmacy, indication for therapy, untreated indication, compliance, OTC drugs, effectiveness, and cost-effectiveness).

Ward round

The clinical pharmacist participated in ward rounds and relevant DRPs were discussed with the health care team (physicians, nurses, enrolled nurses) during ward rounds. Advice was given regarding drug selection, dosages and possible monitoring needs. Based on these discussions, physicians in charge made final decisions concerning changes in drug therapy. When interventions were performed in nursing homes, great emphasis was placed on educating health professionals regarding drug use.

PHASE-20

The PHASE-20 symptom rating scale was used to evaluate patients’ symptoms. This is a validated tool for use in connection with medication reviews for identifying possible drug-related symptoms in older people. A registered nurse filled in the form with the patient when possible. The PHASE-20 was then sent to the clinical pharmacist.
**Paper IV - Assessment of drug-related admissions**

In paper IV, three experienced clinical pharmacists at the Department of Clinical Pharmacology, Umeå University Hospital, checked data obtained from medical records at patients’ admission to the hospital, before any medication review had been performed. To get full medication histories of patients’, data from patients’ medication lists, laboratory values, and medical record notes from primary care, from the actual admission, and from earlier contacts with health care were compiled. The group of clinical pharmacists decided whether the hospital admission should be considered drug-related or not, first individually then collectively, discussing all admissions. The group determined the probability that a certain drug had caused or contributed to the acute admission according to the WHO criteria for causality assessment regarding ADR [158]. To be able to include drug-related problems besides ADR, the model published by Cipolle et al. was used with the following additional six subgroups: unnecessary drug therapy, need for additional drug therapy, ineffective drug/inappropriate drug, dosage too low, dosage too high, and noncompliance [134]. An extra category, interactions (pharmacodynamics and pharmacokinetics), was added. Admissions, as they related to drugs, were classified as certain, probable, possible, or unlikely/un-assessable.

**Paper V – Assessment of drug-related readmissions**

In paper V, the study was closed 180 days after the last of the 460 patients was discharged. The number of readmissions was collected during the 180 days of follow-up (from each patient’s discharge date). These data were collected from electronic medical records, which were carefully reviewed and copied to a document. All data that indicated which group the patient was enrolled in was deleted. For each patient, the expert group received the drug-list, laboratory list, doctors’ notes, and epicrisis from the first admission and from any readmission(s). Names and birth numbers were covered before being given to the expert group. An independent, blinded external expert group comprised of one specialist in geriatrics, one specialist in internal medicine, and one clinical pharmacist from another county, all experts with extensive experience within their professions, assessed the outcomes. This expert group decided whether readmissions were drug-related individually and then collectively, discussing the cases with discerning judgments. The clinical pharmacists who performed the interventions also went through all information about the readmissions in the control and intervention groups, and if they found something that could indicate a drug-related problem (for example, an interaction) that the expert group not had noted, the expert
group received this information and judged the readmission again (still blinded). The four classifications for whether or not readmissions were drug-related were *certain*, *probable*, *possible*, or *unlikely/un-assessable*, in accordance with the World Health Organization (WHO) criteria for causality assessment of ADR [158].

**Drug data collection/coding**

In the physical restraint use data collection, information about dose and type of antipsychotic drugs/psychotropic drugs was collected at the study start and at follow-up, and indication for antipsychotic treatment when this was reported in prescription records. In the AC2007 and AC2013 collections, information about doses and *pro re nata* was not coded, only ongoing medication. In the medication review 2012 collection, both ongoing and *pro re nata* concerning inappropriate drugs were coded. In the clinical pharmacist intervention data collection, ongoing medication, doses, and *pro re nata* for all drugs were collected.

**Drugs selected for investigation**

The WHO ATC (Anatomical Therapeutic Chemical Index) classification system was used in papers I and II. Antipsychotics (N05A) were investigated in paper I, and antidepressants (N06A), anxiolytics, hypnotics, and sedatives (N05B&C) were investigated in paper II. In these papers, lithium (N05AN01) was not included, since it differs from antipsychotics in both mechanism of action and use.

In paper II, potentially inappropriate drugs in the antidepressant (N06A), anxiolytic, hypnotic, sedative (N05B&C), and antipsychotic (N05A) groups were investigated according to National Board of Health and Welfare recommendations. In paper III, six drug-specific indicators identified by the National Board of Health and Welfare were investigated: anticholinergic drugs, propiomazine, tramadol, long-acting benzodiazepines, antipsychotic drugs, and NSAIDs.
ETHICS

In the physical restraint use study, AC2007 and AC2013 datasets, no informed consent was received from residents. The physical restraint use study was approved by The Regional Ethical Review Board of Umeå (registration number 02-105). AC2007 and AC2013 data collections did not include personal data of the residents (names, birth numbers) and all data were reported at a group level. The Regional Ethical Review Board of Umeå approved the study (registration number 07-028M and 2012-646-31M).

In the medical reviews 2012 data collection, no informed consent was received from the residents, since reviews were made in the context of the clinical pharmacist’s normal work. The Regional Ethics Review Board in Umeå reviewed the project (analysis of the effects of medication reviews) and decided that the Swedish legislation concerning ethical review was not applicable to the project. The Board instead issued an advisory statement to the effect that no ethical problems with the project could be discerned (registration number 2014-141-31M).

The main ethical consideration with the clinical pharmacist intervention study was the fact that study participants suffered from dementia and cognitive impairment. In accordance with the Ethical Review Law § 20-21, permission was sought and approved for research without consent (registration number 2011-148-31M). Information was given to both patients and relatives in an appropriate format (written and oral), and people who did not want to participate were able to refuse. In all other respects, the demands of Ethical Review Law § 20-21 were met, including that the intervention was unlikely to pose any negative consequences to the participants.

STATISTICS

All statistical calculations were performed using the SPSS/PASW Statistic software for Mac version 18 (papers I and II) and version 22 (papers III, IV, and V). P-values of <0.05 were considered statistically significant.

Descriptive statistics

Dichotomous variables were analyzed using chi-square test and continuous variables using t-test. In paper I, people who did and did not take
antipsychotics were compared using these tests. In paper III, these statistical calculations were used to compare basic characteristics in 2007 and 2013 and also, the use of inappropriate drugs between those who had a medication review performed with a clinical pharmacist involved and the rest of the population. In paper IV, people who were admitted because of drug-related problems and people admitted for other reasons were compared using chi-square test and t-test. In paper V, these statistical tests were used to compare the intervention and control groups to baseline data. Mann-Whitney $U$ test was used to compare differences between the numbers of readmissions. In paper II, McNemars test without Yates correction was used to compare the prevalence of symptoms at baseline and follow-up. In paper III, the same test was used to compare inappropriate drugs before and after a medication review.

**Regression analysis**

The relationship between the use of different classes of psychotropic drugs and BPSD was investigated using multiple logistic regressions in papers I and II. Drug use was the dependent variable and BPSD, sex, age, level of cognitive impairment were included as independent variables. As many of the behavioral and psychological symptoms were strongly correlated, the behaviors and symptoms were tested in a stepwise logistic regression model procedure, where the behavior that had the strongest bivariate correlation was included first, and all other behaviors and symptoms were included subsequently, one by one, to see if any of them contributed independently. The behavior and symptom factors were: aggressive behavior, wandering behavior, restless behavior, verbally disruptive/attention-seeking behavior, passiveness, hallucinatory symptoms, depressive symptoms, disoriented symptoms and regressive/inappropriate behavior. Ultimately, all significant behaviors and symptoms were included in a final model, one for each drug group.

In paper III, the model had the inappropriate drug as dependent variable, and included sex, age, level of cognitive impairment, level of ADL dependency, and year of investigation (2007 or 2013) as independent variables.
Factor analysis

In papers I and II, behavioral and psychological items were grouped and weighted according to a previously performed factor analysis (Appendix 1) [159]. Material from surveys conducted in 1982 and 2000 in the county of Västerbotten was used in the factor analysis (principal component analysis) with Varimax rotation previously performed to reduce the number of factors from the behavioral and psychological items. Factors with an eigenvalue of 1 or above were extracted.

Cox regression

In paper I, a Cox regression was used to compare survival among people who were treated with antipsychotic drugs at the start of the study with those who were not treated with antipsychotics. The Cox regression also included age, sex and level of cognitive impairment. In paper V a Cox regression was used to compare the risk of drug-related hospital readmissions among people in the control group and intervention group.

Kaplan-Meier

In paper V readmissions were summarized in Kaplan-Meier curves and intervention and control groups were compared using the Mantel-Cox log-rank test.
**RESULTS**

The results are presented according to evaluations of psychotropic drug use (papers I and II), inappropriate drug use (paper III), drug-related hospitalizations (paper IV), and clinical pharmacist interventions (papers III and V).

**PSYCHOTROPIC DRUG USE (PAPERS I AND II)**

The prevalence of psychotropic drug prescriptions found in papers I and II is presented in table 8. In paper I, 38% of the study population was prescribed antipsychotic drugs at the start of the study. Comparison between the group of people with and without antipsychotics indicated no differences in use of antidepressant drugs or in anti-dementia drugs. However, there was an association between antipsychotic drug use and anxiolytic, hypnotic and sedative drug prescriptions. Further, an association was found between antipsychotic drug prescribing and age, but there were no differences in prescription rates between men and women. At the start of the study, 132 people were prescribed antipsychotic drugs; risperidone and haloperidol accounted for the largest share (table 9). Of the 62 people receiving risperidone, 52 received the recommended dose, \( \leq 1.5 \text{ mg daily} \). Hence, 52/132 (39%) received both the recommended antipsychotic drug and the recommended dose, assuming that antipsychotics were used solely for the treatment of BPSD.

**Table 8. Characteristics of study population and prevalence of psychotropic drug use at baseline**

<table>
<thead>
<tr>
<th></th>
<th>Paper I</th>
<th>Paper II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases, n (%)</td>
<td>344</td>
<td>278</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>245 (71.2)</td>
<td>209 (75.2)</td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>82.1 ± 7.8</td>
<td>82.0 ± 8.0</td>
</tr>
<tr>
<td>ADL score (4-24) mean ± SD</td>
<td>12.1 ± 5.3</td>
<td>12.6 ± 5.4</td>
</tr>
<tr>
<td>Cognitive score (0-27) mean ± SD</td>
<td>10.2 ± 7.3</td>
<td>10.7 ± 7.3</td>
</tr>
<tr>
<td>Antipsychotic (N05A) use, n (%)</td>
<td>132 (38.4)</td>
<td>111 (39.9)</td>
</tr>
<tr>
<td>Antidepressant (N06A) use, n (%)</td>
<td>180 (52.3)</td>
<td>150 (54.0)</td>
</tr>
<tr>
<td>Anxiolytics, hypnotics and sedatives (N05B&amp;C) use, n (%)</td>
<td>156 (45.3)</td>
<td>131 (47.1)</td>
</tr>
<tr>
<td>Anxiolytics (N05B) use, n (%)</td>
<td>46 (13.4)</td>
<td>43 (15.5)</td>
</tr>
<tr>
<td>Hypnotics and sedatives (N05C) use, n (%)</td>
<td>139 (40.4)</td>
<td>107 (38.5)</td>
</tr>
</tbody>
</table>

SD, standard deviation; ADL, activities of daily living
The most common indication for prescribing antipsychotic drugs was “treatment of disturbed and restless behavior/sedative”; 67 prescriptions (43%) had this indication. No indication was listed for 19 prescriptions (12%). The indication “treatment of delusions/hallucinations/paranoia” was given for 16 prescriptions (10%), and 14 prescriptions (9%) had the indication “treatment of mood/irritability/anxiety”. “Treatment of aggression” was given as indication for 13 prescriptions (8%), and 12 prescriptions (8%) had the indication treatment of insomnia. Further, the indication “treatment of psychosis” was given for seven prescriptions (5%), and three (2%) for “treatment of confusion”. Finally, the indication “behavioral disorders/BPSD” was given for two prescriptions (1%) and three prescriptions (2%) had “other indications”.

In paper II, 229 of 278 people (82%) had at least one psychotropic drug prescribed. One hundred and fifty persons (54%) used antidepressants, 131 (47%) used anxiolytics, hypnotics and sedatives, and 111 (40%) used antipsychotics (table 8). Furthermore, 74 people (27%) had anxiolytics/hypnotics/sedatives and antidepressant drugs prescribed simultaneously. Sixty-two persons (22%) were co-medicated with anxiolytics/hypnotics/sedatives and an antipsychotic drug. Sixty-one people (22%) showed combined prescriptions of antidepressant and antipsychotic drugs. There were 61 people (22%) who were prescribed three or more psychotropic drugs concomitantly.

SSRIs were the drugs mainly prescribed among the 150 persons who used antidepressant drugs. Citalopram accounted for 53% of the antidepressants prescribed followed by sertraline (20%) and mirtazapine (16%) (table 9). Oxazepam accounted for the main part of the anxiolytics and among hypnotic and sedative drugs, propiomazine was most frequently prescribed.

Among antipsychotics (N05A), antidepressants (N06A), anxiolytics (N05B) and hypnotics and sedatives (N05C), 64 people (23%) used inappropriate drugs according to criteria set by the National Board of Health and Welfare [1] (levomepromazine, clozapine, clomipramine, hydroxyzine, diazepam, flunitrazepam and propiomazine). Eight people used two inappropriate drugs concomitantly.
Table 9. Characteristics of psychotropic drugs at baseline

<table>
<thead>
<tr>
<th>Drug</th>
<th>n (%)</th>
<th>Dose, mean (mg) ± SD</th>
<th>Range (mg)</th>
<th>Dose, median (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation AP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>25 (43.9)</td>
<td>2.1±3.1</td>
<td>0.5-16</td>
<td>1.0</td>
</tr>
<tr>
<td>Levomepromazine</td>
<td>12 (21.1)</td>
<td>19.6±15.6</td>
<td>5-50</td>
<td>15.0</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>6 (10.5)</td>
<td>3.7±2.0</td>
<td>2-6</td>
<td>3.0</td>
</tr>
<tr>
<td>Dipyridazine</td>
<td>5 (8.8)</td>
<td>32.0±38.3</td>
<td>10-100</td>
<td>20.0</td>
</tr>
<tr>
<td>Melperone</td>
<td>4 (7.0)</td>
<td>33.8±11.1</td>
<td>25-50</td>
<td>30.0</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>4 (7.0)</td>
<td>7.8±5.9</td>
<td>3-16</td>
<td>6.0</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1 (1.8)</td>
<td></td>
<td>100.0</td>
<td></td>
</tr>
<tr>
<td><strong>Second generation AP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>62 (68.9)</td>
<td>1.1±1.1</td>
<td>0.25-8</td>
<td>0.8</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>18 (20.0)</td>
<td>6.9±5.1</td>
<td>3-20</td>
<td>5.0</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>6 (6.7)</td>
<td>60.0±31.0</td>
<td>40-120</td>
<td>50.0</td>
</tr>
<tr>
<td>Clozapine</td>
<td>3 (3.3)</td>
<td>216.7±332.0</td>
<td>25-600</td>
<td>25.0</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1 (1.1)</td>
<td></td>
<td>50.0</td>
<td></td>
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<tr>
<td><strong>Antidepressants (N06A)</strong></td>
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</tr>
<tr>
<td>Citalopram</td>
<td>84 (52.5)</td>
<td>19.6 ± 6.1</td>
<td>10-40</td>
<td>20.0</td>
</tr>
<tr>
<td>Sertraline</td>
<td>32 (20.0)</td>
<td>68.0 ± 31.3</td>
<td>25-150</td>
<td>50.0</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>26 (16.3)</td>
<td>30.6 ± 7.9</td>
<td>15-60</td>
<td>30.0</td>
</tr>
<tr>
<td>Mianserine</td>
<td>8 (5.0)</td>
<td>27.5 ± 10.3</td>
<td>10-40</td>
<td>30.0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>8 (5.0)</td>
<td>112.5 ± 56.7</td>
<td>75-225</td>
<td>75.0</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>1 (0.6)</td>
<td>175.0</td>
<td></td>
<td>175.0</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>1 (0.6)</td>
<td>10.0</td>
<td></td>
<td>10.0</td>
</tr>
<tr>
<td><strong>Anxiolytics (N05B)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxazepam</td>
<td>31 (70.5)</td>
<td>24.0 ± 26.8</td>
<td>5-135</td>
<td>15.0</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>7 (15.9)</td>
<td>32.9 ± 22.1</td>
<td>10-75</td>
<td>25.0</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>4 (9.0)</td>
<td>2.6 ± 2.5</td>
<td>0.5-6</td>
<td>2.0</td>
</tr>
<tr>
<td>Diazepam</td>
<td>1 (2.3)</td>
<td>3.3</td>
<td></td>
<td>3.3</td>
</tr>
<tr>
<td>Buspironone</td>
<td>1 (2.3)</td>
<td>15.0</td>
<td></td>
<td>15.0</td>
</tr>
<tr>
<td><strong>Hypnotics and sedatives (N05C)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propiomazine</td>
<td>37 (27.8)</td>
<td>33.4 ± 12.5</td>
<td>12-50</td>
<td>25.0</td>
</tr>
<tr>
<td>Clometiazol</td>
<td>35 (26.3)</td>
<td>651.4 ± 273.7</td>
<td>300-1500</td>
<td>600.0</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>27 (20.3)</td>
<td>6.9 ± 2.2</td>
<td>5-15</td>
<td>7.5</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>19 (14.3)</td>
<td>6.4 ± 2.5</td>
<td>2.5-10</td>
<td>5.0</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>15 (11.3)</td>
<td>0.7 ± 0.3</td>
<td>0.5-1</td>
<td>0.5</td>
</tr>
</tbody>
</table>

AP, antipsychotics; n=number of prescriptions, percent is calculated within each drug group
*Paper I (n=344) **Paper II (n=278)
Long-term use of psychotropic drugs (papers I and II)

In papers I and II, long-term use of antipsychotic drugs and other psychotropic drugs were investigated, respectively.

Antipsychotic drugs

After six months, 80/111 people (72%) were still treated with antipsychotic drugs, and 63/111 (57%) with the same dose as at baseline (figure 3). Seventy-eight people of 80 were taking the same antipsychotics as at study start. After six months, 31/111 (28%) persons had stopped using antipsychotics. Of those who were not treated with antipsychotics at baseline, 10 people were receiving antipsychotics at the six-month follow-up.

Fig 3. Flow chart of participants from baseline to 6-month follow-up. Reproduced with permission from the publisher.
There was no significant difference in mortality between the group who received antipsychotics at the start of the study and the group without antipsychotics (Hazard ratio [HR], 0.69 [95% CI, 0.36-1.32]; *p*-value 0.26).

**Antidepressant drugs**

At the start of the study, 150 persons (54%) were prescribed antidepressant drugs. After six months, 100 out of these 150 (67%) were still being treated with the same antidepressant drug at the same dose. In addition, 29 persons were being treated with antidepressant drugs, but dose or type of antidepressant had been changed. Accordingly 129/150 (86%) people were still being treated with antidepressant drugs after six months. Four people had an extra antidepressant added to their drug list. Six people had switched to another antidepressant drug, and seven received an increased dose. In total, 17 patients showed amendments in their prescriptions consistent with an escalation of treatment. In total, 33 people reduced their antidepressant treatment in various ways. In twelve patients doses were lowered or the number of antidepressant drugs reduced, and 21 stopped antidepressant medication completely. Among the 128 not taking antidepressant drugs at the start of the study, eight people were prescribed an antidepressant drug after six months. There was a significant decrease in the proportion of people with at least one of the three depressive symptoms (sad, crying, and anxious and fearful) from baseline to the six-month follow-up among people who were treated with antidepressants on both occasions (from 88/120 (73.3%) to 72/120 (60.0%), *p*-value 0.008).

**Anxiolytic drugs**

In total 43 patients (15%) were prescribed anxiolytics at the start of the study. After six months, 19/43 patients (44%) were still being treated with the same drug at the same dose. Four people had higher doses, and one changed to another anxiolytic drug after six months. Also, 19 people reduced their anxiolytic treatment. Five were on a lower dose, and 14 ended anxiolytic treatment. In total, 29/43 (67%) people were still being treated with anxiolytic drugs after six months. After six months an additional ten people were prescribed an anxiolytic drug. There was no significant change from baseline to follow-up in the proportion of people judged to be anxious and fearful among those treated with anxiolytics on both occasions.
Hypnotic and sedative drugs

A total of 107 persons (38%) in the study population used hypnotic and sedative drugs at the start of the study. After six months, 84/107 (78%) people were still being treated with hypnotics and sedatives. Of those who continued on hypnotic or sedative drugs, 61/107 (57%) were being treated with the same drug at the same dose, and 23 persons were being treated with a different dose or type of hypnotic or sedative drug. Fifteen changes in prescriptions were consistent with an escalation in treatment during the six-month period. Of these, eight had another hypnotic and sedative drug added. Three changed to an alternative hypnotic or sedative drug, and four were given an increased dose. In total 31 people treatment intensity appeared to be reduced. Eight reduced their dose or took fewer hypnotic and sedative drugs, and 23 finished their treatment. After six months four more people were prescribed hypnotic and sedative drugs. There was no significant difference between baseline and follow-up in the proportion of people with interrupted sleep among those treated with hypnotics and sedatives.
Factors associated with prescription of psychotropic and anti-dementia drugs (papers I and II)

Table 10 shows the results from regression analyses performed in paper I-II regarding associations with BPSD and antipsychotic drugs (paper I) and psychotropic drugs except antipsychotics (paper II). People who exhibited aggressive behavior or passiveness were at increased risk of being prescribed antipsychotics. Further, those who exhibited verbally disruptive/attention-seeking behavior were at increased risk of being prescribed an anxiolytic drug and those who exhibited disoriented symptoms were at increased risk of being prescribed hypnotic and sedative drugs.

Younger age was associated with different drug classes in both papers. People who were younger were at increased risk of being prescribed antipsychotic drugs, antidepressant drugs, and hypnotic and sedative drugs. Papers I and II showed no significant associations between psychotropic drug use and sex. However, significant associations between cognitive function and psychotropic drug use were found. In paper I, people with mild cognitive impairment were at higher risk of being prescribed an antipsychotic drug compared to those with severe cognitive impairment. Further, moderate cognitive impairment were associated with antidepressant drug use, and mild cognitive impairment with hypnotic and sedative drug use, as shown in paper II.
<table>
<thead>
<tr>
<th>Factor</th>
<th>Paper I*</th>
<th>Paper II**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wandering behavior</td>
<td>Antipsychotics: 1.980</td>
<td>Anxiolytics: 2.193</td>
</tr>
<tr>
<td></td>
<td>(1.515-2.588)</td>
<td>(1.389-3.462)</td>
</tr>
<tr>
<td>Aggressive behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbally disruptive/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>attention-seeking behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regressive/inappropriate behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passiveness</td>
<td>Antipsychotics: 1.548</td>
<td>Hypnotics and sedatives:</td>
</tr>
<tr>
<td></td>
<td>(1.150-2.083)</td>
<td>1.545 (1.169-2.041)</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinatory symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disoriented symptoms</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The numbers in the table represent odds ratios and 95% confidence intervals. Only significant factors are included in the table. *Antipsychotics (N05A) were investigated **Antidepressants (N06A), Anxiolytics (N05B) and Hypnotics and Sedatives (N05C) were investigated. The model included background variables (age, sex, and level of cognitive impairment).
In Paper III, the frequency of potentially inappropriate drug use was compared between the years 2007 and 2013, comprising 2772 and 1902 people, respectively. The comparison was made using six quality indicators. There were no significant differences among the basal characteristics other than the mean age, which was significantly higher in 2013 than in 2007.

After controlling for age, sex, ADL and cognitive impairment, there was a significant improvement in five out of six quality indicators between 2007 and 2013 (table 11). In general, the use of all potentially inappropriate drugs declined significantly among old people living in nursing homes, except for NSAIDs, which showed borderline significance. In 2013, 26.4% of the study population was exposed to one or more potentially inappropriate medications, compared to 44.1% in 2007. Of those prescribed antipsychotics, 67.3% (405/602) were given atypical antipsychotics in 2007, compared to 76.2% (244/320) in 2013. At both occasions, the most commonly prescribed antipsychotic substance was risperidone, and the most commonly prescribed conventional antipsychotic substance was haloperidol.

**Table 11. Potentially Inappropriate Medication in 2007 and 2013**

<table>
<thead>
<tr>
<th></th>
<th>2007</th>
<th>2013</th>
<th>Odds ratio&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of people</td>
<td>2772</td>
<td>1902</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticholinergic drugs, n (%)</td>
<td>303</td>
<td>117</td>
<td>0.547</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Propiomazine, n (%)</td>
<td>241</td>
<td>38</td>
<td>0.215</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tramadol, n (%)</td>
<td>184</td>
<td>17</td>
<td>0.116</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long-acting BZ, n (%)</td>
<td>179</td>
<td>37</td>
<td>0.292</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antipsychotic drugs, n (%)</td>
<td>602</td>
<td>320</td>
<td>0.737</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSAID, n (%)</td>
<td>134</td>
<td>67</td>
<td>0.735</td>
<td>0.064</td>
</tr>
<tr>
<td>Potentially inappropriate medication, n (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1222 (44.1)</td>
<td>502 (26.4)</td>
<td>0.448</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<sup>a</sup>Corrected for sex, age, ADL and level of cognitive impairment
<sup>b</sup>Defined as exposure to at least one of the following quality indicators: use of anticholinergic drugs, use of propiomazine, use of tramadol, use of long-acting benzodiazepines, use of antipsychotics or use of NSAID.

BZ, Benzodiazepine drug; NSAID, Non Steroidal Anti-inflammatory Drug

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A total of 458 people aged 65 years or older with dementia or cognitive impairment were included in the study. The mean age of the study population was 83.2 years, and 62.4% of the individuals were women. Of 458 acute hospital admissions, 189 (41.3%) were judged drug-related. Table 12 shows the categorization of drug-related problems according to Cipolle et al [134]. One extra category, interactions, was added. The most common drug-related problems were adverse drug reactions. Too high doses and non-compliance also accounted for a large proportion of drug-related problems. The causal relationship between the drug-related problem and index admission was judged as certain in 25, probable in 78, and possible in 86 cases. In total 264 drugs were involved in 189 drug-related admissions, of which cardiovascular (29.5%) and psychotropic (26.9%) drugs were the most prominent drug classes (table 13). These drugs accounted for 149 of 264 involved drugs (56.4%). Analgesics, drugs for obstructive airway diseases, anticoagulants, and antidiabetic drugs also contributed to several drug-related hospital admissions. Drug-related admissions were more common among people with a higher number of drugs and among younger people. No associations were found between drug-related admission and gender, type of living, or type of ward. Further, no associations were seen between drug-related admissions and any specific medical history finding. In a multivariate model with drug-related admission as the dependent variable and number of drugs at admission, age, and stroke as independent variables, the total number of drugs (Odds ratio [OR], 1.06 [95% CI, 1.00-1.12]; p-value 0.035) and age (OR, 0.97 [95% CI, 0.94-1.00]; p-value 0.031) remained significant.

**Table 12. Categorization of drug-related problems leading to hospitalization (in total 189 DRPs)**

<table>
<thead>
<tr>
<th>DRP</th>
<th>Numbers of DRPs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse drug reactions</td>
<td>86 (45.5)</td>
</tr>
<tr>
<td>Dosage too high</td>
<td>24 (12.7)</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>20 (10.6)</td>
</tr>
<tr>
<td>Ineffective drug/inappropriate drug</td>
<td>20 (10.6)</td>
</tr>
<tr>
<td>Interactions</td>
<td>13 (6.9)</td>
</tr>
<tr>
<td>Needs additional drug therapy</td>
<td>12 (6.3)</td>
</tr>
<tr>
<td>Dosage too low</td>
<td>9 (4.8)</td>
</tr>
<tr>
<td>Unnecessary drug therapy</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Drug class involved</td>
<td>Frequency (%)</td>
</tr>
<tr>
<td>---------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Cardiovascular drugs</td>
<td>78 (29.5)</td>
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</tbody>
</table>
Nitro-glycerine (2)  (needs additional drug therapy), orthostatic hypotension, nausea
Ramipril (2)  Angina (needs additional drug therapy)
Spironolactone (6)  Acute renal failure, heart failure (dosage too low), hyperkalemia
Verapamil (1)  Fall

<table>
<thead>
<tr>
<th>Psychotropic drugs</th>
<th>71 (26.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam (2)</td>
<td>Confusion, fall</td>
</tr>
<tr>
<td>Amitriptyline (2)</td>
<td>Confusion, sedation</td>
</tr>
<tr>
<td>Buspirone (1)</td>
<td>SIADH</td>
</tr>
<tr>
<td>Citalopram (13)</td>
<td>Bleeding, orthostatic hypotension, diarrhea, fall, hallucinations, anemia, hemorrhage, hyponatremia</td>
</tr>
<tr>
<td>Clomethiazole (2)</td>
<td>Fall</td>
</tr>
<tr>
<td>Clozapine (1)</td>
<td>Fall</td>
</tr>
<tr>
<td>Diazepam (2)</td>
<td>Sedation</td>
</tr>
<tr>
<td>Escitalopram (2)</td>
<td>Fall, hyponatremia</td>
</tr>
<tr>
<td>Haloperidol (2)</td>
<td>Fall, pulmonary embolism</td>
</tr>
<tr>
<td>Lithium (1)</td>
<td>Confusion</td>
</tr>
<tr>
<td>Mianserin (1)</td>
<td>Fall</td>
</tr>
<tr>
<td>Mirtazapine (4)</td>
<td>Fall, sedation</td>
</tr>
<tr>
<td>Nitrazepam (2)</td>
<td>Fall</td>
</tr>
<tr>
<td>Olanzapine (3)</td>
<td>Fall, sedation, pulmonary embolism</td>
</tr>
<tr>
<td>Oxazepam (3)</td>
<td>Fall, sedation</td>
</tr>
<tr>
<td>Perphenazine (1)</td>
<td>Fall</td>
</tr>
<tr>
<td>Propiomazine (6)</td>
<td>Sedation, confusion, fall</td>
</tr>
<tr>
<td>Risperidone (4)</td>
<td>Dyspnea, dizziness, fall, pulmonary embolism</td>
</tr>
<tr>
<td>Sertraline (4)</td>
<td>Fall, hemorrhage</td>
</tr>
<tr>
<td>Venlafaxine (3)</td>
<td>Fall, hyponatremia</td>
</tr>
<tr>
<td>Zolpidem (5)</td>
<td>Fall, confusion</td>
</tr>
<tr>
<td>Zopiclone (7)</td>
<td>Fall, sedation</td>
</tr>
</tbody>
</table>

These drugs accounted for 149 of a total of 264 drugs that may have been involved in drug-related hospital admissions (56.4%). TIA, Transient Ischemic Attack; NSTEMI, Non ST-segment Elevation Myocardial Infarction; SIADH, Syndrome of Inappropriate Antidiuretic Hormone (ADH) Secretion
CLINICAL PHARMACIST INTERVENTION (PAPERS III AND V)

In primary care (paper III)

In the survey population from 2013, medication reviews were conducted in 72.6% of the individuals, and a clinical pharmacist was involved in 39.9% of the reviews. There was no difference in the number of potentially inappropriate drugs between those who had a medication review with a clinical pharmacist involved and the rest of the population, except for antipsychotic drugs, where use was higher when a clinical pharmacist was involved. Those who had a medication review where a clinical pharmacist was involved had a lower cognitive score and ADL score, and they were slightly younger. The results from the medication reviews performed in the county of Västerbotten are presented in table 14. In 2012, clinical pharmacists performed 895 medication reviews among people living in nursing homes. The number of people using potentially inappropriate drugs (all investigated) was significantly lower after medication review than before.

**Table 14. Number and percentage of people using inappropriate drugs before and after medication review. Total number of medication reviews = 895**

<table>
<thead>
<tr>
<th></th>
<th>Before MR</th>
<th>After MR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic drugs, n (%)</td>
<td>72 (8.0)</td>
<td>59 (6.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Propiomazine, n (%)</td>
<td>29 (3.2)</td>
<td>18 (2.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Tramadol, n (%)</td>
<td>17 (1.9)</td>
<td>8 (0.9)</td>
<td>0.003</td>
</tr>
<tr>
<td>Long-acting benzodiazepines, n (%)</td>
<td>80 (8.9)</td>
<td>65 (7.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antipsychotic drug use, n (%)</td>
<td>179 (20.0)</td>
<td>160 (17.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSAID, n (%)</td>
<td>51 (5.7)</td>
<td>42 (4.7)</td>
<td>0.007</td>
</tr>
<tr>
<td>Potentially inappropriate medicationa</td>
<td>335 (37.4)</td>
<td>283 (31.6)</td>
<td>&lt;0.001</td>
</tr>
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</table>

MR, Medication review aDefined as exposure to at least one of the following quality indicators: use of anticholinergic drugs, use of propiomazine, use of tramadol, use of long-acting benzodiazepines, use of antipsychotics or use of NSAID. McNemars test without Yates correction was used to analyze the data.
In hospital care (paper V)

Between January 9, 2012, and December 2, 2014, 473 patients aged 65 years or older were invited to participate in the trial. Thirteen declined. Of 460 randomized patients (230 intervention and 230 control), one individual in the control group was excluded before discharge. In addition, 31 patients (18 intervention and 13 control) died before discharge and consequently could not provide follow-up data. These 31 individuals were excluded from the analysis, leaving a final sample of 429 patients. Baseline characteristics of the study population were generally similar between groups. However, more patients in the intervention group had a history of heart failure compared to the control group (34% vs 25%, $p$-value 0.04) (table 15).

Clinical pharmacists identified at least one DRP in 66% (140/212) of participants in the intervention group, for a total of 310 DRPs. Suggested actions were carried out for 82% of the identified DRPs (74% during the hospital stay and 8% were written in the discharge notes as a suggestion to the general practitioner) (figure 4). Eighteen per-cent of the suggestions were not adopted. The DRPs were distributed as follows: ADR (n=103), ineffective drug/inappropriate drug (n=54), unnecessary drug therapy (n=54), dosage too high (n=44), needs additional drug therapy (n=37), dosage too low (n=14), and noncompliance (n=4). The total time of pharmacist participation per patient (participation in ward rounds not included) was on average 32 minutes (range 10–90 minutes).

Fig 4. Actions to the clinical pharmacists’ suggestions
A Kaplan-Meier survival analysis showed no significant difference in time to all-cause readmission during 180 days of follow-up between the intervention and control groups (132.7 [SD, 4.7] days vs 126.2 [SD, 4.0] days, Mantel-Cox log rank test, \( p\text{-value} 0.63 \)), or within 30 days (27.5 [SD, 0.47] days vs 26.8 [SD, 0.53] days, Mantel-Cox log rank test, \( p\text{-value} 0.30 \)) (figure 5 and 6).

During the 180 days follow-up, 40/212 (19%) and 50/217 (23%) of patients were readmitted for drug-related reasons in the intervention and control group respectively \( (p=0.29) \). A Kaplan-Meier survival analysis showed no significant difference in time to drug-related readmission within 180 days between the intervention and control groups (160.0 [SD, 3.3] days vs 150.1 [SD, 4.0] days, Mantel-Cox log rank test, \( p\text{-value} 0.28 \)) (figure 7). We observed a significant difference in the frequency of DRP readmissions within 30 days between the intervention, 11/212 (5%) and the control groups, 24/217 (11%), \( p\text{-value} 0.03 \), in the total study population. Kaplan-Meier curve analysis revealed significant differences in time to drug-related readmission during the first 30 days after discharge between the intervention and the control group in the total study population (29.1 [SD, 0.30] days vs 28.1 [SD, 0.43] days, Mantel-Cox log rank test, \( p\text{-value} 0.03 \)) (figure 8).

Heart failure was significantly more common in the intervention group \( (p=0.04) \) and after adjustment for heart failure, the intervention was found to significantly reduce the risk of drug-related readmissions \( (HR, 0.49 [95\% CI, 0.27-0.90]; p\text{-value} 0.02) \).

Subgroup analyses among patients without heart failure were performed. A Kaplan-Meier survival analysis showed that the time to drug-related readmission within 180 days was significantly different between the intervention and control groups (171.2 [SD, 2.7] days vs 153.1 [SD, 4.5] days, Mantel-Cox log rank test, \( p\text{-value} 0.02 \)) (figure 9). Also, time to drug-related readmission within 30 days was significantly different between the intervention and control groups among patient without heart failure (29.5 [SD, 0.29] days vs 28.3 [SD, 0.49] days, Mantel-Cox log rank test, \( p\text{-value} 0.02 \)) (figure 10).
<table>
<thead>
<tr>
<th></th>
<th>Control (n=217)</th>
<th>Intervention (n=212)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>138 (64%)</td>
<td>133 (63%)</td>
<td>0.854</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>83.1 (6.6)</td>
<td>83.1 (6.6)</td>
<td>0.996</td>
</tr>
<tr>
<td><strong>Laboratory values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium level, mean (SD), mEq/L</td>
<td>139.1 (4.1)</td>
<td>138.9 (5.1)</td>
<td>0.568</td>
</tr>
<tr>
<td>Potassium level, mean (SD), mEq/L</td>
<td>4.1 (0.5)</td>
<td>4.1 (0.5)</td>
<td>0.774</td>
</tr>
<tr>
<td>Hb, mean (SD), g/dL</td>
<td>12.4 (1.9)</td>
<td>12.5 (1.8)</td>
<td>0.515</td>
</tr>
<tr>
<td>Creatinine clearance, mean (SD), mL/s&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3401.2</td>
<td>3209.6</td>
<td>0.145</td>
</tr>
<tr>
<td>Duration of index admission, mean (SD), days</td>
<td>9.1 (7.9)</td>
<td>8.3 (7.2)</td>
<td>0.302</td>
</tr>
<tr>
<td>Drugs, mean (SD), number</td>
<td>8.3 (3.6)</td>
<td>8.4 (3.6)</td>
<td>0.622</td>
</tr>
<tr>
<td><strong>Type of living, No. (%)</strong></td>
<td></td>
<td></td>
<td>0.369</td>
</tr>
<tr>
<td>Living at home</td>
<td>158 (73%)</td>
<td>146 (69%)</td>
<td></td>
</tr>
<tr>
<td>Nursing home</td>
<td>59 (27%)</td>
<td>66 (31%)</td>
<td></td>
</tr>
<tr>
<td><strong>Dementia subtype, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimers disease</td>
<td>68 (31%)</td>
<td>64 (30%)</td>
<td>0.797</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>30 (14%)</td>
<td>42 (20%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Other or unspecified dementia</td>
<td>119 (55%)</td>
<td>106 (50%)</td>
<td>0.316</td>
</tr>
<tr>
<td>MMSE, mean (SD)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>20.1 (4.3)</td>
<td>19.6 (4.8)</td>
<td>0.537</td>
</tr>
<tr>
<td><strong>Medical history, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>54 (25%)</td>
<td>72 (34%)</td>
<td>0.039</td>
</tr>
<tr>
<td>Hypertension</td>
<td>105 (48%)</td>
<td>116 (55%)</td>
<td>0.190</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>58 (27%)</td>
<td>62 (29%)</td>
<td>0.561</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>47 (22%)</td>
<td>61 (29%)</td>
<td>0.090</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>18 (8%)</td>
<td>16 (8%)</td>
<td>0.774</td>
</tr>
<tr>
<td>Malignant disease, past or present</td>
<td>20 (9%)</td>
<td>27 (13%)</td>
<td>0.243</td>
</tr>
<tr>
<td>Myocardial infarction, past</td>
<td>25 (12%)</td>
<td>36 (17%)</td>
<td>0.105</td>
</tr>
<tr>
<td>Stroke, past</td>
<td>46 (21%)</td>
<td>50 (24%)</td>
<td>0.533</td>
</tr>
</tbody>
</table>

**MMSE,** Mini Mental State Examination; Hb, hemoglobin. <sup>a</sup>Creatinine clearance was estimated from plasma creatinine values using the Cockcroft-Gault equation. <sup>b</sup>Data missing for 154 patients in the control group and 119 patients in the intervention group. SI conversion factor: to convert sodium from mEq/L to mmol/L, multiply by 1. To convert potassium from mEq/L to mmol/L, multiply by 1. To convert Hb from g/dL to g/L, multiply by 10. To convert creatinine clearance from mL/s to mL/min, multiply by 0.0167.
Fig 5. Kaplan-Meier plots for all-cause readmissions within 180 days in the total sample. HR and CI according to univariate Cox regression analysis and p-value from log rank test.

Fig 6. Kaplan-Meier plots for all-cause readmissions within 30 days in the total sample. HR and CI according to univariate Cox regression analysis and p-value from log rank test.
Fig 7. Kaplan-Meier plots for drug-related readmissions within 180 days in the total sample. HR and CI according to univariate Cox regression analysis and p-value from log rank test.

Fig 8. Kaplan-Meier plots for drug-related readmissions within 30 days in the total sample. HR and CI according to univariate Cox regression analysis and p-value from log rank test.
Fig 9. Kaplan-Meier plots for drug-related readmissions within 180 days in people without heart failure. HR and CI according to univariate Cox regression analysis and p-value from log rank test.

Fig 10. Kaplan-Meier plots for drug-related readmissions within 30 days in people without heart failure. HR and CI according to univariate Cox regression analysis and p-value from log rank test.
DISCUSSION

MAIN FINDINGS

This thesis shows that psychotropic and inappropriate drugs are used extensively and for long periods of time in people with dementia and cognitive impairment. Identified associations between antipsychotics and other psychotropic drug use and behavioral and psychological symptoms indicate that these drugs are prescribed to treat behavioral and psychological symptoms among cognitively impaired individuals, despite limited evidence of their efficacy.

This thesis also revealed that between 2007 and 2013, the extent of potentially inappropriate drug use declined from 44% to 26% among old people living in nursing homes in the county of Västerbotten. Also, in a separate population from 2012, the frequency of potentially inappropriate drug use was significantly reduced among patients where medication reviews had been performed.

The proportion of hospitalizations where drug-related problems may have contributed to the admission was high, 41%. Participation of a clinical pharmacist on the health care team significantly reduced the risk of drug-related readmissions during the first 30 and 180 days of follow-up after discharge. However, in a subset of patients with concomitant heart failure no effect of the intervention was seen.
Drug-related problems among old people, especially among old people with dementia, are a known issue that has received wide attention. In recent years, many steps have been taken to address and reduce this problem. Despite this progress, DRPs continue to cause a major concern. In the present thesis, inappropriate long-term use of psychotropic drugs and associations with behavioral and psychological symptoms was demonstrated in papers I and II, even though findings in paper III indicated that the use of potentially inappropriate drugs declined from 2007 to 2013. Despite these improvements, paper IV proposed that as much as 41% of hospital admissions among the study population from 2012 to 2014 were judged as drug-related. In paper V, the clinical pharmacist identified at least one DRP in 66% (140/212) of participants in the intervention group, for a total of 310 DRPs. Drug prescribing and use among old people and especially among old people with dementia is very challenging, and there is no single action or simple solution that could resolve the issue of non-optimal drug treatment and unnecessary hospitalizations in this vulnerable patient group. Different treatment options, also including non-pharmacological approaches, must be weighed against each other and benefits against the risk of adverse events. The most desirable approach may involve treating patients with a multi-professional team, combining knowledge from different health care professions.

When conducting comprehensive medication reviews, the clinical pharmacist identifies drug-related problems with respect to impaired organic function, certain drugs known to be associated with medication problems, potential interactions, the patient’s symptoms, and an overall judgment of the patients drug use as a whole. In the present work, clinical pharmacists had full access to medical records and laboratory data (described in detail in the methods section). Medication reconciliations were also conducted. The following section will discuss different aspects to consider when optimizing drug therapy among old people with dementia.
IMPORTANT ASPECTS TO CONSIDER WHEN OPTIMIZING DRUG THERAPY

Impaired body function

Many medications need to be used with caution in the elderly, because of age-related changes in pharmacokinetics and pharmacodynamics. These changes may affect, for example, renal and liver functions. One recent study among the population studied in papers IV and V, found that renal function was impaired (estimated glomerular filtration rate < 60 mL/min) in 65.4% of people at index admission to the hospitals. Of the 326 patients prescribed medications with mainly renal elimination, 13.2% had inappropriate prescriptions (Sönnerstam E et al, unpublished data). An even higher prevalence of inappropriate drugs prescribed to patients with renal impairment has been reported in a study from Australia. More than 28% of patients had evidence of inappropriate prescriptions with respect to their renal function [160]. In paper V, examples of drugs prescribed inappropriately in patients with impaired renal function were oral antidiabetics such as metformin and glibenclamide. Also, contraindications, allergies, and swallowing problems need to be identified more thoroughly to prevent inappropriate prescriptions.

Certain drugs that need special attention

It is important to take certain drugs, especially drugs that have the potential to cause problems for patients, into consideration. For example, drugs with a narrow therapeutic index, such as digoxin and warfarin, or drugs that might give serious adverse reactions, such as methotrexate. The identification of potentially inappropriate drugs is also important. As found in papers I and II, use of psychotropic drugs, antipsychotic drugs in particular, is extensive and often occurs for a long time. Paper I showed that 57% of people with antipsychotics at baseline were still treated with the same antipsychotics and the same dose after six months. These drugs are, in many cases, apparently used to treat behavioral and psychological symptoms. Indeed, paper I showed that the most common indication for prescribing antipsychotic drugs among the study population was “treatment of disturbed and restless behavior/sedative,” an indication not approved according to guidelines [26]. These results are supported by other studies [124, 125].

Identification of potentially inappropriate drugs is important, since these drugs have been associated with avoidable ADEs [4] and hospitalizations [3,
In paper IV, 20 of 189 (10.6%) drug-related hospitalizations were due to ineffective/inappropriate drugs, of which the most were inappropriate according to the definition of the Swedish National Board of Health and Welfare [1]. Use of potentially inappropriate drugs has also been associated with higher mortality [162].

Paper III showed a considerable decrease in the use of potentially inappropriate drugs between 2007 and 2013 where a significant improvement in five out of six quality indicators between the years was shown. These results were consistent with another Swedish study, indicating that the decrease is national [123]. Also psychotropic drug prescriptions declined between 2007 and 2013 among people with cognitive impairment, without any large changes in behavioral and psychological symptoms [163]. The shift from conventional towards atypical antipsychotics seen in paper III is desirable for the patient, since atypical drugs have a better tolerability and safety profile compared to first-generation antipsychotic drugs [63].

The reason for the decline in use of inappropriate and psychotropic drugs may be a result of increased attention in recent years. Besides the quality indicators concerning antipsychotics and other inappropriate drugs developed by the Swedish National Board of Health and Welfare in 2003 (updated in 2010) [1] and guidelines from Swedish Medical Products Agency concerning the appropriate use of antipsychotics among people with BPSD [26], in 2012 the Swedish government offered a reward to those counties that reduced the prevalence of drugs included in the six indicators of potentially inappropriate drugs by 10 % in persons aged 65 years and older. The introduction of medication reviews, a service that involved clinical pharmacists as part of the health care team starting in Västerbotten in 2003, may have contributed to improve proper use of drugs in elderly people in general, not only by performing medication reviews but also by the contribution of clinical pharmacists in continuous medical education.

International warnings on inappropriate drug use have also been issued. For example the FDA and the European Medicines Agency (EMA) have issued warnings concerning the risk of increased mortality in patients with dementia using both atypical and conventional antipsychotics [164, 165]. Still, DRPs were found in the intervention study (paper V) related to potentially inappropriate drugs, such as long-acting benzodiazepines, antipsychotics and anticholinergic drugs.
**Interactions**

Potential drug interactions must be considered when evaluating a medication list or when prescribing a new drug. Potential drug-drug interactions can lead to adverse drug events and can be the reason for hospital admissions [166]. In paper IV, 13 of a total of 189 drug-related hospitalizations were associated with drug-drug interactions. Examples of drug-drug interactions in paper V were co-administrations with warfarin and SSRIs, which increases risk of bleeding [167]. Interactions between warfarin and St. John's wort, which may decrease the effects of warfarin, were also found [168]. In the primary care and hospital care setting in Västerbotten County, prescribers have access to an interaction module in the electronic medical record system that is intended to identify and prevent important interactions. However, this module is rather crude and non-selective and does not distinguish between clinically relevant and non-relevant interactions. Also, well-known and established interactions, such as the interaction between ACE-inhibitors and spironolactone, will generate an unnecessary warning to the prescriber. As a result, the prescribers can easily be subject to information overload with relevant and non-relevant warnings, resulting in poor functionality and compliance to the module. Certainly, electronic information sources on drug interactions have the potential of further improvements.

*The patient's clinical symptoms in relation to drug treatment*

Since old people, and especially those suffering from cognitive impairment, are more sensitive to side effects of drugs than younger people, the possibility that clinical symptoms may be a result of adverse drug reactions should always be borne in mind before prescribing a new additional drug. The initiation of anti-Parkinson therapy for symptoms arising from an antipsychotic drug is a well-known example that illustrates the risk of introducing so-called prescribing cascades [169]. The anti-Parkinson drug may cause new symptoms, including orthostatic hypotension and delirium, triggering prescription of new drugs for treatment of symptoms caused by earlier prescribed drugs.
Overall view on the patients’ medication

In order to get an overview of the patients’ potential drug-related problems, there are many factors that have to be considered, such as proper drug selection, dosage, duration of treatment, polypharmacy, indication for therapy, untreated indication, compliance, OTC drugs, cost effectiveness, and if the drug has the desired effect. Regarding current indication for existing drug therapy, mechanistic renewal of prescriptions is probably a major reason for why people have the same medications for prolonged times without critical review whether there is a continued indication for further treatment with the drug of interest. For example, in paper V, an 89-year old patient with dementia who had been prescribed haloperidol as an antiemetic in 2005, was still treated with this drug at the time of the admission in 2012. Indication for therapy and duration of the indication is essential when it comes to inappropriate drug prescription, but it is important for other drugs as well. Antihypertensive medications, ferrous, and antihistamines without current indication are examples from paper V. Symptoms may change, and drugs do not always have desired effect. Therefore, monitoring the effects, providing adequate follow-up and reconsidering the indications for medication is of utmost importance. Also, too short duration of treatment and too low dose of antibiotics are examples of drug-related problems from paper V.

Untreated conditions and under-prescriptions of beneficial medicines in older people are important to identify. Under-prescription of drugs for heart failure, lack of gastric protection in people prescribed a combination of hemorrhage prone drugs, and people with morphine prescribed without concomitant laxatives are examples for under-prescription observed in papers IV and V.

Noncompliance accounted for 10.6% of the drug-related admissions in paper IV. It is found that even a small degree of cognitive impairment may have major negative impact on compliance to drug therapy among healthy elderly [49]. Examples from paper IV included people not taken prescribed antibiotics resulting in untreated urinary infections, and seizures because of noncompliance to anticonvulsant therapy with carbamazepine. Other examples were compliance problems in connection with inhalation techniques of antiasthmatic drugs or insulin administration.
**Medication reconciliation**

An accurate medication list is essential for a health care unit to assess a patient's condition, treatment effects of drugs, risks, interactions, and side effects. However, when a patient is admitted to the hospital, discrepancies in admission and discharge medications are common [170]. In one study among patients admitted to an internal medicine ward, approximately 2 out of 5 patients had discrepancies in their medications at discharge. These discrepancies were identified and corrected by pharmacist intervention [170]. Medication reconciliation has been shown to reduce the frequency and severity of hospital medication errors when conducted by pharmacists [171].

In paper V, a number of discrepancies were identified, many of which could have resulted in patient harm. For example, in one person an incorrect digoxin dose was prescribed at admission to the ward (0.13 mg once per day instead of the correct dose 0.13 mg every second day). The transfer of information between health care settings in Sweden needs to improve to enhance patient safety. However, in the county of Västerbotten, primary and hospital care use the same electronic medical record system, making it possible to see patients’ drug lists from different health care settings. Surely, this is an important step forward for improved patient security and drug treatment.
Clinical Pharmacy Services

The value of adding the competence of a clinical pharmacist to a health care team has been discussed and studied over the years. Paper III showed an improvement in the quality of drug prescribing after a clinical pharmacist intervention, and many studies support the results of the present thesis [172-175]. Today, there is good evidence that medication reviews improve drug prescribing by reducing polypharmacy and use of inappropriate drugs, for example [176]. However, there is less evidence for the effectiveness of clinical pharmacist involvement when using clinical endpoints such as morbidity as outcome variables. Systematic reviews investigating pharmacists’ impact on clinical outcome in both inpatient and outpatient care are inconsistent. Some show positive effects [141, 145-148, 177] while other reviews found no effect of pharmacist intervention on mortality or hospital admission in older people [178]. The reason for the discordant results between the reviews may be related to heterogeneity in the study design. There is a wide variation in number of participants, whether the intervention is disease specific or cross-therapeutic, who is performing the interventions, and the way recommendations are conveyed to the physician in charge. Differences in acceptance rate, inclusion criteria, and intensity and type of interventions may also affect the efficacy of the intervention.

Acceptance rate and ways to communicate information

Given that recommendations from the clinical pharmacist are appropriate and clinical relevant for the patients, one important factor that may contribute to variable study results are acceptance rates and adherence to recommendations given by clinical pharmacists. In one recent study from Denmark investigating the impact of medication reviews performed by a pharmacist and a clinical pharmacologist in an orthopedic ward, ward physicians adopted approximately only 18% of the proposed amendments to drug therapy, and no effect was seen [179]. In that study, the pharmacist and clinical pharmacologist were not an integrated part of the orthopedic ward team. In contrast, in studies demonstrating higher adherence to drug recommendations, the persons performing the medication reviews had been part of a multi-professional health care team in the ward [180]. In our study, the acceptance rate was quite high, 82% of the recommended amendments to drug therapy were followed by the physician in charge. It is our conviction that it is important to participate in ward rounds and discuss the drug-related problems orally with the health care team since this enables a greater opportunity to explore the patients’ problems and needs. It is suggested that
indirect communication through written recommendations from a pharmacist to a clinician, in the absence of other forms of interactions, only have limited effect [176]. Close collaboration and interaction between the pharmacist and the prescriber is required for a successful intervention [106].

**Inclusion criteria**

Inclusion criteria differ between studies of the effects of clinical pharmacy services. As far as we know, our study is the first to include only persons with dementia or cognitive impairment. The proportion of hospital admissions that were drug-related (before any clinical pharmacist intervention) was high, 41% were judged caused or contributed by DRPs (paper IV). This compares to earlier reported prevalence numbers of about 30% among old people [7]. Old people, in particular old people with dementia, are especially vulnerable to ADEs [181]. However, a higher age alone may contribute to increased risk of adverse drug events. Therefore, this population, which has higher risk of ADE, may benefit more from medication reviews than other populations. Except for our study, also Gillespie et al [180] and Scullin et al [182] demonstrated the efficacy of pharmacist intervention in decreasing drug-related readmissions/ readmissions in a population of patients at high risk for adverse drug events.

Another factor that could explain differences in results between the studies is whether the studies were disease-specific or not. Studies involving clinical pharmacists have been performed among people with a variety of disease states, including hypertension, diabetes mellitus, hyperlipidemia, and anticoagulation therapy [141, 144]. In paper V, only patients with dementia or cognitive impairment were included regardless of co-morbidities. Of note, only effects on 30-day readmissions were seen in patients with heart failure, but no effect of the pharmacist intervention was observed when evaluating the total follow-up time of 180 days. However, other studies including a clinical pharmacist as part of a multidisciplinary heart failure team showed positive effects on hospitalization rates [177, 183]. Why the results differ is unclear, but one important difference is that all patients in our study suffered from cognitive impairment, which might have influenced compliance [49]. Non-compliance is a common cause of hospitalization, particularly in patients with heart failure. Patient education is a very important component of effective drug management of disease [184, 185]. In the studies described above, patient education and adherence aids were an integrative part of the clinical pharmacists’ intervention, and positive outcomes may be attributed to both personal meetings with the patient and
the clinical pharmacists’ help to ensure heart failure medications were properly titrated up to the high-dose targets supported by guidelines.

**Type of intervention**

The type and intensity of an intervention will conceivably influence achievable outcomes. In a recent review from the Cochrane collaboration investigating the impact of medication reviews, one out of five studies included used the STOPP/START criteria to analyze medication lists [186, 187]. As discussed earlier, a comprehensive medication review takes a much broader approach. A study recently showed that the majority of drug-related problems identified by a pharmacist were not related to STOPP/START criteria [188]. In our study, the intervention consisted of medication reconciliation combined with a comprehensive medication review. The clinical pharmacist had full access to medical records and laboratory data, which is a requirement for a thorough medication review. In one meta-analysis the clinical pharmacists did not have access to patient medical records in some of the included studies [178], which may have hampered the ability to conduct a thorough and complete medication review. Besides medication reconciliations and comprehensive medication reviews, Scullin et al in addition conducted patient interviews as part of the intervention and reported a large benefit of the pharmacist’s intervention. For example, patient readmission and time to readmission were significantly reduced [182]. Since the study population in paper V suffered from dementia or cognitive impairment, patient interviews were not conducted. The results may have been even better if a patient contact had been possible, since drug-related problems are often revealed through patient interviews [189]. In the hindsight interviews with relatives of the patient might have been performed. Further research is warranted to investigate the effectiveness of interviews with relatives in the subgroup of elderly with dementia or cognitive impairment.

**Impact of clinical pharmacist intervention on clinical outcome**

Numerous studies have been conducted to assess the impact of clinical pharmacist intervention with a large spectrum of different outcome measures. Intermediate measures such as patient adherence [190, 191] or quality of prescribing [173, 175] are commonly used. The idea of these measures is that patients’ clinical outcomes are probably affected. Therapeutic outcomes, for example blood pressure, cholesterol, and
hemoglobin seem to be more common in studies in for example the US, where the clinical pharmacists frequently participate in disease-specific services [144]. Hospitalizations and hospital readmissions are often used as proxies of patient morbidity [180, 192]. However, many other factors directly and indirectly influence hospitalization rates and are often an indicator of “the progression of disease rather than discrete outcomes of care” [193]. This makes the use of proxies as outcome measures problematic. It is assumed that the majority of avoidable readmissions occurs within the first month of discharge [194]. Of note, paper V demonstrated that the participation of a clinical pharmacist in a ward team significantly reduced the risk of drug-related readmissions within 30 days, and also after 180 days after adjustment for heart failure. Although the most relevant measure to assess the effects of clinical pharmacist intervention is still unclear, we argue that drug-related readmissions might be one of the best measures for clinical pharmacist interventions, due to its relative specificity to drug-related problems.
METHODOLOGICAL CONSIDERATIONS

In papers I and II we used a cohort design to investigate long-term use of psychotropic drugs. In papers III and IV we used a cross-sectional design. Observational studies such as cohort or cross-sectional studies have strengths and weaknesses. One major weakness with these types of studies is the limited ability to draw conclusions about cause and effect. Consider, for example, the associations between psychotropic drugs and different behavioral and psychological symptoms found in papers I and II. These types of studies cannot determine whether the drugs were prescribed because of a particular symptom, or if the symptoms were a consequence of drug-treatment. Moreover, because of the non-randomized nature of observational studies, problems with selection bias and confounding effects may arise. On the other hand it is a strength of observational studies that they reflect the real world and how drugs actually are used. This is in contrast to RCTs that often build on highly selected populations of patients [195]. The physical restraint use study (papers I and II) includes people from 40 specialized care units in nine communities in northern Sweden. These specialized care units were not randomly selected. Of the 99 units that were contacted, those with the highest prevalence of physical restraint use were selected. This may have influenced the study outcomes. However, when antipsychotic use among this population was compared to other studies, the prevalence did not differ [124]. Likewise, no randomization process was performed in the AC2007 and AC2013 procedures. In these collections, data on all people living in nursing homes in the county of Västerbotten were gathered. To what extent the results from the county of Västerbotten can be applied to other parts of Sweden and other Western countries is not known, but similar trends in inappropriate prescribing have been described in other populations. Medication reviews in paper III were performed in nursing homes that actively requested them, and this may have cause a selection bias. Care units or individual residents may have been selected for a medication review on the basis of already existing drug-related problems. The higher prevalence of antipsychotic prescribing among those who had received a drug review is one indication of such a selection bias.

In paper V we used a RCT design, which is considered the method with the highest scientific strength of evidence in intervention research [196]. However, intervention and control patients were recruited and randomized from all wards, which may have introduced the risk of contamination bias. The prescribing physician and the clinical pharmacist discussed DRPs of all patients in the intervention group. However, after medication reviews, physicians may have applied the increased knowledge to control patients as
well. Also, clinical pharmacists had been working in all study wards for as long as eight years, increasing risk of underestimating the true intervention effect.

**STUDY POPULATION AND PARTICIPATION RATES**

The AC2007 and AC2013 materials used in paper III included the total populations of old people living in nursing homes in the county of Västerbotten, although the definition differs slightly between the years. In 2013, no hospital wards were included. People in hospital wards in 2007 were therefore excluded (99 persons). Some demographic differences were seen between the years in the study populations in paper III. This was accounted for by including sex, age, level of cognitive impairment, and level of ADL dependency in the logistic regression analysis. The response rate was lower in 2013 than in 2007, 70.5% compared to 85.8%, although both are considered high participation rates. This may be due to the fact that staff filled in the questionnaires, not the residents. Why the response rate was lower in 2013 is unclear.

In papers IV and V, eligible patients were aged 65 years or older suffering from dementia or cognitive impairment. Dementia diagnoses were collected from medical records. We did not perform any tests as MMSE or other to assess whether the persons were suffering from cognitive impairment or not. People were considered to have cognitive impairment if sufficient information in the medical record was noted before the present hospitalization. This procedure was chosen to avoid the risk of including persons without dementia who had developed a delirious/confusional state during the hospital stay and therefore would score low on a MMSE.

**PROCEDURES**

*Multi-Dimensional Dementia Assessment Scale*

In paper I, II and III, the MDDAS was used to make assessments. The MDDAS has been found to have a good inter- and intra-rater reliability [153]. Apart from the initial reliability measurement, no other quality assessments have been done. Alternative instruments such as the BEHAVE-AD or the NPI-NH could have been considered. However, the MDDAS consists of easily observable behaviors and symptoms and does not require advanced education to be understood. The instrument was originally
developed for these particular studies and has produced predictable and stable results (factor structure, for example) over the years. Another strength of the instrument is that the research group has extensive experience with it, as the same behavioral items and other parts of the MDDAS have been applied since 1975. This also makes it possible to compare data over the years. The quality of recorded data is generally good, based on the high response rates and how the research group judged the quality of the collected MDDAS forms, which, in general, were carefully answered. The BPSD scale and ADL scales are presented in Appendix 1 and 2, respectively.

**Gottfries’ cognitive scale**

In paper I, II and III, cognitive impairment was measured using the scale developed by Gottfries and Gottfries [154, 155]. This scale has been validated against the MMSE cut-off [156]. One of the advantages of using Gottfries’ cognitive scale is that no specific education of staff members is required. Also, no testing or involvement of the resident is required. A comparison between the Gottfries’ cognitive scale and the MMSE indicated that Gottfries’ scale gives a more equal distribution over the scale and also seem to have a smaller floor effect, compared to the MMSE, which is advantageous [197]. The Gottfries’ cognitive scale is presented in Appendix 3.

**Data on drug utilization**

In papers I, II, and III drug data were gathered as part of the MDDAS, often by attaching a copy of the drug list. These data were then grouped and coded by members of the research team. This procedure ensures good quality of drug data. Only ongoing medication was presented in studies I, II, and III, except in the medication review material in paper III, where *pro re nata* was also collected. In Sweden the majority of antipsychotics are not prescribed as *pro re nata*. One study (Brännström J et al, unpublished data) showed that less than 5% of the antipsychotic were *pro re nata* prescriptions. However, other *pro re nata* drugs such as sedatives are used to a somewhat greater extent. A problem though with collecting *pro re nata* drug data in this type of questionnaire study, is that even if we knew what kind of drug the patient was prescribed *pro re nata*, we would normally not have any data on what had actually been given. The number of dosing events may vary greatly, between never and every day. In paper III, the drug use between year 2007 and 2013 was compared. Based on our experiences from working in nursing homes we have not seen any changes in how *pro re nata* drugs have been
used in recent years. Drug use was measured in the same way in both years and may be assumed comparable to each other. In paper IV and V information about both ongoing and pro re nata drug data were collected.

Quality indicators

In papers III we included the use of antipsychotic drugs and NSAID, classified as drug classes where correct and current indication is of particular importance as a quality indicator, although we did not have access to the indications for prescribing these drugs. In some patients, prescription of these drugs may have been medically well motivated and valid, but since these drugs are associated with many side effects and because they are included in the list of quality indicators highlighted by the Swedish government, we chose to include them. As a result, application of these strict criteria for inappropriate drug use may have resulted in classification of certain drug prescriptions as potentially inappropriate even though medically well motivated. For example, drugs belonging to the antipsychotic drugs might be appropriate for some indications.

Clinical pharmacists interventions

Achieving patient safety in health care requires clinical pharmacy skills higher than those acquired during basic training. The three clinical pharmacists who performed the interventions in paper V had all passed postgraduate courses in clinical pharmacy and had extensive experience performing medication reviews. We believe that pharmacists who have passed certified postgraduate courses in clinical pharmacy are well prepared to meet the specific challenges of clinical pharmacy work in primary care and in hospital care and that the three clinical pharmacists that performed the interventions in the study are representative of clinical pharmacists with these qualifications. Some of the discrepancies in the effects of clinical pharmacist intervention in the present work and earlier published [198] may be attributed to the fact the clinical pharmacists who performed the intervention in the present work were experienced. At least the work of Wallerstedt et al. indicates that involvement of inexperienced pharmacists without postgraduate education is not (cost-) effective [199].

All three clinical pharmacists had been working at the selected study wards before the study started, one for as long as eight years. This together with the fact that patients from the same wards were randomized to the intervention
and the control group may have caused a risk of contamination bias as already mentioned earlier. It is possible that the intervention would have had a stronger impact on readmission rates if carried out in a ward without previous involvement of clinical pharmacists and if the intervention and control patients had been recruited from different wards. On the other hand, the acceptance rates at wards unacquainted with clinical pharmacist services might have been lower. Still, the design of the present study reflects a real-life setting and shows that the intervention had an effect, even though the clinical pharmacists had been working at the selected wards before the study started.

The intervention in paper V consisted of medication reconciliation, medication review and discussion of clinical relevant DRPs in ward rounds. We did, however, not evaluate if the DRPs identified by the clinical pharmacists were clinically relevant and significant. However, based on the high acceptance rate (82%) it is reasonable to assume that most of the DRPs were judged to be clinically relevant by the physician in charge. Further, we did not specifically evaluate if the medication reviews were performed in a uniform manner between three clinical pharmacists. However, the clinical pharmacists performed structured medication reviews according to a standardized form. This, together with the fact that the three clinical pharmacists regularly met throughout the study period and discussed the interventions, makes it reasonable to assume that medication reviews were performed similarly at all study wards.

**ASSESSMENT OF DRUG-RELATEDNESS**

In papers IV and V, the primary outcome, drug-related admissions/readmissions, was not an objective measure. What qualifies as a drug-related outcome is, to some extent, subjective, and there will always be cases that are more and less clear. Different experts will judge a certain admission differently, as to whether a certain drug has or has not contributed. Falls are one example of events that are difficult to decide whether drugs contributed, as there are often several predisposing and precipitating factors for a fall. However, in other cases, such as bleeding after too high doses of anticoagulants, the causality is easier to assess. Different experts might have come to conclusions deviating from our experts. However, to capture all aspects of DRPs, three experienced and competent individuals with different and complimentary professional backgrounds comprised the expert group in paper V. In contrast, in paper IV only one profession participated. Involving a physician in paper IV may have provided
a more comprehensive perspective of patients’ drug-related problems. Data related to each readmission were anonymized, and experts were blinded before analysis in paper V, but not so in paper IV. In paper IV, the proportion of hospital admissions that were drug-related was 41% (189/458), compared to 48% (68/141) seen in the control group in paper V.
CLINICAL IMPLICATIONS

Hospitalization rates due to drug-related problems among old people with dementia or cognitive impairment are high, and, even though the use of inappropriate drugs has declined in recent years, drug-related problems are still prevalent in this group of patients. Therefore, improvements in drug prescriptions to old people should be made. Indeed, many hospitalizations due to DRPs appear preventable.

Some of the found drug-related problems were due to noncompliance among the patients with dementia and cognitive impairment selected for this study. The problem is closely related to impaired cognitive function and is difficult to handle. Some hospitalizations were due to the fact that patients did not remember to take their drugs, were unwilling, or because they did not remember how to take them. It is a delicate issue to balance patients’ rights of self-determination and integrity against risks, including harming themselves and others and risks imposed by the drugs themselves. Insulin, for example, is a very potent medication that can be dangerous when used inappropriately. Among heart failure patients, issues such as the need to restrict liquid intake or self-adjust diuretic dosages can arise. These problems are not simple, but some steps could be taken to facilitate compliance. For example, individualizing and adjusting treatment to a patient’s ability to administer medications may help. Examples may include prescribing tablets that can be crushed for patients with swallowing problems and choosing nebulizers or pressurized metered dose inhalers instead of handheld devices, where problems with inhalation technique could arise. Involving relatives in patient care and discussions on appropriate drug use may also be necessary if coherent conversations with the patient are not possible. If there are no relatives who can be engaged in drug management, it must be ensured that home care services and district nurses get involved in patient care as soon as possible after discharge.

Problems related to inappropriate prescribing and inappropriate use of drugs must be reduced, and this is already in progress. Continuous education and information to prescribers and other health care professionals about appropriate drug use must be sustained and extended. Still, even appropriate drug treatment may lead to adverse drug reactions and events. In these cases, it would be desirable to identify patients at special risk of drug-related problems in advance and pay special attention to these individuals in outpatient care to prevent early readmissions. Since people with dementia are extremely vulnerable to drug reactions, a continuous chain of care and thorough follow-up is essential. To improve patient safety, transitional care
management is crucial. Unfortunately, transition of care is a well-known weakness in most health care systems [200]. To address this issue, complex interventions conducted in collaboration between different health care providers in secondary and primary care may be needed.

There is a potential for further development of clinical pharmacy services. Presently, the service has not yet developed effective methods of communication between hospital and primary care to ensure that communication of changes made to drug therapy and planned follow-up activities reaches all staff categories involved in patient care. Some of these problems are not suitable to be solved during short-term hospital stays, and it would be desirable that strategies for "long-term" drug management could be communicated to all involved health care providers more efficiently. Clinical pharmacists could play a more active role in patient follow-up, ensuring that amendments to drug therapy determined during the hospital stay are adhered to, monitored, and that patients are following the instructions. Continuous follow-up strategies could prevent avoidable hospital readmissions. In the future, clinical pharmacists could play an important integrative role between hospital and primary care, and could thus serve as an important link in the chain of care to safeguard drug therapy in old people with dementia.
FUTURE RESEARCH

Awareness of the factual use of psychotropic drugs and potentially inappropriate drug use including frequency, treatment duration and doses among people with dementia and cognitive impairment is crucial. Accordingly, it is important to continue studying the use of these drugs, design appropriate cross-sectional and cohort studies, and to find strategies and methods to improve compliance. An important, related research question is whether the rate of drug-related hospital admissions will remain high in this population or whether it might be possible to find strategies that could reduce the number of these potentially preventable admissions. Although clinical pharmacists intervention had no impact among people with heart failure, the severity of disease has major effects on readmissions, and, in this subgroup of patients, even optimized drug therapy may not avoid early readmissions, and frequent readmission may indeed be necessary to cope with the severity of the condition. It would be of interest to investigate whether certain modifications of the intervention could reduce early readmissions in this group of patients. Such a study would probably demand more complex interventions and require additional external support. For example, involving relatives in patient care and discussions on the patients' drug use could be necessary, and regular monitoring of certain data, e.g. body weight, or telephone consulting to improve compliance, may be a prerequisite for prevention of early readmissions. Also, continuous follow-up after discharge and a more advanced chain of care in connection with transitions between hospital care, primary care, and the patient's family would be desirable.

The clinical pharmacists intervention had an impact on 30-day drug-related readmissions for all people, and also within 180 days of follow-up, except in patients with concomitant heart failure. To summarize, in our opinion, the key factors contributing to the positive effect of adding a clinical pharmacist were: (1) DRPs were discussed face-to-face with the physician in charge and other personnel of the health care team. (2) The acceptance rate was high, probably due to face-to-face discussion and the fact that all participating clinical pharmacists were already established and respected members of the ward teams and acknowledged by the health care team before the study started. (3) Experienced clinical pharmacists with postgraduate education and long practical experience of clinical pharmacy performed the interventions. (4) Medication reconciliations and comprehensive medication reviews were performed individually for every person in the intervention group, with full access to medical records and laboratory data. (5) The clinical pharmacist monitored patients throughout the hospital stay. We
believe these factors were essential for the efficacy of the intervention and should be considered when designing new studies.
CONCLUSION

Drug-related problems represent a major challenge for pharmacotherapy of old people with dementia and cognitive impairment, a group of patients who are especially vulnerable to adverse drug events. People with dementia are at high risk of being prescribed antipsychotic and other psychotropic drugs. Indeed, the results of the work described in this thesis indicate that antipsychotic and other psychotropic drugs are prescribed to treat behavioral and psychological symptoms among cognitively impaired individuals despite their ineffectiveness and warnings. Moreover, problems associated with drug treatment are a contributing factor to a large proportion of hospital admissions among old people. No single action can solve the issue of non-optimal drug therapy resulting in unnecessary hospitalization of the elderly. Several actions at different levels are needed to cope with this situation, one of them being closer coordination between health care providers. We found that adding the competence of a clinical pharmacist to the health care team could significantly reduce the risk of drug-related 180-day readmissions. However, in a subset of patients with concomitant heart failure no effect was seen. This thesis therefore indicates that clinical pharmacist contribution in health care teams may help optimize drug therapy among old people with dementia or cognitive impairment and might be an important strategy for improving their care.
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REFERENCES


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APPENDIX

APPENDIX 1, *The Multi-Dimensional Dementia Assessment Scale, Behavioral and Psychological Symptoms*, including English translation

APPENDIX 2, *The Multi-Dimensional Dementia Assessment Scale, The activities of daily living (ADL) scale*, including English translation

APPENDIX 3, *The Gottfries’ Cognitive Scale, including English translation*