MEDICATION-RELATED PROBLEMS AND PSYCHOTROPIC DRUG USE IN VULNERABLE OLDER POPULATIONS

a focus on acute hospital admissions and cognitive impairment

Jonas Kindstedt
The brain is a kind of time machine — you can travel back and forth in time by simply thinking

Judith Kindstedt, four years old
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Abstract

The ageing process involves several physiological changes that affect both pharmacodynamics and pharmacokinetics and that, in combination with a heavier disease burden and more extensive use of medicines, put older people at higher risk of medication-related problems and associated clinical outcomes. The older population is often treated as a homogenous group, when in fact there are factors that render certain individuals more vulnerable to adverse drug effects and other types of medication-related problems. Older people encountered in the acute medical care setting and/or individuals with varying degrees of cognitive impairment are especially vulnerable in that context.

The overall aim of this thesis was to describe and understand medication use in certain vulnerable subgroups of older people, which in turn might identify suitable target populations in which medication-related problems can be prevented or managed through interventions or similar efforts.

Paper I presented, in the form of a study protocol, a clinical pharmacist intervention intended to reduce the risk of medication-related readmission to hospital among people aged 75 years or older during transitions of care. Based on 300 participants from the intervention study, approximately 50% had been readmitted to hospital within 180 days of being discharged from the hospital. Both heart failure and cognitive impairment, the latter identified through a four-item test, were predictors of early readmission. Altogether, the study population seems relevant for the purpose of the intervention; whether the intervention model is effective remains to be determined.

Based on the same sample of study participants, paper II found that approximately one third of the 300 index hospital admissions were possibly medication related. Moreover, possibly medication-related hospital admissions were negatively associated with the fewest positive/correct answers on the four-item screening tool for cognitive impairment, which suggests that those clinical events might be less prevalent among people with cognitive impairment when exploring the association cross-sectionally.

Both papers III and IV were registry-based studies, and their overall objective can be summarized as to describe psychotropic drug use and associated factors among older people with major neurocognitive disorder (NCD). Paper III focused on differences between major NCD subtypes,
whereas paper IV compared people with major NCD against matched references from the total older population.

In brief, overall psychotropic drug use was notably higher among people with major NCD, although generally in line with national treatment guidelines in terms of individual drugs of choice. The use of hypnotic drugs was also extensive in the reference group, and deprescribing efforts seem warranted, although longitudinal studies that focus on long-term use could provide a better picture of the potential problem.

Nursing home stay was also positively associated with psychotropic drug use for all classes of psychotropic drugs, and the difference was most prominent for antipsychotic drugs. In that context, over 1,200 people in the reference population, most of them nursing home residents, had filled prescriptions for antipsychotic drugs, a figure indicating that the management of neuropsychiatric symptoms might also be an issue among older people who, due to various circumstances, have not been examined and diagnosed with neurocognitive disorders.

Regarding major NCD subtypes, individuals with Lewy body dementia had, except for antidementia drugs, higher odds of psychotropic drug use than did those with Alzheimer’s disease. For example, the odds of antipsychotic drug use were more than twice as high, which is a worrying figure given that people with Lewy body dementia are extremely sensitive to the adverse effects of those specific drugs.

In conclusion, this thesis illustrates the heterogeneity of demographics and drug use among older people and indicates that certain types of medication-related problems may be more relevant in certain older subpopulations. Medicines appear to be involved in many hospital admissions of older people, and the acute medical setting and subsequent care transitions are likely an important focus of pharmaceutical interventions. However, psychotropic drugs are probably not a major issue in that specific context. Efforts to reduce psychotropic drug use are likely more relevant to people with major NCD, especially in the nursing home setting. Antipsychotic drug exposure among persons with Lewy body dementia could be one such focus, especially since there are other better-balanced pharmacological treatment options for these individuals in terms of efficacy and safety profile.

Key words: older people, cognitive impairment, medication-related problems, psychotropic drugs
Original papers

This thesis is based on the following scientific papers and preliminary results:


The original papers are reproduced with the permission of their respective publishers and will henceforth be referred to by their Roman numerals.
# Abbreviations, acronyms and definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AChEIs</td>
<td>Acetylcholinesterase inhibitors</td>
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<tr>
<td>ACT system</td>
<td>Anatomical Chemical Therapeutic system</td>
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<td>AD</td>
<td>Alzheimer’s disease</td>
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<td>ADR</td>
<td>Adverse drug reaction</td>
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<td>AT-HARM-10</td>
<td>Assessment Tool for Hospital Admissions Related to Medications</td>
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<tr>
<td>BZD</td>
<td>Benzodiazepine</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>COVID-19</td>
<td>Coronavirus disease 19</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<td>DLB</td>
<td>Dementia with Lewy bodies</td>
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<tr>
<td>DSM-5</td>
<td><em>Diagnostic and Statistical Manual of Mental Disorders</em>, fifth edition</td>
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<tr>
<td>GABA</td>
<td>Gamma-aminobutyric acid</td>
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<tr>
<td>GEE</td>
<td>Generalized estimating equation</td>
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<tr>
<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>ICD</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
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<td>LBD</td>
<td>Lewy body dementia (i.e. dementia with Lewy bodies or Parkinson’s disease dementia)</td>
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<td>MMSE</td>
<td>Mini-Mental State Examination</td>
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<td>MRA</td>
<td>Medication-related hospital admission</td>
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<td>MRP</td>
<td>Medication-related problem</td>
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<td>NBHW</td>
<td>Swedish National Board of Health and Welfare</td>
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<td>NCD</td>
<td>Neurocognitive disorder</td>
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<td>NPS</td>
<td>Neuropsychiatric symptoms</td>
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<td>OR</td>
<td>Odds ratio</td>
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<td>PDD</td>
<td>Parkinson’s disease dementia</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
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<tr>
<td>SveDem</td>
<td>Swedish registry for cognitive/dementia disorders</td>
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<tr>
<td>VaD</td>
<td>Vascular dementia</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>Z-drugs</td>
<td>Umbrella term for zopiclone and zolpidem</td>
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Sammanfattning

Åldrandet medför flera fysiologiska förändringar, som påverkar både farmakodynamiska och farmakokinetiska aspekter av läkemedelsbehandling. Äldre har dessutom högre sjukdomsförekomst och mer utbredd läkemedelsanvändning. Därmed blir risken mer påtaglig för läkemedelsrelaterade problem och dess kliniska konsekvenser.

Den äldre populationen betraktas ofta, felaktigt, som en homogen grupp, trots att det finns faktorer som gör vissa individer mer sårbara för biverkningar. Det gäller särskilt patienter som vårdas akut och personer med kognitiv nedsättning.

Det primära syftet med denna studie var att beskriva och förstå läkemedelsanvändning och relaterade problem i populationer av sårbara äldre personer, med fokus på akuta sjukhusinläggningar och kognitiv svikt, för att kunna identifiera lämpliga målpopulationer för interventioner ämnade att förebygga och hantera läkemedelsrelaterade problem.

I det första delarbetet presenterades, i form av ett studieprotokoll, en farmaceutisk intervention som rör vårdöverföring och kliniska apotekare, och som är utformad för att minska risken för läkemedelsrelaterad återinläggning på sjukhus, för patienter 75 år eller äldre i vårdöverföringsfasen mellan sjukhus och primärvård.


Det finns således indikationer på att studiepopulationen är relevant för interventionens syfte, samt att hjärtsvikt och kognitiv nedsättning är viktiga prognostiska faktorer som ökar risken för återinläggning. Det återstår att avgöra om interventionen i slutändan kan minska risken för läkemedelsrelaterad återinläggning.

I det andra delarbetet om samma urval av akut inlagda patienter klassades 108 av de 300 indexinläggningarna som möjliga läkemedelsorsakade. Dessa inläggningar var negativt associerade med kognitiv nedsättning. Detta indikerar alltså att läkemedelsorsakade sjukhusinläggningar är
ovanligare bland personer med kognitiv nedsättning, när man undersöker sambandet ur ett tvärsnittsperspektiv.

Det tredje och fjärde delarbetet var registerbaserade tvärsnittsstudier med syfte att beskriva hur användningen av psykofarmaka ser ut bland äldre personer med kognitiva sjukdomar, även kallade demenssjukdomar, och vilka faktorer som är associerade till denna läkemedelsanvändning. Dels jämfördes psykofarmakaanvändningen vid olika kognitiva sjukdomar, dels i relation till användning av psykofarmaka hos matchade referenspersoner från totalbefolkningsregistret som saknade uppgift om sådan diagnos.

Användningen av psykofarmaka var betydligt högre bland personerna med kognitiva sjukdomar än bland referenspersonerna, men låg i linje med nationella riktlinjer för läkemedelsbehandling av äldre individer. Andelen äldre personer som hade hämtat ut sömnmedel var dock oroendeväckande hög i både studiepopulationen och referenspopulationen. Det förefaller relevant att vidta åtgärder för att minska denna breda förskrivning av sömnläkemedel. Longitudinella studier skulle ge en mer komplett bild av problemets omfattning i form av långtidsbruk.

Särskild boendeform var starkt positivt associerad med användning av alla klasser av psykofarmaka. Den största skillnaden fanns för antipsykotiska läkemedel. Det bör nämnas att det även i referenspopulationen var många som hade hämtat ut antipsykotiska läkemedel – fler än 1 200 individer. Detta kan indikera att dessa potentiellt riskfyllda läkemedel skrivs ut till personer som har kognitiv nedsättning eller påtagliga neuropsychiatriska symptom, men utan att de formellt har utretts och diagnostiserats med demenssjukdom.

En jämförelse mellan olika kognitiva sjukdomar visade att personer med Lewy body demens med högre sannolikhet använder psykofarmaka. Exempelvis har de mer än två gånger högre odds för användning av antipsykotiska preparat jämfört med personer med Alzheimers sjukdom. Detta resultat är mycket oroande, eftersom personer med Lewy body demens är särskilt känsliga för biverkningar av antipsykotiska läkemedel.

Sammantaget visar delarbetena att sårbara äldre är en långt ifrån homogen grupp. Likaså skiljer sig potentiella läkemedelsrelaterade problem som kan uppstå, och hur de bör angripas, på faktorer som boendeform och kognitiv nedsättning.
Läkemedel förefaller vara involverade i många sjukhusinläggningar av äldre personer. Den akuta vården, och den efterföljande vårdöverföringen, är därför ett viktigt fokusområde för farmaceutiska interventioner.

Introduction

The prevalence of chronic diseases and use of medication increase considerably with age. Due to a variety of causes related to pharmacodynamics, pharmacokinetics, social situation and other clinical circumstances, older people are on average more vulnerable to the undesired effects of medicines than are younger individuals. A clear and updated picture of medication use and its potential problems is important for interventions and other strategies intended to increase patient safety by reducing hospital admissions and other undesired clinical outcomes.

This thesis primarily relates to the branches of clinical pharmacology, geriatric psychiatry and pharmacy, or to any other field that deals with understanding and optimizing drug use in vulnerable older populations. The first section clarifies concepts and terms that can have different meanings depending on context, but that are essential when interpreting the results. Thereafter follows an overview of old age in relation to cognitive decline and neuropsychiatric manifestations, since cognitive impairment is a common denominator of all papers included in this thesis. The next section of the introduction depicts the settings where the studies were conducted and to which the results can primarily be generalized. The field of clinical pharmacy is also specifically addressed. Although many different professions are involved in optimizing medication use, understanding the concept of clinical pharmacy provides a better understanding of the intervention model described in paper I. In the final section, there are basic presentations of each psychotropic drug class targeted in this thesis and summaries of their associated risks for older people, individuals with cognitive impairment in particular. That section, depending on the reader’s prior medical knowledge, may not be necessary for interpreting the findings presented and discussed later.

Terminology and definitions

Older people

This thesis targets the use of medication and associated problems among vulnerable older people. Therefore, it is essential to immediately clarify the criteria for being considered older or elderly, concepts frequently defined in the scientific literature. First, the word elderly might be considered a somewhat ageist and misleading stereotype that groups relatively fit and independent individuals together with multimorbid and
frail persons [1]. That term is therefore generally avoided in this thesis in favour of older when describing the study populations, although elderly does occur in individual papers. Age can both be measured in terms of birth years (i.e. chronological age) and estimated through biological markers, which are affected by various factors related to lifestyle and health [2]. The number of birth years is therefore, as shown in Figure 1, not always representative of physical condition, mental state and overall functional capacity. In this thesis, the term older people applies to people aged 65 years or above, a standard definition in research and among Swedish authorities [3-5]. A common denominator of the study populations in focus here is that they present additional characteristics, in terms of hospital admissions and/or cognitive impairment, that in various ways might affect their overall risk and vulnerability to the undesired effects of drugs.

![Figure 1. The continuum of the ageing process. Ageing is in many circumstances better interpreted from the perspective of health and functional capacity rather than chronological age. The circled individuals represent those primarily in focus of this thesis. The illustration was inspired by a figure describing the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale [6].)](image)

**Drugs, medicines and medications**

The terms drugs, medicines and medications are used synonymously throughout this thesis. They all refer to any licensed chemical substance with pharmacological properties that is used in health care to treat, cure, prevent or diagnose disease, or by other means enhance the mental or physical health of the individual; any form of illegal drug use is not included in this definition. To emphasize that some issues could be due to administration difficulties or other practical barriers rather than to unwanted pharmacologic effects, the term medication-related problem (MRP) is generally preferred to drug-related problem throughout this thesis, although the latter will likely be relevant from the long-term
perspective. Still, the term drug-related does occur frequently in paper I, where it has the same meaning as medication-related.

**Medication-related problems**

A drug-related problem has been defined by Strand et al. as ‘an undesired patient experience that involves drug therapy and that actually or potentially interferes with a desired patient outcome’ [7]. A similar description was proposed by the Pharmaceutical Care Network Europe: ‘A Drug-Related Problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes’ [8]. The concept of MRPs should therefore be interpreted according to the definitions above. Thus far, there has been little consensus on a universal classification system for MRPs. A comparison of classification tools revealed that few systems had ever been validated, but that the Pharmaceutical Care Network Europe (version 4.0) classification came closest to meeting the specified requirements of an optimal system [9]. Another common classification system is the one of Strand et al. which is structured into fewer and broader categories of MRPs [7]. Given the definitions outlined above, MRPs comprise a plethora of different medication-related issues, for example, orthostatic blood pressure from hypertensive medicines, failure to notice the need of diuretics in symptomatic heart failure (HF), infections following immunosuppressive treatment with corticosteroids and increased risk of gastrointestinal bleeding due to drug interactions.

Three other important terms that are related to the MRP definition but that still have their own distinct meanings are medication errors, adverse drug events (ADEs) and adverse drug reactions (ADRs). A medication error can be defined as ‘a failure in the treatment process that leads to, or has the potential to lead to, harm to the patient’ [10]. Hence, they can be regarded as preventable events that occur during the prescribing, dispensing or administration of medicines. According to the World Health Organization (WHO), an ADE is ‘any untoward experience that may present during treatment with a medicine but which does not necessarily have a causal relationship with this treatment’, whereas an ADR can defined as ‘a response to a medicine which is noxious and unintended, and which occur at doses normally used in man’ [11]. Hence, all ADRs can be considered ADEs, but the reverse is not always the case, since ADEs also encompass issues such as poor medication adherence and drug treatments that were already inappropriate when they were first initiated. In summary, the terms medication errors, ADEs and ADRs partly overlap one another and can in those cases always be viewed as typical examples of MRPs (Figure 2).
Figure 2. Explanation of medication-related problems and adverse events. Medication errors, adverse drug events, adverse drug reactions and medication-related problems partly overlap but can still be regarded as distinct concepts.

Medication-related hospital admissions

Medication-related hospital admissions (MRAs), including readmissions, are a major focus of this thesis. The term refers to unplanned events that are at least possibly medication related if no other degree of probability is specified. The concept of MRA does not necessarily imply that medication was the only suspected cause or that the MRA was even preventable, only that it was considered one of many possible factors contributing to hospital admission. For clarification, readmissions do not have to be related to the previous hospital admission in terms of causality or principal diagnoses; they are simply another non-elective hospital admission within a specified time period.

Prevalence and predictors of unplanned hospital admissions

Hospital admission is probably one of the most undesired health consequences resulting from MRPs and may be especially chaotic experiences from a patient perspective. Older people account for a disproportionately large number of hospital admissions and emergency department visits [12]. Although prevalence estimates vary considerably between different settings and populations [13], up to 30% of all unplanned hospital admissions might at least partly be attributed to ADRs [14, 15]. Furthermore, hospital admissions resulting from ADRs and other MRPs have been associated with higher costs, longer hospital stays and
higher mortality rates than admissions resulting from other causes [16]. Regarding more age-specific predictors of unplanned hospital admissions, a higher number of medicines increases the probability of all-cause admission and readmission in different older populations [17-19]. Multimorbidity [20] and old age itself [21] are other recognized risk factors for unplanned hospital admission. In that context, older people with a high co-morbidity index and receiving home care seem to be at higher risk of readmission [19]. Nevertheless, solely addressing the actual numbers of drugs and diseases oversimplifies the situation; the strength of the association between number of medicines and hospital admission is reduced in people with more underlying conditions [22]. Furthermore, some classes of drugs are more relevant than others when discussing polypharmacy. Opioids, psychotropics and cardiovascular drugs are apparently involved in many unplanned hospital admissions resulting from fall-related injuries [23, 24]. Among the social predictors of unplanned hospitalization, people with home care has been reported to be at higher risk of admission, and, according to the authors, possibly due to economic cutbacks that keep old frail individuals at home with support instead of in nursing homes or similar forms of institutional care [25]. Regarding cohabitation, unmarried status is another important circumstance that may increase the risk of hospital admissions [26], with a plausible explanation being that members of couples might encourage each other to seek medical help at an earlier stage [26].

Importantly, the principal or primary diagnoses of readmissions often differ from those documented at previous hospital admissions. However, in cases of progressive diseases (e.g. chronic obstructive pulmonary disorder or HF), seeking emergency care due to exacerbations of those conditions is associated with previous hospital admission due to similar causes within the last 30 days [27-29]. Hospitalizations due to HF have also been identified as among the most important modifiable risk factors of readmission within 30 and 180 days [27, 29]. Treatment of HF typically involves a multi-drug regime, including beta-receptor antagonists, drugs acting on the renin-angiotensin-aldosterone system, mineralocorticoid-receptor antagonists and loop diuretics, and poor adherence and infrequent weight monitoring can be devastating for patient outcome, even from a short-term perspective [27, 30, 31]. Despite these overall distressing figures, a crucial aspect of hospital admissions among older people is the evidence that many of the underlying MRPs seem to be preventable [32-34] and are therefore an interesting target for interventions.
Classifying medication-related hospital admissions

A difficult yet crucial methodological aspect of medication-related outcomes in research is how to properly assess and classify the causal link between an MRP and the clinical event of interest. One option is to rely on an expert group of clinicians to identify potential MRPs, preferably according to a validated classification system, and then agree on the probability of a causal association with the outcome. The likelihood of hospital admissions being medication-related can, for example, be judged using the WHO criteria for the causality assessment of ADRs [35]. These criteria, together with the application of a clinical expert group, can probably be considered a gold-standard method in clinical research [36-38]. Due to the difficulty of recruiting a clinical expertise group in combination with the time required for every assessment, other classification tools have been validated in recent years in hope of finding more feasible alternatives. One such example is the Assessment Tool for Hospital Admissions Related to Medications (AT-HARM10), which has been validated against the gold-standard method outlined above to be used by post-graduate or final-year-undergraduate pharmacy students for assessing MRAs in the context of older people [39].

Ageing, multimorbidity and polypharmacy

Over the last century, life expectancies have risen by approximately 30 years in Western Europe, North America and other developed countries [40]. In combination with lower fertility rates, advances in disease prevention and other health-related areas have inevitably resulted in a demographic shift towards an increasingly older population that entails significant challenges to modern society and its healthcare systems. Even in the absence of disease, several important physiological changes gradually emerge in the ageing human body [41]. For example, there is a progressive reduction in muscle tissue, body water and lean body mass, and the immune system gradually weakens and leaves the older individual more susceptible to infectious diseases.

From a pharmacological viewpoint, the reduced metabolic capacity of the liver and declining glomerular filtration rate are of particular clinical importance in older patients. There is also an increased sensitivity in the central nervous system (CNS) due to altered concentrations of important neurotransmitters, especially dopamine and acetylcholine. Because of those modifications in pharmacodynamics and pharmacokinetics, older people are on average much more susceptible to both desired and unwanted effects of drugs [42, 43]. In that respect, patients in geriatric
departments and acute medical care commonly exhibit the onset of various symptoms that do not fit single disease categories, so-called geriatric syndromes that are often multi-factorial and loosely defined. Urinary incontinence, dizziness, a tendency to fall, syncope, delirium and frailty are all typical examples of geriatric syndromes [44]. Frailty is a condition that should be distinguished from the gradual normal ageing process and can be viewed as either a classifiable phenotype due to an unknown underlying cause or an accumulation of multiple deficits that together affect the probability of frailty [45, 46]. Regardless of the interpretation model, frail geriatric patients are characterized by an impaired ability to maintain homeostatic balance and functional capacity following relatively small stressors (e.g. initiation of new drugs or drug alterations), often resulting in disproportionate and atypical deteriorations in health state, for example, in the form of postural instability or delirium. In brief, geriatric syndromes generally emerge in the upper half of the ageing continuum (Figure 1), and they demand the more targeted treatment of the individual rather than the management each diagnosis separately.

The age-progressive susceptibility to various diseases is also clearly reflected by the clinical presentation of multimorbidity in older people; for example, a Swedish study revealed that 55% of people older than 77 years were multimorbid, defined as having at least two chronic diseases [47]. Moreover, hypertension, dementia and HF where the most frequent conditions with prevalence estimates of 38%, 21% and 18%, respectively, and multimorbidity was significantly more common among the oldest-old (i.e. aged 85 years or older). The number of underlying conditions corresponds to an increased need for medications, and according to the Swedish National Board of Health and Welfare (NBHW), multimorbid older people take on average 7–12 different medicines [48]. Although the number itself does not necessarily confirm excessive or irrational prescribing, review data indicate correlations between the total number of medicines and various undesired outcomes comprising ADRs, poor adherence, hospitalizations, falls, increased healthcare costs and reduced functional capacity [49]. Polypharmacy is a common term in the context of older people and usually refers to the use of five or more different medicines [50], a definition that will henceforth be used in this thesis, unless explicitly stated otherwise. Given the susceptibility to adverse drug effects and the need for more comprehensive pharmacological treatment, an increasing number of medicines undoubtedly increases the need for the close monitoring and evaluation of each pharmacological treatment initiated in older people.
In summary, older people comprise a significant and rapidly growing proportion of the population, and numerous age-related physiological changes generally make them much more susceptible to illness and the undesired effects of medicines. The following sections describe different aspects of disease and medication use that make certain groups of older people especially vulnerable in that regard.

Neurocognitive disorders

Nomenclature and diagnostic classifications

Some cognitive changes are associated with the normal ageing process. In addition to an overall slower processing speed, there are measurable declines in several cognitive domains, such as new learning abilities, attention and executive functions (e.g. multi-tasking) [51, 52]. Many older individuals, however, present with a cognitive decline that is more pronounced than what could be expected from increasing age alone and will eventually meet the diagnostic criteria for a neurocognitive disorder (NCD), a progression visualized in Figure 3 using Alzheimer's disease (AD) as an example.

![Diagram showing the continuums of cognitive decline in Alzheimer's disease versus normal ageing. The figure is adapted from an illustration by Sperling et al. [53].](image)

*AD, Alzheimer's disease; NCD, Neurocognitive disorder*
The *Diagnostic and Statistical Manual of Mental Disorders* (DSM), developed by the American Psychiatric Association, provides diagnostic criteria regarding mental disorders and is commonly used worldwide in both research and clinical practice. In the fifth and most recent version (i.e. DSM-5), dementia was renamed major neurocognitive disorder (NCD), a collective noun that covers various age-progressive and neurodegenerative subtype disorders that negatively affect several important brain functions [54]. Furthermore, DSM-5 specifies six cognitive domains that could be affected in major NCD: complex attention, executive ability, learning and memory, language, perceptual–motor function and social cognition. A significant decline from a previous functional level, not attributable to delirium or other mental disorders, in at least one of these domains must be present for a diagnosis. In addition, the deficit must be of a severity that substantially interferes with independence in daily activities. The International Statistical Classification of Diseases and other Related Health Problems (ICD), which is endorsed by the WHO, has kept the term *dementia* in the most recent version (i.e. ICD-11) [55], but as the diagnostic criteria are similar between the two classification systems, the terms *dementia* and *major NCD* can generally be used interchangeably. Nevertheless, the more modern terminology in DSM-5 can be interpreted as a more proper description of the disorder. The term *major NCD* has consequently been applied in all papers included in this thesis and will as far as possible be used in preference to *dementia* from this point onwards.

Despite differences in terminology, both DSM-5 and ICD-11 outline classifiable subtypes based on the aetiology of the cognitive decline, for example, AD, Lewy body pathologies or neurovascular disease. The classification of subtypes requires additional criteria, but they are also similar between DSM-5 and ICD-11. Since Swedish healthcare applied diagnostic codes and nomenclature from ICD-10 for the periods during which the studies in this thesis were conducted, those codes and terminology were used for the major NCD subtypes presented and discussed here, even if they include the term *dementia*. Besides major NCD, DSM-5 recognizes a form of less severe cognitive impairment defined as mild NCD [54]. This diagnosis is based on the same cognitive domains as is major NCD but requires only a modest cognitive decline that does not interfere notably with activities of daily living. Milder forms of cognitive impairment can often stabilize, or even improve, but mild NCD is nonetheless a risk factor for developing major NCD later in life (AD in particular) [56] with an annual conversion rate to the more severe form of approximately 5–10% depending on the exact definitions of the disorders [57]. In summary, cognitive function in relation to older age can be
visualized as a non-linear curve that differs substantially between older individuals, for which reason it is crucial to distinguish between the natural signs and symptoms of ageing and clinical manifestations of NCDs when addressing these people within the confines of health care and research.

Epidemiology

The global population with major NCD has recently been suggested to be in the vicinity of 50 million people, a population expected to reach 150 million individuals by 2050 [58]. Moreover, the prevalence of major NCD increases rapidly with age, from around 1.5% in the 60–64-year age group to over 40% among patients 90 years or older [59]. In Sweden, there are probably around 130,000–150,000 people who theoretically would meet the diagnostic criteria for major NCD [60]. These persons make up around 8% of the older population; with an estimated yearly incidence of 20,000–25,000 individuals, the total number of people with major NCD is expected to double in Sweden over the next 30 years.

Among the subtypes of major NCD, AD is the most common form and is found in more than half of cases [59]. This particular neurodegenerative disorder is characterized by an insidious onset with a subsequent progressive cognitive decline that primarily affects episodic memory function [61]. The pathogenesis of AD is still not fully understood, and the pharmaceutical alternatives are mainly limited to disease-modifying drugs. Vascular pathologies, mainly different types of infarcts, are another distinguished subtype of major NCD. Vascular dementia (VaD) comprises approximately 15% of major NCD, although estimates vary substantially between different sources [62]. Importantly, many patients present clinical markers of both AD and VaD, which makes the interpretation of epidemiological data uncertain. Several disorders of varying aetiology and neuropathology account for the remaining subtypes of major NCD, for example, frontotemporal dementia and Lewy body dementia (LBD). The latter is an umbrella term for dementia with Lewy bodies (DLB), Parkinson’s disease dementia (PDD), two subtypes that share many pathological and clinical features.

Neuropsychiatric symptoms

Another problematic aspect of major NCD is the occurrence of several non-cognitive manifestations. This heterogeneous cluster of neuropsychiatric symptoms (NPS) occurs in approximately 90% of all patients with major NCD and usually develops concurrently with the cognitive decline [63]. Of note, the occurrence of NPS is not included
among the diagnostic criteria for major NCD (54). Despite the lack of a universal classification system, NPS are generally categorized into the affective disturbance, psychosis and hyperactivity groups [64-66], while apathy, depression, anxiety, aggression and agitation are common examples of individual symptoms [67-69]. The NPS typically begin and worsen simultaneously with the cognitive decline until the NPS eventually diminish in the last stage of disease progression [70]; still, as illustrated by Lövheim et al. [71], it must be underlined that relationships between different NPS and cognitive function can vary substantially, and the parabolic shape shown in Figure 4 should therefore only be regarded as illustrating a hypothetical average case.

Figure 4. The continuum of Alzheimer's disease regarding changes in cognitive function, activities of daily living and neuropsychiatric symptoms. The image is an interpretation of models presented by Gale et al. [72], Kikuchi et al. [73] and Lövheim et al. [71].

Treating NPS is complicated due to its wide range of manifestations and the high risk of potential side-effects; hence, non-pharmacological options should always be considered and ideally properly evaluated before proceeding with pharmacological alternatives [74, 75]. If pharmacotherapy is nonetheless warranted, the treatment should target the type of individual symptoms present. Selective serotonin reuptake inhibitors (SSRIs) as well as mirtazapine are recommended for many different manifestations, including both depressive and hyperactive
symptoms. According to the review literature, second-generation antipsychotics are, despite a problematic safety profile, an alternative in certain highly psychotic or hyperactive individuals [76]. A relatively safe and evidence-based alternative is antidementia drugs, which seem to have a modest effect on some NPS in addition to their benefit of relieving cognitive symptoms [77]. In summary, the diverse NPS are as clinically relevant as are the cognitive deficits, posing a challenge to treatment and causing severe hardship for both the afflicted individuals and their relatives or caregivers [78].

Aspects of depression and neurocognitive disorders in old age

Like major NCD, depression is a common burdening disorder in the older population. Strictly applying the DSM diagnostic criteria for major depression, reported point prevalence estimates were 4.4% and 2.7% among older females and males, respectively [79]. Similar epidemiological data have been reported in Swedish geriatric populations with prevalence estimates of 3.9% in the group of people without major NCD [80]. In the group with diagnosed major NCD, on the other hand, the prevalence of depression was as much as 11.8%. In addition, depressive symptoms can still be clinically relevant even if they do not meet all the criteria for major depression. For example, the prevalence of significant depressive symptoms in Alzheimer’s disease has been estimated at 40–50% during the first years following diagnosis [81, 82]; people with VaD or PDD are probably even more likely to experience depressive symptoms at some point during the course of the disease [83, 84].

Apart from the negative impact on the afflicted individual, both cognitive and depressive symptoms impose severe difficulties and demands on both relatives and society, and the relationship between depression and major NCD has been investigated from many different perspectives. In brief, people with early-life depression are at nearly two-fold risk of major NCD later in life [85, 86]; however, a causal relationship is uncertain [87]. Late-life depression, on the other hand, can in part be a prodromal feature of cognitive decline due to the high prevalence of depression in NCDs and the number of overlapping symptoms [88]. That hypothesis is further supported by an Australian study in which antidepressants did not appear to be a modifiable risk factor of major NCD [89]. Taken together, depression in major NCD is complex and can at least in theory be one or more of the following: 1) a risk factor with uncertain causality; 2) a prodrome, or at least sharing the same underlying pathology as major NCD; 3) a manifestation within the NPS spectrum; 4) a natural conscious reaction to and reflection of loss of cognitive function; or 5) simply just a
random concurrent disorder. Those uncertainties are very important to consider when investigating and evaluating antidepressant drug use among older people since they often exhibit both depressive symptoms and varying degrees of cognitive impairment.

Transitional care

Older people frequently undergo relocations between clinical wards, from hospital to home/nursing home or vice versa, as well as other transfers of patient care management from one healthcare provider to another. These events are commonly referred to as transitions of care, whereas the related concept of ‘transitional care’ describes the measures taken to ensure the continuity of health care and patient safety during such transfers. There has been an emerging focus on transitional care since one in five patients, probably even more in the subgroup of older people, are readmitted within the first month following hospital discharge [90], and the importance of successful care transitions has been emphasized by the WHO as a key area for improving patient safety [91]. Care failures during transitions between care providers might be due to several factors, for example, limited training of clinicians, poor communication between healthcare teams, and patients and/or caregivers who are unable or unprepared to assimilate all the information required for the successful continuation of treatment at home; notably, cognitively impaired individuals appear to be at particular risk of such care failures [92]. In addition, many patients have home health care or similar services, while others rely heavily on cohabitants or other relatives to manage their medication and overall care; hence, there are often several actors involved in a care transition, and the need for research on how to optimize these transfers has received more attention in the last decade. Although medication reconciliations, medication reviews, telephone follow-ups and other intervention strategies have shown promising results in individual studies, a more complex and multi-faceted approach is likely needed to reduce readmission rates [93, 94]. Considering the background of MRAs among older people, an increased focus on counselling and on the management of MRPs early in the transition phase from hospital to home and primary care might prevent or delay readmissions in vulnerable subgroups of older people.

In Sweden, the healthcare system is decentralized, which means that it is administered by regions, and to some extent municipalities in the cases of home health care and care in nursing homes. In addition, there are also private healthcare providers, most of which are affiliated with regional councils. As a result, there can be notable differences from one region to
another in how health care is planned and delivered. All study participants in papers I and II were from Region Västerbotten, which is the main tax-funded healthcare provider in the Swedish county of Västerbotten. All specialized and primary care providers mandated by Region Västerbotten use the same electronic medical chart system, so any alterations of the list of medicines during hospital stay are visible to primary care staff and, vice versa, any such alterations made in primary care are visible to hospital-based specialists. Dose dispensing of medicines is carried out through a separate system (Pascal), but any changes made are replicated in the official list of medicines. In brief, the acute medical ward at Umeå University Hospital typically provides care for internal medicine patients admitted via the emergency care unit. Many patients are older individuals in need of rehabilitation and are therefore transferred to the geriatric ward before leaving the hospital. The patients are also given a written summary of their hospital stay, including medication alterations. Follow-up is carried out at either the medical centre or the primary care centre where the patient is listed.

Clinical pharmacy

Clinical pharmacy has been described by the American College of Clinical Pharmacy as ‘that area of pharmacy concerned with the science and practice of rational medication use’ [95]. The European Society of Clinical Pharmacy has a more detailed description [96] emphasizing that these activities are not limited to the hospital setting. The term clinical, in this case, instead refers to patient health, and the involved activities can thus also be conducted in a community setting (e.g. nursing homes or primary care centres). The exact job description of clinical pharmacists varies slightly between different countries and healthcare systems; however, involvement in medication reconciliation and medication review is a common denominator [97]. Medication review can be considered the structured evaluation of a patient’s medicines with the aim of optimizing medicine use and improving health outcomes, which entails detecting MRPs and recommending interventions [98]. In the United States, for example, the practice of clinical pharmacy has steadily grown during the 21st century, and the clinical pharmacist is now an integrated and important part of the healthcare team [99].

According to the literature, medication reviews conducted by clinical pharmacists can improve medication use and reduce healthcare costs [100, 101]. The clinical pharmacist can therefore be considered an asset in the prevention and management of MRPs. Regarding the effect of interventions involving medication review on unplanned hospital
admissions and other clinical outcomes, review data are inconsistent but suggest that at least some of them might be modifiable through intervention [102-105]. For example, medication review conducted by clinical pharmacists during the hospital stay can reduce medication-related readmission rates in different subgroups of older patients [36, 106-107]. Moreover, post-discharge randomized controlled trials (RCTs) involving phone-based interviews by clinical pharmacists have shown a reduction in all-cause readmission rates [108, 109]; however, those trials did not specifically target an older population. A recent review also concluded that there is a need for more RCTs that target medication discrepancies and errors during the sensitive care transition between hospital and primary care [110]. In summary, the clinical pharmacist might play an important role in further reducing the occurrence of MRPs and associated hospital admissions through a combination of medication review and similar activities during care transitions between different healthcare institutions or between such institutions and home. The uncertainty primarily concerns what types of interventions are repeatedly effective in terms of clinical outcomes in specified subgroups of older individuals.

There are currently no formal requirements for pharmacists involved in clinical pharmacy within the Swedish healthcare system except for a Bachelor or Master of Science in Pharmacy. One way to achieve enhanced knowledge and experience in this patient-oriented field is to enrol in the Master’s Programme in Clinical Pharmacy, a postgraduate education programme offered by Uppsala University. In Region Västerbotten, clinical pharmacy services started in 2002 as a collaboration between the County Council and the local hospital pharmacy at Umeå University Hospital. The project lasted approximately five months and was then implemented as a regular service at various wards and clinics after an overall positive response from the healthcare team.

**Nursing homes**

The nursing home context is not a major focus of this thesis, but older people in nursing homes are per definition vulnerable since they cannot fully function independently and to varying degrees rely on others to help them with medical needs or other activities. Nursing home residents are specifically targeted in paper IV. A few clarifying sentences about the Swedish nursing home concept are therefore warranted. In Sweden, nursing homes are governed by a law stating that each municipality is responsible for providing nursing home placements for older people within its geographical boundaries [111]. Older people with special needs
who cannot care for themselves are entitled to a place in a nursing home, but that ultimately must be formally decided on by municipal officials. There are, however, no exact criteria to qualify for nursing home accommodation, and the residents of these facilities can therefore be described as a heterogenous blend of individuals with different physical, behavioural and cognitive deficits. Swedish nursing homes have staff available 24 hours per day and access to a nurse in charge, although that person is not always physically present on site. Every month, each municipality reports and updates all nursing homes activities to the NBHW, and the information is then recorded in the national registry regarding social service efforts for older and disabled people.

Psychotropic drugs

A common denominator of clinically distinct subtypes of major NCD, regardless of aetiology, is the more pronounced deficit of certain neurotransmitters in the CNS than what would be expected from the normal alterations associated with ageing. Although many neurotransmitters are relevant in this respect, cholinergic neurons are generally affected the most \[42\], which makes the individual more susceptible to anticholinergic drugs. Neurochemical imbalances can, for example, trigger delirium or other episodes of temporary confusion \[112\]. 

Psychotropics is a rather broad term commonly applied to a wide range of drugs with affinities for many different receptor types and that in various ways affect behaviour, mood or emotion. There is so far no consensus on an exact definition, but most drugs used to treat mental disorders belong to group N in the Anatomical Therapeutic Chemical (ATC) system, a classification endorsed by the WHO \[113\].

Psychotropic drugs, most notably antipsychotics, have traditionally frequently been utilized in managing NPS, with prevalence estimates of psychotropic users in the range of 60–80% among nursing home residents in Scandinavia \[114-116\]. The sections below present a brief overview of some groups of psychotropics with relevance to older people, especially individuals with major NCD or other forms of cognitive impairment.

Antipsychotics

Although affinity for dopamine receptors is characteristic of antipsychotics, they display a wide range of antagonistic properties (Table 1) that merit acknowledgement when addressing older people with different major NCD subtypes and severities of neurotransmitter deficits. The pharmacodynamics and side-effects of antipsychotics are specific to
individual drugs rather than to generation or potency, yet some generalizations can nonetheless be made regarding their safety profiles. Sedation, weight gain and postural hypotension are common and problematic signs and symptoms of chlorpromazine, a low-potency agent historically widely used in the routine management of psychosis [117]. The high-potency agent haloperidol has been one of the most frequently used antipsychotics in many countries and displays less sedation, orthostatic imbalance and weight gain than do most low-potency agents; however, these advantages come at a cost, as the relative incidence of extrapyramidal symptoms is notably higher [118]. Second-generation antipsychotics, also referred to as atypical antipsychotics, emerged much later and generally display a lower relative incidence of extrapyramidal side effects.

Over the years, both first- and second-generation antipsychotics have been routinely utilized, off label, for treating NPS in major NCD. In that context, risperidone and olanzapine seem to be the most evaluated and effective drugs, producing moderate improvements in individual symptoms such as aggression, agitation and psychosis, but recommendations differ depending on the major NCD subtype [119, 120]. Despite different receptor profiles of second-generation antipsychotics than those of the first-generation drugs, extrapyramidal symptoms can still be problematic side-effects, and these limitations must always be weighed against the potential benefits [121]. Furthermore, even for second-generation antipsychotics, the potential of alleviating burdensome NPS is accompanied by a substantial risk of severe clinical outcomes in terms of mortality and emergency hospital admission [122-124]. Neuroleptic malignant syndrome is an unpredictable and generally life-threatening reaction that occurs in some individuals exposed to antipsychotics [125]. The main symptoms are rigid muscles, fever, perspiration, confusion and autonomic dysfunction, for example, tachycardia and increased blood pressure. In brief, neuroleptic malignant syndrome has been reported for various antipsychotics with different receptor profiles, but dopamine receptor antagonism appears to be an important mechanism of the pathophysiology. Persons with LBD appear to be at particular risk in terms of neuroleptic malignant syndrome, overall mortality and Parkinsonism; sensitivity to antipsychotics is even considered a main characteristic of that specific pathology [126, 127]. In that regard, quetiapine has relatively low affinity for dopamine receptors (Table 1), which is preferable from a safety perspective [119, 120].

In summary, antipsychotics are powerful drugs that can achieve notable therapeutic responses in certain individuals with troublesome symptoms, but because of the risk profile described above, both first- and second-
generation antipsychotics in major NCD should ideally be restricted to cases with pronounced psychotic or hyperactive symptoms and in which all appropriate environmental and non-pharmacological measures have been undertaken and evaluated [74].

Table 1. Relative affinities for different receptors of selected antipsychotics acting in the central nervous system [128].

<table>
<thead>
<tr>
<th>Antipsychotic drug</th>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha_1$</td>
</tr>
<tr>
<td><strong>First generation</strong></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>+++</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>+</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>++</td>
</tr>
<tr>
<td><strong>Second generation</strong></td>
<td></td>
</tr>
<tr>
<td>(atypical)</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>+++</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+++</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>++</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>++</td>
</tr>
</tbody>
</table>

$\alpha_1$, alpha$_1$-adrenoreceptors (all subtypes); $D_2$, dopamine receptor subtype 2; $H_1$, histamine receptor subtype 1; $M_1$, muscarine acetylcholine receptor subtype 1; $5-HT_2$, serotonin receptor subtype 2

+++ high affinity, ++ moderate affinity, + low affinity

**Anxiolytics, sedatives and hypnotics**

The anxiolytic, sedative and hypnotic drugs addressed in this thesis either enhance gamma-aminobutyric acid (GABA) transmission or block histamine $H_1$ receptors. Benzodiazepines (BZDs) are positive allosteric modulators of the GABA$_\text{A}$ receptor, thereby increasing the inhibitory effect of GABA. Because of varying affinities for different GABA$_\text{A}$ receptor complexes, which in turn are unevenly distributed in the CNS, different BZDs lead to varying anxiolytic and/or sedative effects. The pharmacokinetics of BZDs (Table 2) are also highly relevant since they are
relatively lipid-soluble substances with large volumes of distribution and prolonged elimination half-lives in older people, whose body composition gradually shifts over time towards more adipose tissue with less water and lean body mass. Moreover, there are also a few short-acting hypnotic drugs that differ from BZDs on a structural level but function via similar mechanisms from a pharmacodynamic viewpoint, for example, zopiclone and zolpidem (so called Z-drugs).

**Table 2. Comparison of elimination half-lives of several drugs acting through GABA<sub>A</sub> receptors.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Elimination half-life in hours &lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxazepam</td>
<td>5–14</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>12–15</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10–20</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>16–35</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>24–29</td>
</tr>
<tr>
<td>Diazepam</td>
<td>20–50</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>3.5–6.5</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>2.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> The time intervals indicate individual differences; older people with less lean body mass and relatively more fat are generally better represented by the upper limits.

Anxiolytics, sedatives and hypnotics, especially BZDs, are associated with both falls and fall-related injuries [129, 130]. Furthermore, the sedating antihistamines are generally best avoided in older people due to daytime sedation and an increased risk of confusion or other undesired anticholinergic side effects [131, 132]. According to quality indicators from the NBHW, the general recommendation in cases of anxiety and/or insomnia among older patients is to utilize Z-drugs and short-to-intermediate-acting BZDs (e.g. zopiclone and oxazepam) in preference to long-half-life BZDs or sedating antihistamines (48). Even though the risk of daytime sedation may decrease through this principle, the association with fall-related hospitalizations still appears to be quite similar across various BZDs and Z-drugs, regardless of the half-life [133-136]. In addition, BZDs may induce cognitive decline, and their long-term use is associated with problematic physical dependency and withdrawal symptoms that severely impede discontinuation [137]. Hence, both Z-drugs and BZDs are to be used with caution in older people; the potential
benefits of these medications must be carefully weighed against the risk of fall-related injuries and other MRPs.

Antidepressants

As mentioned in previous sections, older people often present with depressive symptoms, which in turn display an intricate and troublesome relationship with cognitive impairment. Nowadays, SSRIs are commonly utilized against depressive symptoms in major NCD, but as with the effect of antidepressants among older people in general \([138, 139]\), the degree of remission and symptom relief among individuals with major NCD is debatable and at best limited to specific subgroups of individuals \([140]\). In addition, many SSRIs have also displayed some efficacy against other types of NPS, for example, agitation and aggression \([141, 142]\). The reasons for using antidepressants can thus range from severe major depression to more fluctuating depressive symptoms and other manifestations within the NPS spectrum.

Despite their potential benefits, there are clinically relevant MRPs associated with antidepressants that should be acknowledged. Many antidepressants, especially the SSRIs, may cause hyponatremia \([143]\), a condition for which older people can be considered a particularly high-risk group due to age-related factors and concomitant use of diuretics \([144]\). Furthermore, there are several potentially clinically relevant interactions between antidepressants and other common drugs among older people. For instance, SSRIs are known to increase the risk of bleeding, which should be considered during treatment with antithrombotic agents, anticoagulants or certain analgesics \([145]\). In terms of individual substances, both citalopram and escitalopram can produce a dose-dependent prolongation of the QT interval \([146]\), and that delay in ventricular repolarization can in turn increase the risk of Torsade de pointes, at least in the presence of other factors affecting QT time \([147]\). Antidementia drugs (e.g. donepezil), proton-pump inhibitors and thiazide diuretics are all examples of drugs that have been recognized to induce QT prolongation \([148-151]\). Acting through both serotonin and adrenergic receptors, mirtazapine is an alternative to SSRIs in managing depressive symptoms as well as NPS. Mirtazapine also exhibits pronounced sedative properties \([152]\) and stimulates weight gain \([153]\). Those two side-effects may often be desirable in cases of sleep disturbance or malnutrition, clinical features that are typical in geriatric patients and major NCD, but that also apply to older people in general \([154-156]\).

Taken together, antidepressants can provide a reasonable alternative for managing both depression and other NPS in some older individuals; however, close and continuous follow-up regarding effect is important.
Antidementia drugs

Antidementia drugs comprise a relatively small group of therapeutic agents intended to relieve cognitive symptoms in certain major NCD subtypes. Except for memantine, a glutamatergic antagonist, all current antidementia drugs approved by the Swedish Medical Products Agency are acetylcholinesterase inhibitors (AChEIs). As the name suggests, these drugs inhibit the enzymatic breakdown of acetylcholine in the CNS and can thus be regarded as a type of replacement therapy to balance the cholinergic deficits associated with AD and certain other subtypes of major NCD. As of 2023, there are three AChEIs approved for the Swedish market: donepezil, galantamine and rivastigmine. Despite small pharmacological differences between the drugs, all AChEIs produce modest yet significant improvements in cognition, behaviour, activities of daily living and global assessment of change in people with mild to moderate AD \([157-159]\). Clinically relevant effects within some of these domains could also be achieved in people with moderate or severe AD \([160, 161]\), even beyond the point of moving to a nursing home \([162]\). In addition, registry data have shown that AChEIs may reduce mortality risk \([163]\) and prevent, or at least delay, initiation of antipsychotics and sedative drugs \([164]\), which are both typical indicators of burdensome NPS.

The current scientific evidence regarding AChEIs is mostly generalizable to people with AD; the use of AChEIs is not encouraged in non-mixed type VaD or frontotemporal dementia \([165-167]\). In LBD, on the other hand, they can stabilize or even improve cognitive symptoms and have also come to fill an important therapeutic role in managing the characteristic visual hallucinations that typically emerge at some point during disease progression \([168-170]\). In terms of safety and tolerability, the most common side-effects associated with AChEIs are gastrointestinal symptoms, for example, nausea and diarrhoea, whereas sleep disturbances, agitation, syncope, bradycardia and headache are less frequently reported \([171]\). In contrast to AChEIs, memantine appears to be exclusively effective in the moderate to severe stages of AD, for which review data suggest a small clinical benefit, irrespectively of concomitant treatment with AChEIs \([172]\).

In summary, there are currently few antidementia drugs, and those available offer only modest clinical improvements, effects that appear to be symptomatic rather than neuroprotective, and the long-term benefits are still uncertain, at least from a health economic perspective. Nevertheless, these drugs may provide symptom relief at an individual level, which can be an aspect of great value from the perspectives of
caregivers and relatives, and AChEIs can in general be considered a quality indicator regarding the care and treatment of AD and LBD provided that the clinical response is properly evaluated over time.

Medication adherence

Although adherence to medication is not a focus of this thesis, poor adherence is an important aspect of MRPs and MRAs. Improving adherence is one path through which the intervention model described in paper I might affect rates of medication-related hospital readmission. According to the WHO, rates of medication adherence reach only approximately 50% in developed countries [173], and this poor figure obviously undermines the foundation for optimal clinical outcomes and may trigger a vicious spiral of increasing health care costs [174].

Non-adherent behaviour is often multifactorial and can roughly be rated on five different dimensions: 1) patient-related factors; 2) therapy-related factors; 3) condition-related factors; 4) social factors, including economic status; and 5) factors related to healthcare systems. Importantly, patient-related factors constitute only one of these dimensions, and the lack of research into other predictors of medication adherence does not necessarily mean that they are of minor importance. Perceptions of personal need for medicines, concerns regarding possible side-effects and dependence, personal value of the treatment versus cost and insufficient knowledge are all examples of potential barriers to optimal adherence [173]. Regarding patient decision-making, adverse iatrogenic events are often more relevant to the patient than are negative outcomes associated with the illness itself, and medication harm generally seems to outweigh potential benefit [175]; consequently, a seemingly questionable act of non-adherence may appear fully rational from the patient’s own perspective [176]. Individuals who deliberately avoid their medication due to side-effects or for other reasons fall within the category of intentional non-adherence, a behaviour that does not necessarily worsen the clinical outcome from the short-term perspective. For example, the term intelligent non-adherence has even been coined by the WHO to emphasize that, in many instances, non-adherence actually derives from reasoned choices and rational decision-making rather than forgetfulness [173].

Even though there is little evidence to support old age as an independent predictor of adherence, older people are still at higher risk due to multiple morbid conditions, polypharmacy and complex medication regimens [177], which may be especially relevant to consider during the hospital
admissions of older people. From a patient perspective, hospital admissions are often chaotic and can lead to significant alterations in medication regimens—important changes that might be unnoticed or misunderstood by the patient following discharge [178]. Furthermore, the phase of transfer between hospital and primary care is also susceptible to discrepancies and miscommunication between the different health care providers, further increasing the possibility of potential MRPs due to adherence issues [179, 180]. Even though most prescription medicines in Sweden are covered by a public subsidiary system that limits the yearly cost for each patient, there are still substantial differences in adherence between different socioeconomic groups, even within certain age categories [181]. Concerning dosage regimens, adherence rates display an inversely proportional relationship with dosage frequencies [182]; for example, changing from a thrice-daily to a once-daily regimen might improve adherence by as much as 40% in patients with inconsistent drug use [183]. Moreover, self-reported adherence has been found to be higher among older people using a drug dispensing service than among patients who rely on manual dispensation [184]. Regimen complexity and treatment duration obviously depend on the morbid conditions present, but the disease itself can also negatively affect adherence. Notably low adherence rates are generally found among patients with chronic and relatively symptom-free conditions (e.g. hypertension) [185, 186]. As another example, depression is associated with poor adherence, according to the review literature [187, 188], and overcoming adherence issues has been discussed as a strategy to improve the poor clinical outcomes and quality of life observed in depressed patients with cardiovascular diseases [189]. Among other mental disorders, and especially relevant to this thesis, even milder forms of cognitive impairment have severe consequences for medication adherence [190]. There is sparse evidence of factors related to healthcare systems, but higher cost for the patient and co-payment have all been suggested to negatively affect adherence [191].
Rationale

Within the heterogeneous older population, there are several circumstances, such as high age, transitions of care and cognitive impairment, that may increase the risk and consequences of MRPs. Improving the use of medication among these often-frail individuals may in turn be accomplished through different approaches. One strategy is to address which medications are being initiated in the first place and to improve knowledge of the use of psychotropics and other potentially inappropriate medicines that are associated with mortality and hospital admission, which potentially could be avoided by relying more on safer drugs and non-pharmacological initiatives. Prevalence studies of psychotropic drug use in various settings and through different methods have previously been conducted; still, trends in drug utilization are not static and may change due to novel drugs on the market, new scientific evidence, revised treatment guidelines, as well as information campaigns or other efforts initiated by the authorities. More population-wide comparative data on psychotropic drug use are warranted among older people with and without different subtypes of major NCD to better identify potential areas for improving medication use. The extensive information provided by Swedish quality registries and health databases, facilitated by the opportunities to interlink these vast sources of information within legal frameworks, enables such research.

Successful medication therapy is, however, not merely the result of choosing theoretically appropriate drugs in the first place; the outcome could be affected by numerous factors, for example, deteriorating kidney function, insufficient monitoring of therapeutic response and unwanted effects, misunderstandings, medication discrepancies following care transitions, practical administration barriers and poor adherence. Previous studies have identified drugs as a major reason for hospital admissions among older people. Clinical pharmacists can be involved in preventing and managing MRPs. The current evidence regarding pharmaceutical interventions, especially in the context of older people and transitional care, is limited, and no single intervention model has yet proven to be universally effective in different settings. Instead, different interventions have displayed shifting results depending on the study population, outcome and follow-up time. There are, however, indications that addressing medication review, transitions of care and adherence issues might be a means to optimize treatments for older people, even though more complex interventions that incorporate a mixture of these elements need to be tested and validated in a clinical setting. Therefore,
much emphasis is placed on the aetiology of hospital admissions among older individuals, possible associations with cognitive impairment, as well as how such MRPs could be avoided or resolved at an early stage through intervention by clinical pharmacists.
Aims

The overall aim of this thesis was to describe and understand medication use in certain vulnerable subgroups of older people to identify suitable target populations in which MRPs can be prevented or managed through interventions or similar efforts. Paper I described, in the form of a study protocol, the design of a clinical trial investigating the effect of a clinical pharmacist intervention on medication-related hospital readmissions among individuals aged 75 years or older. Moreover, the index admissions of 300 study participants in that trial were assessed regarding causality, and the relationship between MRAs and cognitive impairment became the primary aim of paper II. In paper III, the aim was to describe psychotropic drug use and associated factors among older people with different subtypes of major NCD. Paper IV aimed to compare the use of psychotropic drugs in relation to nursing home residency among older people with major NCD and among matched controls from the total older population.

Objectives

Paper I
To specify the intervention protocol and clinical endpoints, as well as describe the pre-planned statistical analyses and methodological considerations.

Paper II
To estimate the proportion of MRA in the population of acutely admitted older people and analyse the association between MRA and cognitive impairment, as measured according to a four-item version of Gottfries’ cognitive scale.

Paper III
To estimate psychotropic drug use among older people with major NCD and explore associations between major NCD subtypes and different classes of psychotropics.

Paper IV
To investigate how much the proportions of psychotropic drug users differ between the population of older people diagnosed with major NCD and a reference population matched by age and sex but without records of the disorder. A second objective was to analyse subgroup and interaction effects regarding major NCD, nursing home residency and psychotropic drug use.
Methods

This research was primarily epidemiological in nature, including a blend of descriptive, analytical and comparative approaches to quantifying and evaluating drug use in populations of vulnerable older people (Table 3). The first data collection was based on index data for 300 patients admitted to the acute medical ward at Umeå University Hospital and enrolled in the clinical trial described in paper I, and those individuals comprised the study sample of paper II. Papers III and IV used data from several national registries, which are further outlined in the following section. Although based on the same registries, and to some extent covering the same population, these were two separate data collections.

Table 3. Summary of the data collections, study periods and study designs for each paper included in this thesis.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Data source</th>
<th>Time period</th>
<th>n&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Principal study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Clinical trial participants</td>
<td>2018–2021</td>
<td>300</td>
<td>RCT</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
<td>Cross-sectional</td>
</tr>
<tr>
<td>IV</td>
<td>National registries</td>
<td>2007–2019</td>
<td>204,838</td>
<td>Cross-sectional with reference group</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial

<sup>a</sup> Individuals selected for the primary analysis

Study populations and sampling

Papers I and II

The collection of data on index admissions and readmissions was based on participants in the RCT presented in paper I. Hence, the study population comprised acutely admitted patients aged 75 years or older who lived in ordinary private homes. Due to the coronavirus disease (COVID-19) that emerged in late 2019 and then escalated in the spring of 2020, the inclusion of new participants in the intervention study was officially paused during April–September 2020. Except for those who declined to participate (n = 71) or withdrew consent at some point during the follow-up (n = 19), all individuals enrolled in the clinical trial during
September 2018–October 2021 (n = 300) were simultaneously included in the causality assessment of index admissions in paper II. The whole sample was recruited during ward stay.

Paper III

The data collected for this study covered 71,298 persons aged 65 years or older and registered in the Swedish registry for cognitive/dementia disorders (SveDem) and diagnoses from 1 May 2007 to 31 December 2017 regarding any major NCD subtype. People with registered death dates before 2018 were excluded, leaving a total of 38,251 individuals in the final dataset.

Paper IV

The study population in paper IV was based on all individuals recorded in SveDem from 1 May 2007 to 31 December 2019 who had reached an age of at least 65 years by the end of that period. Using the same age criterion, persons with ICD codes related to major NCD subtypes (i.e. F00, F01, F02, F03, F09, F10, G30 or G31) documented in the Swedish Patient Register from 1 January 2007 to 31 December 2019 and/or who filled prescriptions for antidementia drugs (ATC subgroup N06D) were added. The first record of any of those criteria was considered the index date. References were matched 1:1 by sex and age from the Total Population Register and from the same year as the index date for the corresponding individual in each matched pair. All individuals already included as cases of major NCD were excluded from the total population dataset before the matching occurred. People with ICD codes F05, F06, F07 and G32 recorded in the Swedish Patient Register were also excluded. Consequently, the reference group was based on individuals who had not been registered in SveDem or the National Patient Register, nor started treatment with antidementia drugs. As a last step, all matched pairs in which at least one individual had died before the end of 2019 were excluded from the dataset, resulting in a total of 102,419 matched pairs finally being compared and analysed.

Data sources

For the registry-based studies (i.e. papers III and IV), several sets of national health data were combined and analysed. Apart from the exceptions mentioned in the subsequent section, all demographic data and information on diagnoses, drug dispensations and social services were extracted from national population-wide health databases organized
by the NBHW. All specific health databases involved are further mentioned and explained in the description of the data cross-linking procedure.

Medical charts: papers I and II

The whole dataset used in paper II as well as the preliminary results of the clinical trial were gathered from electronic medical charts. In summary, the collected data comprised laboratory values, lists of medicines and physicians’ notes written during hospital stays. The electronic list of medicines from the day before hospital admission was used for the data collection.

The Swedish registry for cognitive/dementia disorders (SveDem): papers III and IV

As mentioned, the whole study population in paper III and a substantial proportion of the study population in paper IV were identified through SveDem. The registry also provided important data on major NCD subtypes and diagnosis dates. In brief, SveDem is a national quality registry started in 2007; the number of registrations it contains is continuously growing, with more than 90,000 people registered by the end of 2019 [192]. This registry provides an important means for improving the quality of care for people with major NCD and contains extensive information related to functional state, cognitive function and medical history. In total, more than 900 primary care centres, special care units and nursing homes currently report data to SveDem. Baseline registrations are made when people are newly diagnosed, and follow-ups are generally conducted yearly. Of all 6,455 basal registrations made in 2019, 56.9% were made by specialized care units and 43.1% by primary care. According to the annual report, the degree of coverage of SveDem registrations in relation to the whole estimated Swedish population with major NCD is expected to be approximately 30%.

The National Patient Register: papers III and IV

Data dating back to 2007 from the National Patient Register was used in paper IV to identify additional individuals with confirmed major NCD who were not recorded in SveDem. It was also applied as a source of data on certain comorbidities (e.g. schizophrenia). This registry contains data on diagnoses documented by specialized care, both inpatient and outpatient units; however, it does not cover diagnoses confirmed by primary care. The diagnoses used were all coded according to ICD-10 and are further detailed in paper IV.
The Swedish Prescribed Drug Register: papers III and IV

The Swedish Prescribed Drug Register was another major data source for the registry-based studies and provided all the information required to identify psychotropic drug users. Moreover, this registry was also used to identify cases of major NCD based on prescription fills for antidementia drugs. This registry contains information regarding all prescription drugs dispensed at Swedish community pharmacies, for example, prescribing and dispensing dates, ATC code, dose per unit, number of units, cost and information about the prescriber. Data are continuously transferred from pharmacies to the Swedish eHealth Agency through an automated process. The information is then summarized and delivered to the NBHW, from which it can finally be requested for research or other purposes. Importantly, only prescriptions that have been dispensed are recorded; if a prescription has never been filled, there is consequently no information in the registry that it was ever issued in the first place. That limitation is important to consider when interpreting the proportions of drug users in papers III and IV.

Procedures

Clinical pharmacist interventions

The intervention described in paper I was still ongoing when this thesis was printed. The intervention being investigated is carried out by a clinical pharmacist, beginning when the study participant is discharged from the hospital and then continuing for 180 days. In summary, the intervention protocol comprises two main activities to detect MRPs at the earliest possible stage: medical chart reviews and phone-based follow-up. The medical chart reviews focus on any new laboratory values or notes (e.g. by specialized care or primary care physicians) that might be relevant in terms of medication use, for example, signs of electrolytic imbalance, inadequate blood pressure control or healthcare contacts due to new or worsening symptoms that at a first glance could be related to the use of medication, including insufficient therapy. Phone-based follow-ups are carried out within the first week following discharge and after 30 and 60 days. The conversations are customized to each individual patient but at least involve verification that all decisions made during the ward stay have been fully implemented since the care transition and determination of whether the patient has experienced any deterioration in health. As part of the preparation for the first phone call, there is also a medication reconciliation regarding the list of medicines before, during and after the ward stay. In the case of more extensive medication alterations, such as a
hospital visit resulting in new medicines and dosage regimens, the pharmacist can decide to invest time in a more structured medication review. If a potential MRP has been identified during any of these activities, the matter is presented to the physician responsible for that specific treatment and is accompanied, as far as possible, with a concrete suggestion on how to manage the issue.

Four-item version of Gottfries’ cognitive scale: papers I and II

In papers I and II, cognitive impairment was measured as test scores on a modified version of a validated rating tool, initially developed by Gottfries and Gottfries [193]. The original questionnaire, simply referred to as Gottfries’ cognitive scale, measures a person’s level of cognitive function through 27 items; a result less than 24 is considered an indicator of cognitive impairment and correlates to the Mini-Mental State Examination (MMSE) cut-off with a sensitivity and specificity of 90% and 91%, respectively [194]. When examining the psychometric properties of Gottfries’ cognitive scale, Lövheim et al. [195] showed that short screening based on four items (i.e. item numbers 16–19 in the original scale) related to time orientation could detect cognitive impairment, reaching a sensitivity of 97.8% and a specificity of 92.5% when allowing one negative/incorrect answer out of four. These four questions, henceforth referred to as Gottfries’ four-item test, enabled a feasible and relatively time-efficient procedure to screen for cognitive impairment before randomization in the intervention study. A result of less than three out of four correct answers was chosen as the cut-off for cognitive impairment and divided the participants into two different strata from which they were ultimately assigned to their respective treatments through random allocation. In paper II, in which cognitive impairment functioned as one of the main variables of interest, participants were compared regarding different Gottfries’ four-item test scores and odds of MRA.

Medication-related hospital admissions: papers I and II

The causality of 300 index admissions from the intervention study was classified by two different assessors using AT-HARM10 [39]. In short, AT-HARM10 is an instrument developed to be used by final-year undergraduate or postgraduate pharmacy students to identify possible MRAs in populations of older people. In a sensitivity analysis, all hospitalizations considered possibly medication related by both AT-HARM10 assessors were further assessed by a clinical pharmacist, a procedure in which the probability of a medication-related admission was classified as certain, probable, possible, unlikely, conditional or
unclassifiable according to a slightly modified interpretation of the WHO-UMC system [35].

The causality assessments of readmissions will be performed by an external group of three clinical experts, all unaware of the treatment assignments, a procedure that has been used before in various settings [36-38]. For each assessment, the group has to reach a consensus decision regarding whether or not the event was medication related, and regarding the probability of a causal link according to the previously mentioned WHO-UMC criteria [35].

Clinician–patient relationships, blinding and allocation concealment: paper I

The participants in the intervention study were exclusively recruited by pharmacists or nurses to prevent patient–physician relationships from affecting the inclusion rates. Furthermore, none of the clinical experts involved in treating a study participant during index admission or readmission is to be involved in the causality assessment of that specific readmission. The expert group will also be blinded in terms of treatment assignment. A similar procedure was used in paper II in which only one out of three assessors had knowledge of the cognitive stratification. The concept of blinding will also apply for any statisticians consulted during the analysis of the trial. Because of the design of the intervention, the clinical pharmacists are not unaware of the assigned treatment of randomized study participants, but are only blinded to the computer-generated allocation sequences.

Mini-Mental State Examination (MMSE): paper III

The MMSE is a 30-point questionnaire with 20 specific items in 11 separate domains that cover orientation in time and space, language, memory and visual–spatial skills. A result of fewer than 24 points indicates cognitive impairment of a severity comparable to major NCD (primarily AD). Importantly, the scale is not a specific diagnostic test for major NCD in older people but should rather be considered one of several important components of a proper basal cognitive examination and a valuable aid during the assessment and follow-up of disease progression [196]. In Paper III, the MMSE score from basal registrations to SveDem was included as a covariate in the regression models to account for differences in baseline cognitive level when analysing the association between major NCD subtypes and psychotropic drug use.
Interlinking national registry data: papers III and IV

All persons found in any of the registries used for inclusion were filtered through the Swedish Cause of Death Register to exclude individuals who were no longer alive by the end of the time periods of interest. They were then linked to three different registries by NBHW using personal identification numbers: 1) the Swedish Prescribed Drug Register; 2) the National Patient Register, in which diagnoses had been coded according to ICD-10; and 3) the registry regarding social service efforts for older and disabled people, a national health database in which nursing home services are updated monthly.

Measurement of psychotropic drug use: papers III and IV

In both papers III and IV, drug use was based on prescription fills recorded in the Swedish Prescribed Drug Register during a time window of six months and given a dichotomized value, i.e. not accounting for repeated prescription fills during those periods. Moreover, psychotropic drugs were classified according to the ATC system, as both individual drugs and third-level subgroups (Table 4). That specific classification system is endorsed and recommended by the WHO, and the measure is commonly applied in drug utilization research [113].

*Table 4. The different levels of the Anatomic Therapeutic Chemical (ATC) system.*

<table>
<thead>
<tr>
<th>Level</th>
<th>Group properties</th>
<th>Example (ATC code)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anatomic or pharmacological</td>
<td>Nervous system (N)</td>
</tr>
<tr>
<td>2</td>
<td>Pharmacological or therapeutic</td>
<td>Psychoanaleptics (N06)</td>
</tr>
<tr>
<td>3 a</td>
<td>Pharmacological, therapeutic or chemical</td>
<td>Antidepressants (N06A)</td>
</tr>
<tr>
<td>4</td>
<td>Therapeutic or chemical</td>
<td>Selective serotonin reuptake inhibitors (N06AB)</td>
</tr>
<tr>
<td>5 a</td>
<td>Chemical substance</td>
<td>Citalopram (N06AB04)</td>
</tr>
</tbody>
</table>

a Psychotropic drug use was analysed on the third and fifth levels.

An important aspect of the ATC system is that the subgroups are not always classified according to the same principle: some subgroups describe chemical properties while others are based on the pharmacological mechanism of action or even on the therapeutic area
(Table 4). Drugs with similar therapeutic areas and indications can therefore be found in different subgroups. Similarly, drugs with adjacent chemical structures and pharmacological properties can have different clinical applications (e.g. BZDs). In both papers III and IV, psychotropics were represented by the following ATC subgroups: antipsychotics (N05A), anxiolytics (N05B), sedatives and hypnotics (N05C), and antidepressants (N06A). Antidementia drugs (N06D) were only considered in paper III.

Ethics

Informed consent and ethical approval

Due to the nature of cognitive disorders, it is often uncertain whether people with major NCD or other types of cognitive impairment can provide fully informed consent to participate in research, and that ethical dilemma applies to all the studies on which this thesis is based. For the registry-based studies, informed consent was not formally required, in accordance with Swedish Ethical Review regulations [197], which only mandate that informed consent be obtained in clinical research on humans or biological material. Instead, the interests and integrity of the research participants were represented by the Swedish Ethical Review Authority, which approved the registry-based studies presented in papers III and IV (registration numbers 2017-256-31M and 2020-04663). It should also be clarified that participation in SveDem is voluntary, and participants are given information about the registry before being registered; however, that type of approval is not necessarily fully informed. In papers I and II, informed consent was provided by all participants except in confirmed cases of major NCD. In the latter case, both the participants and their next of kin had to provide their consent. The intervention study was registered at Clinicaltrials.gov (NCT03671629) and approved by the Swedish Ethical Review Authority (diary numbers 2017-69-31, 2018-83-32, 2018-254-32, 2020-03699 and 2020-05426) in a review process that also covered the essential ethical considerations of paper II.

Data handling

All analyses and presentations of personal data were performed at group level with no chance of distinguishing specific individuals. In the dataset provided by NBHW, names and personal numbers were replaced by individual codes, before being delivered to the researchers. Similarly, personal data generated from the intervention study were coded, and the
translation key was stored separately. Access to data has been exclusively restricted to personnel involved in the projects. All data have been stored in locked archives and will remain so for at least 10 years.

Statistics

Several statistical methods were applied in the different papers and can simply be summarized as a combination of descriptive methods or various types of regression analyses. An alpha level of 0.05 was applied for all statistical tests.

Descriptive statistics

All papers include some elements of descriptive statistics, for example, proportions, means, medians and standard deviations, to present relevant characteristics of the samples and study populations. Furthermore, in both papers III and IV, the proportions of drug users were a major focus and given equal weight as the inferential statistics of these papers. Other descriptive statistical methods, such as correlation matrices and scatterplots, were utilized to check for the assumptions on which the different regression models were based. Finally, for the clinical trial outlined in paper I, Kaplan–Meier survival curves were chosen to illustrate time-to-event data. Differences in proportions, for example, differences regarding psychotropic drug use, were investigated using Pearson’s chi-square tests for papers II–IV.

Logistic regression: papers II and III

The associations between ATC subgroups of psychotropics and major NCD subtypes were analysed using both simple and multiple logistic regressions with psychotropic drug use as the dependent variable in the models. Regarding major NCD subtypes, AD was selected as the reference category against which VaD, frontotemporal dementia and LBD were compared. Age, sex, years since diagnosis and basal MMSE score were treated as covariates in all regression models presented in paper III. These independent variables were all expected to be related to major NCD subtype, disease progression and psychotropic drug use, so they were included as covariates for a more nuanced comparison of associated factors, regardless of whether or not the crude ORs were statistically significant.

In paper II, the multiple logistic regression model originated in the idea of an assumed causal relationship between cognitive impairment and MRA (Figure 5). Because of its negative impact on adherence [190] and
associated increased sensitivity to many psychotropic drugs [122-124, 131, 132], cognitive impairment seemed like a potential cause of MRA, at least indirectly. Since living alone had previously been identified as a risk factor for unplanned hospital admission [198, 199], cohabitation was treated as a potential confounder. Home health care was included in the causal pathway as an effect modifier based on the idea that severe cognitive impairment probably also increases the likelihood of receiving home health care, a service that in turn might reduce the risk of MRA for individuals receiving it. Finally, delirium is strongly positively associated with cognitive impairment [200, 201] but at the same time is a possible cause and result of hospital admission itself. Delirium was regarded as a collision factor [202] rather than a confounder and was therefore excluded from the model for fear of introducing bias into the estimation.

![Directed acyclic graph (DAG) of a theoretical causal pathway between cognitive impairment and medication-related hospital admission (MRA).](image)

**Figure 5.** Directed acyclic graph (DAG) of a theoretical causal pathway between cognitive impairment and medication-related hospital admission (MRA).

Generalized estimating equations: paper IV

In paper IV, generalized estimating equations (GEEs) were used to calculate ORs regarding different covariates and psychotropic drug use. In brief, the method itself is applicable in situations with correlated response data, particularly longitudinal studies with binary outcomes [203], but it can generally replace most common regression analyses (e.g. linear and logistic regressions) to analyse cross-sectional data. Even though the principal study design was not longitudinal, paper IV was
based on a matched dataset; the GEEs partly accounted for the matching sequences between the individuals with major NCD and their respective reference persons from the Total Population Register.

Log-rank test and Cox proportional hazard models: paper I

Group comparisons of time to unplanned hospital readmission and similar time-to-event outcomes will be tested using log-rank tests. Furthermore, Cox proportional hazard models will be applied to further estimate the difference in hazard probability and associated confidence intervals (CIs) and to account for clinically relevant prognostic factors. In addition to standard baseline characteristics covering age and sex, both cognitive impairment and HF are pre-specified factors to be adjusted for in the final Cox regression model, and these two variables will also be used for subgroup analyses and the investigation of interaction effects.
Results

Clinical trial outcomes: paper I

The data collection (except for the causality assessment of readmissions) had been completed for the 300 individuals who comprised the sample explored in paper II (Table 5).

*Table 5. Sample characteristics according to treatment assignment.*

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n = 154)</th>
<th>Control (n = 146)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex, % (n)</td>
<td>64.9 (100)</td>
<td>60.3 (88)</td>
</tr>
<tr>
<td>Age, (a) mean ± SD</td>
<td>84.4 ± 6.0</td>
<td>83.9 ± 5.6</td>
</tr>
<tr>
<td>Median age (IQR)</td>
<td>84 (9)</td>
<td>83 (8)</td>
</tr>
<tr>
<td>Major NCD, % (n)</td>
<td>10.4 (16)</td>
<td>8.9 (13)</td>
</tr>
<tr>
<td>Heart failure, % (n)</td>
<td>40.9 (63)</td>
<td>35.6 (52)</td>
</tr>
<tr>
<td>Cardiovascular disease, (b) % (n)</td>
<td>57.8 (89)</td>
<td>58.2 (85)</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>73.4 (113)</td>
<td>69.2 (101)</td>
</tr>
<tr>
<td>Diabetes type 2, % (n)</td>
<td>28.6 (44)</td>
<td>47.6 (40)</td>
</tr>
<tr>
<td>Cancer (previous or current), % (n)</td>
<td>33.1 (51)</td>
<td>37.0 (54)</td>
</tr>
<tr>
<td>Number of medicines, (c) mean ± SD</td>
<td>8.2 ± 4.2</td>
<td>8.1 ± 3.6</td>
</tr>
<tr>
<td>Cohabitant, % (n)</td>
<td>38.3 (59)</td>
<td>48.6 (71)</td>
</tr>
<tr>
<td>Home care, (d) % (n)</td>
<td>46.4 (71)</td>
<td>40.0 (58)</td>
</tr>
<tr>
<td>Home health care, % (n)</td>
<td>15.6 (24)</td>
<td>4.8 (7)</td>
</tr>
<tr>
<td>Dose dispensing, % (n)</td>
<td>30.5 (47)</td>
<td>26.0 (38)</td>
</tr>
</tbody>
</table>

\(a\) Officially registered sex and a dichotomous variable, the opposite being male sex  

\(b\) Age refers to number of birthdays  

\(c\) Atrial fibrillation and/or myocardial infarction (present or previous) and/or stroke (previous or present)  

\(d\) Treatments lasting >14 days with orally administered medicines or injections  

\(e\) Data missing for two individuals
Regarding preliminary results of the intervention study, there were some available clinical outcome data for 296 of the 300 study participants (Table 6). After 180 days, approximately 50% of the sample had either been readmitted to hospital or died, regardless of treatment assignment (Figure 6). Of note, 24 participants were readmitted within one week of being discharged from hospital. Based on the same sample, almost 60% of the study participants with confirmed HF at baseline had experienced at least one readmission, compared with approximately 45% of the participants without HF ($p = 0.022$ according to the Mantel–Cox log-rank test) (Figure 7).

Table 6. Clinical outcomes within 180 days among the clinical trial participants included in paper II.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intervention ($n = 154$)</th>
<th>Controls ($n = 142$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one unplanned readmission,(^a)</td>
<td>48.7 (75)</td>
<td>45.1 (64)</td>
<td>0.532</td>
</tr>
<tr>
<td>% ($n$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of unplanned hospital readmissions, $n$</td>
<td>182</td>
<td>124</td>
<td>n/a</td>
</tr>
<tr>
<td>Time to first hospital readmission,(^b)</td>
<td>40.8 ± 49.4</td>
<td>49.2 ± 43.3</td>
<td>0.283</td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased, % ($n$)</td>
<td>14.3 (22)</td>
<td>7.7 (11)</td>
<td>0.074</td>
</tr>
</tbody>
</table>

\(^a\)Regardless of causality

\(^b\)Participants with at least one readmission

Four individuals died after randomization but before hospital discharge and were consequently excluded from the survival analysis.
Figure 6. Kaplan–Meier curves for all-cause readmissions to hospital within 180 days according to type of treatment.

Figure 7. Kaplan–Meier curves regarding all-cause readmissions to hospital within 180 days for study participants with and without diagnosed heart failure.
Associations between medication-related hospital admissions and cognitive test scores: paper II

The proportion of MRAs in the sample of 300 acutely admitted older people was 36% (95% CI 31–42%). This result was based on the 108 admissions that both assessors classified as possible MRAs. In comparison, 170 admissions were considered possible MRAs according to at least one of the assessors, so the remaining 130 admissions were unanimously regarded as unlikely to be medication related. The overall inter-rater agreement was 79% with a Cohen’s kappa statistic of 0.59.

Among the types of drugs and symptoms that both assessors agreed on as possible causes of admission, 28 hospital admissions were regarded as possibly related to cardiovascular causes (e.g. dizziness, syncope or orthostatic blood pressure), with beta-blocking agents being involved in 17 of those cases. Suboptimal treatment, poor adherence and/or failure to acknowledge any obvious symptoms of worsening HF over a period of several weeks were considered contributing factors in 16 admissions. Some other types of MRPs that were identified by both assessors were: electrolyte imbalance (n = 7), primarily because of diuretics or selective serotonin inhibitors; infections due to drugs with immunosuppressive properties or medicines that otherwise could increase susceptibility to such diseases (n = 6); issues with glycaemic control (n = 5); or anaemia in patients using one or more drugs that increase bleeding risk (n = 5).

Gottfries’ four-item test scores were compared against a reference category of all patients with 4/4 positive/correct answers in a simple logistic regression model. In that comparison, those with the lowest score (i.e. 0/4 positive answers) had the lowest odds of MRAs (OR, 0.34 [95% CI 0.11–1.07]; p = 0.064), so that result was treated as a potential cut-off for cognitive impairment in the subsequent analyses. The odds of possible MRAs were lower in patients who scored 0/4 positive answers than in the rest of the sample (OR, 0.28 [0.10–0.84]; p = 0.028). There was only a marginal difference (adjusted OR, 0.31 [0.10–0.93]; p = 0.037) when including home health care and cohabitation in the regression model (Table 7). In summary, patients with the lowest cognitive test scores had consistently lower odds of MRAs in all three regression models, but the statistical significance varied depending on reference category.
Table 7. Multiple logistic regression output regarding cognitive test score and medication-related hospital admission.

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Adjusted OR (95% CI)</th>
<th>Crude OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottfries’ four-item test score: 0/4 a</td>
<td>0.31 (0.10–0.93)</td>
<td>0.28 (0.10–0.84)</td>
</tr>
<tr>
<td>Home health care</td>
<td>0.48 (0.19–1.19)</td>
<td>0.49 (0.20–1.17)</td>
</tr>
<tr>
<td>Cohabitation</td>
<td>0.64 (0.39–1.01)</td>
<td>0.67 (0.41–1.08)</td>
</tr>
</tbody>
</table>

a Using (1–4)/4 positive answers as reference category

There were also differences in hospital readmission depending on Gottfries’ four-item test scores. When just looking at the sample, the cumulative proportions of individuals without unplanned readmission were higher among the study participants with 4/4 positive answers (Figure 8). The Mantel–Cox log-rank test regarding the difference between test scores of 0/4 and 4/4, i.e. the most contrasting curves, was statistically significant (p = 0.042).

Figure 8. Kaplan–Meier curves for all-cause readmissions to hospital within 180 days depending on Gottfries’ four-item test score.
Proportions of psychotropic drug users: papers II, III and IV

Most people registered in SveDem and still alive during the second half of 2017 had filled at least one prescription for any psychotropic drug during that six-month period (Table 8). Antidepressants and antidementia drugs were the most frequently prescribed subgroups of psychotropics, at least when treating drug use as a dichotomized variable. That result was also reflected at the substance level, since four individual drugs with prevalence estimates in the range of 10–20% belonged to either of those ATC subgroups. In paper IV, the notably larger dataset based on the corresponding six-month period for 2019 displayed similar patterns regarding all ATC subgroups and individual drugs, regardless of the data source (Table 8).

The comparison between the SveDem-based populations and persons found in the National Patient Register but not registered in SveDem revealed notable differences in drug use; for example, the proportion of antidementia drug users was almost three times larger in the SveDem-based subpopulation (Table 8). There were also 17,380 individuals who were not found in those two registries but were instead included based on records of having had one or more prescriptions for antidementia drugs filled at community pharmacies from 2007 to 2019 according to the Swedish Prescribed Drug Register. Apart from the antidementia drugs, for which the comparison would be biased due to the choice of inclusion criteria, this subgroup was overall characterized by smaller proportions of psychotropic drug users.

Paper II targeted a different study population that was older and contained more females than did the registry-based datasets (Table 9). Regarding medicines, the hospital-based sample had proportions of psychotropic users that were on average smaller than those in paper IV with major NCD, but larger than the reference group. One exception to that pattern was the proportion using sedatives or hypnotics, primarily zopiclone, which was larger in paper II than either of the two groups compared in paper IV.
Table 8. Characteristics and proportions of psychotropic drug users among people with major neurocognitive disorder identified through different registries.

<table>
<thead>
<tr>
<th></th>
<th>SveDem, 1 July to 31 December 2017</th>
<th>SveDem, 1 July to 31 December 2019</th>
<th>National Patient Register, 1 July to 31 December 2019</th>
<th>Swedish Prescribed Drug Register, 1 July to 31 December 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals, $n$</td>
<td>38,251</td>
<td>40,911</td>
<td>61,426</td>
<td>17,380</td>
</tr>
<tr>
<td>Female, % ($n$)</td>
<td>61.4 (23,476)</td>
<td>60.9 (24,918)</td>
<td>46.2 (28,384)</td>
<td>61.3 (10,662)</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>82.5 ± 6.7</td>
<td>83.5 ± 6.7</td>
<td>79.8 ± 7.9</td>
<td>83.9 ± 6.7</td>
</tr>
<tr>
<td>Any psychotropic drug, $^c$ % ($n$)</td>
<td>82.9 (31,712)</td>
<td>60.1 (24,607)</td>
<td>60.3 (37,029)</td>
<td>55.3 (9,613)</td>
</tr>
<tr>
<td>Antipsychotics, % ($n$)</td>
<td>12.0 (4,594)</td>
<td>12.7 (5,203)</td>
<td>13.4 (8,230)</td>
<td>10.6 (1,839)</td>
</tr>
<tr>
<td>- Risperidone</td>
<td>7.2 (2,762)</td>
<td>8.1 (3,273)</td>
<td>6.7 (3,887)</td>
<td>5.8 (998)</td>
</tr>
<tr>
<td>- Haloperidol</td>
<td>1.5 (569)</td>
<td>1.4 (578)</td>
<td>1.6 (937)</td>
<td>1.0 (172)</td>
</tr>
<tr>
<td>- Olanzapine</td>
<td>1.4 (530)</td>
<td>1.4 (567)</td>
<td>2.4 (1,422)</td>
<td>1.5 (253)</td>
</tr>
<tr>
<td>- Quetiapine</td>
<td>1.4 (530)</td>
<td>1.9 (757)</td>
<td>2.7 (1,593)</td>
<td>2.0 (334)</td>
</tr>
<tr>
<td>Antidepressants, % ($n$)</td>
<td>43.2 (16,511)</td>
<td>44.3 (18,139)</td>
<td>40.6 (24,916)</td>
<td>39.3 (6,834)</td>
</tr>
<tr>
<td>- Mirtazapine</td>
<td>20.2 (7,711)</td>
<td>23.0 (9,826)</td>
<td>21.5 (12,564)</td>
<td>20.3 (3,483)</td>
</tr>
<tr>
<td>- Citalopram</td>
<td>14.0 (5,366)</td>
<td>10.7 (4,307)</td>
<td>9.5 (5,523)</td>
<td>8.6 (1,467)</td>
</tr>
<tr>
<td>- Sertraline</td>
<td>8.8 (3,349)</td>
<td>10.5 (4,242)</td>
<td>9.0 (5,246)</td>
<td>10.2 (1,752)</td>
</tr>
<tr>
<td>- Escitalopram</td>
<td>3.9 (1,475)</td>
<td>5.1 (2,049)</td>
<td>4.4 (2,571)</td>
<td>3.5 (593)</td>
</tr>
<tr>
<td>- Venlafaxine</td>
<td>1.8 (695)</td>
<td>1.8 (711)</td>
<td>2.8 (1,651)</td>
<td>2.1 (366)</td>
</tr>
<tr>
<td>- Amitriptyline</td>
<td>0.9 (350)</td>
<td>1.1 (450)</td>
<td>1.8 (1,057)</td>
<td>1.7 (295)</td>
</tr>
<tr>
<td>- Duloxetine</td>
<td>0.9 (353)</td>
<td>1.1 (449)</td>
<td>1.7 (1,012)</td>
<td>1.0 (175)</td>
</tr>
<tr>
<td>- Paroxetine</td>
<td>0.4 (139)</td>
<td>0.4 (158)</td>
<td>0.6 (360)</td>
<td>0.4 (77)</td>
</tr>
<tr>
<td>- Fluoxetine</td>
<td>0.3 (117)</td>
<td>0.3 (137)</td>
<td>0.6 (359)</td>
<td>0.3 (54)</td>
</tr>
</tbody>
</table>
**Table 8. Continued.**

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Proportion</th>
<th>(n)</th>
<th>Proportion</th>
<th>(n)</th>
<th>Proportion</th>
<th>(n)</th>
<th>Proportion</th>
<th>(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiolytics, % (n)</td>
<td>22.0 (8,430)</td>
<td>21.5 (8,786)</td>
<td>22.8 (14,002)</td>
<td>18.8 (3,264)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Oxazepam</td>
<td>19.9 (7,626)</td>
<td>19.9 (8,014)</td>
<td>18.8 (10,981)</td>
<td>17.1 (2,920)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Hydroxyzine</td>
<td>1.4 (526)</td>
<td>1.2 (490)</td>
<td>3.3 (1,916)</td>
<td>1.4 (239)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Diazepam</td>
<td>1.1 (428)</td>
<td>1.0 (392)</td>
<td>2.4 (1,420)</td>
<td>0.8 (142)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sedatives or hypnotics, % (n)</td>
<td>23.0 (8,783)</td>
<td>22.3 (9,119)</td>
<td>28.9 (17,765)</td>
<td>20.7 (3,602)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Zopiclone</td>
<td>16.0 (6,124)</td>
<td>15.1 (6,069)</td>
<td>18.8 (10,972)</td>
<td>13.7 (2,351)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Zolpidem</td>
<td>2.6 (986)</td>
<td>2.5 (991)</td>
<td>5.0 (2,932)</td>
<td>0.6 (661)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clomethiazole</td>
<td>4.0 (1,525)</td>
<td>4.2 (1,674)</td>
<td>3.7 (2,172)</td>
<td>2.2 (374)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Melatonin</td>
<td>2.0 (774)</td>
<td>3.2 (1,273)</td>
<td>3.5 (2,044)</td>
<td>2.5 (432)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Propiomazine</td>
<td>1.0 (400)</td>
<td>1.0 (406)</td>
<td>5.2 (3,050)</td>
<td>1.2 (199)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidementia drugs, % (n)</td>
<td>56.7 (21,686)</td>
<td>57.8 (23,666)</td>
<td>21.2 (13,053)</td>
<td>74.8 (12,996)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Donepezil</td>
<td>25.7 (9,828)</td>
<td>25.8 (10,390)</td>
<td>8.9 (5,199)</td>
<td>43.3 (7,417)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Rivastigmine</td>
<td>8.3 (3,185)</td>
<td>8.0 (3,213)</td>
<td>3.8 (2,192)</td>
<td>7.6 (1,308)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Galantamine</td>
<td>6.2 (2,384)</td>
<td>5.8 (2,352)</td>
<td>1.9 (1,137)</td>
<td>3.2 (551)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Memantine</td>
<td>26.8 (10,269)</td>
<td>30.3 (12,188)</td>
<td>12.0 (6,994)</td>
<td>28.1 (4,809)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* Individuals registered in the National Patient Register but not in SveDem

*b* Individuals with a history of filled prescriptions for antidementia drugs (N06D) from 1 July to 31 December 2019 but registered in neither SveDem nor the National Patient Register

*c* ATC subgroups N05A, N05B, N05C, N06A and N06D

*d* ATC subgroups N05A, N05B, N05C and N06A

All p-values < 0.001 when comparing proportions from the three different registry-based populations from 2019 through Pearson chi-square tests.

The presentation includes individuals from incomplete matching pairs, so there are more than those analysed in paper IV.

Psychotropic drugs with user proportions <0.5% in all four categories are not included in the presentation.
Table 9. Comparison of psychotropic drug use in patients admitted to acute medical wards, people with major NCD and references without diagnosed major NCD from the total older population.

<table>
<thead>
<tr>
<th></th>
<th>Paper II</th>
<th>Major NCD</th>
<th>Reference group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals, n</td>
<td>300</td>
<td>102,419</td>
<td>102,419</td>
</tr>
<tr>
<td>Female, % (n)</td>
<td>62.7 (188)</td>
<td>52.9 (54,208)</td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>84.2 ± 5.8</td>
<td>80.7 ± 7.3</td>
<td></td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>83 (8)</td>
<td>81.0 (11)</td>
<td></td>
</tr>
<tr>
<td>Dose dispensing of medicines, % (n)</td>
<td>28.3 (85)</td>
<td>53.5 (54,773)</td>
<td>9.9 (10,162)</td>
</tr>
<tr>
<td>Any psychotropic drug, % (n)</td>
<td>48.3 (145)</td>
<td>58.9 (60,343)</td>
<td>28.2 (28,891)</td>
</tr>
<tr>
<td>Antipsychotics, % (n)</td>
<td>2.3 (7)</td>
<td>12.8 (15,273)</td>
<td>1.4 (1,439)</td>
</tr>
<tr>
<td>- Risperidone</td>
<td>1.7 (5)</td>
<td>6.6 (6,733)</td>
<td>0.5 (466)</td>
</tr>
<tr>
<td>Antidepressants, % (n)</td>
<td>23.0 (69)</td>
<td>41.2 (42,204)</td>
<td>13.3 (13,581)</td>
</tr>
<tr>
<td>- Mirtazapine</td>
<td>11.3 (34)</td>
<td>21.5 (21,272)</td>
<td>5.7 (5,227)</td>
</tr>
<tr>
<td>- Sertraline</td>
<td>4.7 (14)</td>
<td>9.7 (9,551)</td>
<td>2.6 (2,411)</td>
</tr>
<tr>
<td>- Citalopram</td>
<td>3.7 (11)</td>
<td>9.4 (9,252)</td>
<td>3.4 (3,092)</td>
</tr>
<tr>
<td>- Amitriptyline</td>
<td>2.0 (6)</td>
<td>1.6 (1,573)</td>
<td>1.9 (1,724)</td>
</tr>
<tr>
<td>- Venlafaxine</td>
<td>1.7 (5)</td>
<td>2.5 (2,442)</td>
<td>0.8 (722)</td>
</tr>
<tr>
<td>- Duloxetine</td>
<td>1.7 (5)</td>
<td>1.5 (1,460)</td>
<td>0.6 (508)</td>
</tr>
<tr>
<td>- Escitalopram</td>
<td>1.3 (4)</td>
<td>4.5 (4,499)</td>
<td>1.3 (1,182)</td>
</tr>
<tr>
<td>Anxiolytics, % (n)</td>
<td>7.3 (22)</td>
<td>21.3 (21,789)</td>
<td>7.3 (7,521)</td>
</tr>
<tr>
<td>- Oxazepam</td>
<td>5.7 (17)</td>
<td>18.3 (18,128)</td>
<td>5.9 (5,420)</td>
</tr>
<tr>
<td>- Hydroxyzine</td>
<td>1.7 (5)</td>
<td>2.4 (2,351)</td>
<td>1.4 (1,290)</td>
</tr>
<tr>
<td>- Sedatives or hypnotics, % (n)</td>
<td>30.0 (90)</td>
<td>25.4 (25,994)</td>
<td>17.5 (17,933)</td>
</tr>
<tr>
<td>- Zopiclone</td>
<td>18.3 (55)</td>
<td>16.6 (16,396)</td>
<td>12.6 (11,466)</td>
</tr>
<tr>
<td>- Zolpidem</td>
<td>9.7 (29)</td>
<td>4.1 (4,031)</td>
<td>5.9 (5,416)</td>
</tr>
<tr>
<td>- Propiomazine</td>
<td>3.3 (10)</td>
<td>3.4 (3,357)</td>
<td>2.0 (1,798)</td>
</tr>
</tbody>
</table>

a ATC subgroups N05A, N05B, N05C and N06A

All p-values regarding differences in means or proportions were < 0.001.

Psychotropic drug user proportions <0.5% in the sample from paper II are not included in the presentation.
Factors associated with psychotropic drug use: papers II, III and IV

Major neurocognitive disorder

In paper III, associations between psychotropic drug use and major NCD were investigated in terms of specific subtypes of the disorder. In brief, people with LBD had significantly higher odds of psychotropic drug use than did people with AD, an observation that was consistent for all ATC subgroups except antidementia drugs. The strongest observed association in that regard was the one between LBD and antipsychotic drug use (adjusted OR, 2.40 [95% CI 2.04–2.82]). There was a similar association between frontotemporal dementia and antipsychotic drug use (adjusted OR, 1.73 [1.35–2.23]), although not with the same effect size as that of LBD. Similarly, using AD as the reference subtype and excluding mixed or unspecified subtypes, the odds of being exposed to antidepressants, anxiolytics, or sedatives and hypnotics were all slightly higher among people categorized as VaD, with adjusted ORs of 1.21 (1.14–1.29), 1.09 (1.01–1.17) and 1.32 (1.23–1.41), respectively. Among other independent variables analysed, longer time since being diagnosed was also positively associated with drug use for all classes of psychotropics, except antidementia drugs.

Compared with individuals without diagnosed major NCD from the total older population, more than twice as many people with major NCD (59% versus 28%) had filled a prescription for at least one psychotropic drug belonging to ATC subgroups N05A, N05B, N05C and N06A. Even when adjusted for sex and type of residency, all ORs regarding major NCD and psychotropic drug use were positive. The most obvious difference was the OR of 6.94 regarding antipsychotic drugs, followed by antidepressants (OR, 3.96), anxiolytics (OR, 2.46), and sedatives and hypnotics (OR, 1.54), with p-values < 0.001 for all observed differences in user proportions. Even though only 29 individuals in paper II had a documented major NCD, there was still a larger proportion of psychotropic drug use in that group than in the rest of the sample, with percentages of 79% and 45%, respectively (OR, 4.68 [95% CI 1.85–11.86]). In summary, major NCD was positively associated with overall psychotropic drug use, regardless of study population and setting.

Type of residency

Paper IV reported a positive association between nursing home residency and psychotropic drug use: adjusted for age, sex and major NCD, the ORs
were 2.23 (95% CI 2.07–2.40), 4.98 (4.60–5.39), 6.28 (5.85–6.73) and 18.57 (16.46–20.95) for the ATC subgroups N05C, N05B, N06A and N05A, respectively, compared with people living in ordinary private homes. When accounting for type of residency through interaction terms and subgroup comparisons, the positive associations between major NCD and psychotropic drugs were more pronounced among people with ordinary private homes; for example, the OR regarding antipsychotic use and major NCD was almost four times higher for people living in ordinary private homes (adjusted OR, 7.13 [95% CI 6.65–7.64]) than for nursing home residents (adjusted OR, 1.85 [1.67–2.05]). The only ATC subgroup that showed a contrasting result was sedatives and hypnotics, for which the association with major NCD was negative (adjusted OR, 0.74 [0.69–0.80]) among nursing home residents.

Sex differences in psychotropic drug use

In the regression models applied in papers III and IV, female sex showed positive relationships with all ATC subgroups of psychotropic drugs, except antipsychotics. Moreover, in a direct comparison of psychotropic drug users in paper IV, the proportions of psychotropic drug users were consistently larger in the female group than the male population (Table 10). A similar pattern was found in the sample targeted in paper II although the differences were only statistically significant for ATC subgroup N05C and overall psychotropic drug use (Table 11).

Table 10. Proportions of psychotropic drug users in paper IV according to sex.

<table>
<thead>
<tr>
<th>Psychotropic drug class</th>
<th>Female (n = 108,416)</th>
<th>Male (n = 96,422)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All psychotropic drug classes, a % (n)</td>
<td>65.4 (41,825)</td>
<td>52.8 (29,424)</td>
</tr>
<tr>
<td>Antidepressants N06A, % (n)</td>
<td>32.5 (35,219)</td>
<td>21.3 (20,566)</td>
</tr>
<tr>
<td>Antipsychotic N05A, % (n)</td>
<td>7.9 (8,611)</td>
<td>5.9 (5,735)</td>
</tr>
<tr>
<td>Anxiolytics N05B, % (n)</td>
<td>17.3 (18,764)</td>
<td>10.9 (10,546)</td>
</tr>
<tr>
<td>Sedatives/hypnotics N05C, % (n)</td>
<td>24.9 (27,016)</td>
<td>17.5 (16,911)</td>
</tr>
<tr>
<td>Antidementia drugs N06D, % (n)</td>
<td>46.5 (29,768)</td>
<td>35.8 (19,947)</td>
</tr>
</tbody>
</table>

aATC subgroups N05A, N05B, N05C and N06A

Pearson chi-square test p-values were <0.001 for all listed differences in proportions.
Table 11. Proportions of psychotropic drug users among acutely admitted older people in paper II according to sex.

<table>
<thead>
<tr>
<th>Psychotropic drug class</th>
<th>Female ((n = 188))</th>
<th>Male ((n = 112))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All psychotropic drug classes, (^a) % ((n))</td>
<td>54.8 (103)</td>
<td>37.5 (42)</td>
<td>0.004</td>
</tr>
<tr>
<td>Antidepressants N06A, % ((n))</td>
<td>26.1 (49)</td>
<td>17.9 (20)</td>
<td>0.102</td>
</tr>
<tr>
<td>Antipsychotic N05A, % ((n))</td>
<td>2.1 (4)</td>
<td>2.7 (3)</td>
<td>0.760</td>
</tr>
<tr>
<td>Anxiolytics N05B, % ((n))</td>
<td>9.0 (17)</td>
<td>4.5 (5)</td>
<td>0.141</td>
</tr>
<tr>
<td>Sedatives/hypnotics N05C, % ((n))</td>
<td>34.0 (64)</td>
<td>23.2 (26)</td>
<td>0.048</td>
</tr>
<tr>
<td>Antidementia drugs N06D, % ((n))</td>
<td>3.2 (6)</td>
<td>1.8 (2)</td>
<td>0.465</td>
</tr>
</tbody>
</table>

\(^a\) ATC subgroups N05A, N05B, N05C and N06A

Of note, the distribution of males and females diagnosed with major NCD displayed apparent discrepancies between the three registries used to generate the study population for paper IV (Table 8). Males were in the clear majority among the individuals found in the National Patient Register but not in SveDem, whereas approximately 60% of the cases from the remaining data sources were females.
Discussion

Main findings

This thesis addressed drug use among populations of older people who can be considered especially vulnerable due to varying levels of cognitive impairment and/or acute medical care. Although all study populations may be regarded as vulnerable in some respects, one of the most conspicuous findings was that they were actually very different from one another when compared descriptively in terms of demographic variables, disease burden and medication use. These observations highlight the complexity of addressing older people in research and the danger of treating them as one homogenous group. For example, even though cognitive impairment seemed to be a major issue among the inpatients studied in paper II, one of the most obvious differences compared with the registry-based datasets was that only 29 out of 300 individuals had confirmed major NCD. Furthermore, the overall proportion of psychotropic drug users was approximately 50% and thus apparently smaller than the proportions found in the registry-based populations.

Paper I described a clinical pharmacist intervention initiated immediately after discharge from the acute medical ward to detect and manage MRPs as early as possible and thereby prevent readmission among people aged 75 years or older living in ordinary private homes. Paper II showed that MRPs may be involved in about one third of emergency hospital admissions in this specific patient group, who therefore at least theoretically should be an appropriate target population for pharmaceutical interventions like the one outlined in paper I. The association between MRAs and cognitive impairment is still uncertain, but the results indicate that MRAs are less common among patients with the lowest cognitive test scores (adjusted OR, 0.31 [95% CI 0.10–0.93]; $p = 0.037$). The Gottfries’ four-item test score also seems to be a predictor of all-cause readmission. In that comparison, however, it was those with the lowest test scores who had the highest risk of readmission. These findings are worth exploring further to determine the utility of cognitive screening as a means for setting eligibility criteria in clinical trials or identifying patients at higher risk of undesired clinical outcomes.

Based on papers III and IV, several drugs with ambiguous yet well-documented associations with falls, fractures, cognitive deterioration and other undesired outcomes appear to be commonly used by older Swedish people with major NCD. In paper III, there was a worrisome association
between antipsychotic use and LBD (adjusted OR, 2.40 [95% CI: 2.04–2.82]). Even though that figure could be interpreted as a sign that people with severe visual hallucinations are being recognized and treated, it nonetheless indicates a problematic situation, since those who are most sensitive to antipsychotic medications seem to have more than twice the odds of being exposed to such drugs than those with AD [204]. In particular, the utilization of potentially harmful drugs among vulnerable older individuals with major NCD indicates a clinical dilemma, and the need for improved treatment strategies, in terms of both medicines and non-pharmacological options, deserves increased attention in research, health care and public debate. There were discrepancies in psychotropic drug use based on sex and between people found in different registries, both of which might signal inequalities in the care of people with major NCD.

Paper IV confirmed that psychotropic drugs are strongly associated with nursing home residency. Nursing homes could thus be an appropriate setting for interventions that focus on the appropriateness of psychotropic drug use. Of note, a substantial number of individuals in the reference group used antipsychotics, which indicates that even in the absence of a NCD diagnosis it may be equally relevant to consider any psychotic symptoms among older people as potential manifestations within the NPS spectrum.

Improving medication use through interventions in transitions of care

Transitions of care have been highlighted as a crucial phase in the prevention of readmission [91], and it is also well-documented that a substantial proportion of readmission events are caused by various problems in some way related to the use of medicines [14, 23]. Based on the preliminary results of the clinical trial, almost half of the study participants experienced at least one readmission within the first 180 days of being discharged from hospital, and about one third of the index admissions reported in paper II were considered at least possibly medication related. Of note, 24 participants were readmitted within one week, which may be recognized as a sign that some care transitions were suboptimal in one way or another. Moreover, as shown in Figure 7, participants with HF at baseline had a higher readmission rate than those without the condition, supporting the assumption that HF, as suggested in the literature [14, 27, 30], is a relevant prognostic factor in terms of readmission. Hence, including HF as a covariate in the planned Cox regression analysis, as specified in paper I, makes sense and could
improve the statistical efficiency. Taken together, the study population and the context of the intervention (i.e. transitional care) remain promising, and the idea of combining medication reviews with additional pharmaceutical actions may be an effective means for reducing MRAs, according to an extensive review from 2021 by Dautzenberg et al. [205]. Other reviews have come to similar conclusions [206, 207], indicating that the chosen primary outcome is probably a valid measure of this type of intervention, and that that effective interventions are typically initiated during ward stay and then prolonged during care transitions. On the other hand, since the recruitment and enrolment of participants for the intervention study began, several inconsistent trial results of medication reviews or similar pharmaceutical interventions conducted in Scandinavian healthcare contexts have been published [208-212]. The MedBridge trial [210], for example, which also incorporated elements of phone-based follow-up after hospital discharge, unexpectedly found higher readmission rates in the intervention group, despite comparing the intervention model against standard care without medication review.

Hospital admissions of older people can be due to multiple causes, for example, accidents, progression of previous conditions or onset of new diseases. Therefore, the contradictory findings described above add some doubt as to whether clinical events really are the most appropriate outcome measure with which to assess the effect of clinical pharmacists on medication use in a Swedish healthcare context, even though MRA has been identified as a core outcome of pharmacist interventions [213, 214]. The lack of strong evidence indicates that a complex post-discharge intervention targeting multimorbid older people might be difficult to design; the focus should perhaps instead be on addressing specific subgroups of older individuals with more tailored intervention models. Improvements in patient behaviour, for example, better medication adherence to long-term treatments of hypertension, hyperlipidaemia and diabetes type 2, that are not sustained are perhaps insufficient to ultimately affect clinical endpoints [215]; specific critical conditions with complex medication regimens (e.g. HF) are a notable exception [29, 216, 217].

Cognitive impairment and medication-related hospital admission

As mentioned, it was theorized that cognitive impairment would be an important factor in the context of MRAs since it might impede adherence and similar practical aspects of medication therapy. Although some cases of admissions due to suboptimal adherence were reported in paper II, for
example, involving diuretics among people with HF or insulin regimens in diabetes type 2, the data were too sparse to draw any conclusions regarding adherence and cognitive impairment. It must also be stressed that optimal medication adherence was assumed by the assessors if not otherwise hinted at in the admission notes. In hindsight, the association between adherence and MRAs is perhaps better explored separately using different methods.

Contrary to the assumption outlined above, the results in paper II showed that people with the lowest cognitive test scores had approximately three times lower odds of MRA than did the rest of the sample. This finding highlights that cognitive impairment is an important factor to consider in the context of MRAs. Whether the results indicate decreased risk for cognitively impaired individuals and applies in the context of readmission remains to be confirmed; the ORs could simply reflect a competing risk from co-morbidities and polypharmacy and indicate that those with cognitive impairment have a much higher incidence of non-MRAs that make the proportion of MRAs appear small in comparison.

It could also be interesting to take the discussion one step further and speculate as to whether or not the relationship is causal, even though there is no such evidence in paper II. Based on the negative impact cognitive impairment has on adherence and similar aspects of medication use [190], the idea was that persons with the highest cognitive test scores would have lower odds than the others, a difference that would become less apparent after controlling for home health care and cohabitants in the regression model – in other words, a causal theory that the effects of cognitive impairment could be balanced by medical and social support (Figure 5). However, as mentioned above, the association was in the opposite direction and only marginally affected by those two covariates. There could, however, be several plausible underlying explanations for this contradictory result. First, paper II was based on cross-sectional data, which are not the most reliable type of data when it comes to hypothesizing about causality, and the observed difference in odds does not necessarily translate into a similar estimation when cognitive screening and MRAs are compared longitudinally. For example, the Kaplan–Meier curves in Figure 8 and the corresponding log-rank test regarding categories 0/4 and 4/4 positive answers showed that those with lowest test scores had a higher probability of unplanned all-cause readmission at any time point during the 180 days of follow-up ($p = 0.042$). The difference in survival was even similar in magnitude to the one observed between patients with and without HF (Figure 7). Although the observation reveals little about MRAs, it indicates that those with lower cognitive test scores have higher frequencies of hospital admissions.
overall, supporting the theory of competing risk discussed previously. Therefore, given the limitations of the cross-sectional study design, the association needs to be further explored through longitudinal approaches to find out how well Gottfries' four-item test can predict the risk of MRA.

Another plausible explanation for the associations found in paper II is that delirium is a potential confounder, and it was therefore tempting to identify cases of suspected delirium based on notes from the medical charts and to use those data as an independent variable in the regression model. However, doing so might have introduced collider bias since delirium could be affected by both underlying cognitive impairment and circumstances arising during the admission itself [201, 218].

In summary, there is probably not a true negative causal association between low cognitive test scores and risk of MRA; the results are more likely a random finding or an association due to competing comorbidities or similar factors. Regardless of the exact relationship, a short and feasible cognitive screening test may still be a highly valuable tool with which to identify individuals at higher risk of MRA and hopefully direct more attention and resources towards those specific individuals. The cross-sectional approach at least shows that it may be more efficient to look for and manage MRPs among people with higher test scores, which is an important observation in its own right, while the survival curves indicate that the Gottfries' four-item test can also be of use to predict all-cause readmission in this patient group.

Potentially inappropriate medication use among people with major neurocognitive disorder

Paper III shows that many individuals with major NCD are at potential risk of harm because of exposure to psychotropic medication. For example, both oxazepam and zopiclone show troublesome associations with falls in older people [133-135, 219], and the drugs seemed to be used, at least sporadically, in approximately one fifth of all individuals with a diagnosis of major NCD. Zopiclone was also relatively common in the sample of acutely admitted older people in paper II and was used by more than 12% of the reference population in paper IV. Even though anxiolytics with relatively short elimination half-lives (Table 2) seem to be the drugs of choice, the combined results nonetheless raise the question of whether it is reasonable that 10–20% of the older population seem to need pharmacological management of sleep disorders. Moreover, the effect of Z-drugs is, although clinically relevant, relatively small compared with placebo [220], and a key factor when weighing risk versus safety would
thus be the degree of chronic long-term use [221]. None of the studies in this thesis was properly designed to investigate time trends in drug use; however, changing the time frame from six to four months in the sensitivity analysis in paper III only decreased the proportion of zopiclone users from 16.0% to 14.8% (i.e. by approximately 8%). In other words, the variation did not correspond linearly to the 33% decrease in the time window and can thus be seen as a weak indication that a substantial number of people with major NCD seem to have prescriptions for zopiclone filled on a regular basis.

Regarding the other classes of psychotropics, antidepressants had been dispensed to more than 40% of all people diagnosed with major NCD, which might be seen as a warning flag given the need to follow up on such an extensive number of treatments. The association between antidepressants and fall injuries probably deserves to be mentioned in that context [130, 222-225], even though there is limited evidence that the relationship is causal. For example, untreated depression itself is a well-known independent risk factor for falls among older people [135, 225]. The current scientific evidence is mostly based on either observational data or RCTs that are not primarily designed and powered to study fall injuries or other specific ADEs [224, 226]; therefore, it would be heedless to neglect the influence of ‘confounding by indication’, since depression itself is also a recognized risk factor for falls [224]. There are even findings suggesting that the ORs regarding antidepressant use and hip fractures remain more or less unchanged before and after treatment initiation [227]. Of note, mirtazapine was one of the most common individual drugs, even more common than any individual SSRI. The sedative properties of mirtazapine could be desirable in patients with sleep disturbances and come with minimal, if any, anticholinergic properties. It is therefore easy to understand why it has become so popular among prescribers. However, in contrast to SSRIs, mirtazapine has often been omitted from research or grouped with antidepressants that have completely different receptor affinities and pharmacodynamic profiles [135, 226, 228], which makes interpretation of safety studies difficult. Moreover, according to a cohort study of older people in the United Kingdom that compared different antidepressant drugs, mirtazapine was associated with the highest risk of several adverse outcomes [229]. Since its therapeutic indications seem to be expanding, more studies regarding the relationship between mirtazapine and potential outcomes, both desired and unwanted, would be valuable. In summary, the numbers regarding antidepressant use are difficult to evaluate due to the lack of treatment indications. On the positive side, the high percentages could be interpreted as indicating that
mirtazapine is a better alternative to other drugs provided that its effects are properly evaluated.

Antipsychotic exposure was low in relation to other ATC subgroups. Compared with earlier findings of antipsychotic use among people with cognitive impairment in nursing homes [115, 116, 230, 231], the data presented in paper III may reflect a previously recognized and ongoing transition from antipsychotics to antidepressants in the treatment of NPS [232, 233]. The relationship between LBD and antipsychotics is, although expected and easily explained by the characteristic occurrence of visual hallucinations [156, 234], extremely worrying from a risk perspective, since these individuals are the ones most susceptible to potential adverse effects [126, 127, 235-237]. Moreover, people with LBD had lower odds of using antidementia drugs than did those with AD, which suggests that the pharmacological management of NPS had not always been optimized.

In paper IV, there was an incidental finding concerning a substantial number of antipsychotic users in the reference group. Looking back to paper III, the proportion of confirmed LBD (i.e. DLB and PDD combined) was 3.1%, which is far below the prevalence estimates of 4.6% and 9.7% reported from the United Kingdom for DLB and PDD, respectively [238]. Since the observed percentage of LBD was lower than those reports, the suspected cases of undiagnosed major NCD in the reference group possibly included many people with previously unnoticed LBD, which makes exposure to antipsychotics even more serious. People with Lewy body pathologies can present with a complex blend of cognitive deficits, psychiatric symptoms and neurologic malfunctions in combination with autonomic dysregulation [235, 239], and may therefore end up in psychiatric emergency departments with severe hallucinations or be admitted to medical emergency wards due to delirium instead of receiving proper geriatric/psychiatric evaluation. It is crucial to identify and treat these individuals as early as possible, especially since psychotic manifestations can often be effectively managed through antidementia drugs, which, in comparison with antipsychotics, provide a relatively safe treatment option [168, 170]. Finally, it could of course be argued that some individuals may be more vulnerable to antipsychotics than others; however, a nationwide Danish study did not show any significant interactions between comorbidities and the mortality risk associated with antipsychotics [124]. The lack of data on cardiovascular diseases and other comorbidities among older people in papers III and IV should therefore not be a major concern regarding the generalizability of the results or the overall interpretation and conclusion.
As a final comment on psychotropic drug use, it is reasonable to question whether there truly is a desired target percentage? The proportions of drug users may appear conspicuous at first glance; however, one must remember that the medicines have been initiated for the purpose of treating burdensome symptoms that cannot be ignored. Furthermore, a psychotropic drug is generally not prescribed as the only solution; rather, they are one of many different tools in the therapeutic arsenal, and are often administered in combination with non-pharmacological interventions, such as reminiscence therapy, music, meaningful activities and multisensory stimulation [240]. The descriptive data on drug use constitute valuable information for cross-country comparisons and time trends and provide a solid basis for the development of future studies, but other factors must ultimately be accounted for to determine whether the quantity of psychotropic drug use is appropriate. Papers III and IV nonetheless suggest several problem areas that merit further elaboration. For instance, why do people with LBD have lower odds of using antidementia drugs than do individuals with AD despite a more pronounced anticholinergic deficit [241]? Or why were many people without documented major NCD exposed to antipsychotics? Have underlying NCDs been thoroughly examined, and could these individuals instead benefit from AChEIs? Although the results give no direct message to clinical practice on these matters, they highlight areas where psychotropic drug use could potentially be optimized.

This thesis targets different study populations with varying extents and types of medication use, different levels of cognitive deficits and many other dissimilarities. Although people with major NCD and patients within acute medical care can both be considered vulnerable groups of older people, there were several inter- and intra-population differences that deserve to be mentioned and discussed. When looking at the different data sources used in paper IV, there were obvious discrepancies regarding demographic data and drug use (Table 8). For example, males constituted the majority of persons included from the National Patient Register, whereas all subpopulations from the other registries were predominantly female. Persons registered in SveDem also had medicine dispensing records that were more in accordance with established criteria regarding medication use among older people [48, 132]. This observation suggests inequalities regarding the care of people with major NCD, a matter that merits further investigation. One rational yet cautious interpretation is that care providers affiliated with SveDem have a greater geriatric focus and therefore pay more attention to such guidelines. The discrepancies could of course also be influenced by factors at the individual patient level; for example, females and/or individuals taking more appropriate
combinations of medicines might for various reasons be more willing to seek out certain care providers and participate in voluntary quality registries such as SveDem.

Paper II targeted a study population with varying degrees of cognitive impairment based on confirmed major NCD diagnoses and Gottfries’ four-item test scores. In comparison with the two groups presented in paper IV, which both displayed clear differences in terms of medication use, acutely admitted older people seem to be somewhere between the other populations when it comes to psychotropic drug use (Table 9). One exception to that observation was the larger proportion of individuals using sedative or hypnotic drugs, mainly Z-drugs, in paper II than in the registry-based study populations. However, when looking at the specific drugs suspected to be involved in the 108 index admissions classified as possible MRAs, Z-drugs were not unanimously suggested by both assessors in any of the cases. Hence, there is little in the assessments pointing to Z-drugs as a major cause of hospital admission among older people, despite several potential risks according to the literature [133, 221]. At the same time, dosages and durations are mentioned as important factors from that perspective, and neither of those variables was accounted for in any of the study designs due to the lack of reliable data on actual dosage regimens.

In summary, the descriptive data in Table 9 strengthen the assumption that older people encountered within acute medical care differ from other subgroups of older people, and recognizing them as certainly vulnerable in terms of medication use makes sense. Finally, a hospital admission inevitably involves some type of care transition, which brings additional problematic factors into the equation. For example, according to the review literature, medication discrepancies are a well-known problem in transitional care in general [242] and do not necessarily emerge at hospital discharge; rather, they are often already present and potentially unrecognized at the time of admission to hospital [243], and are therefore difficult to notice.

Sex differences

Despite longer life expectancy and possibly genetically inherited resistance to fatal disease, females still seem to suffer more from various overall ailments, illnesses and functional limitations, seek more healthcare contacts and use more medicines than do males [244]. Major NCD is another example of that health paradox, with a female overrepresentation of almost 2:1 compared with males [245, 246]. In
brief, many of the expected sex differences were confirmed in the different proportions of females in the clinical study sample and the registry-based populations. One exception, as mentioned, was the relatively smaller proportion of females with major NCD found in the National Patient Register (Table 8). As a suggested explanation, diagnoses recorded in the National Patient Register might more often be secondary findings during hospital stay, whereas people registered in SveDem have originally sought help for cognitive deficits or NPS. This would also be in line with the previous observation that females have a more positive help-seeking attitude in terms of mental health problems [247]. Regarding sex differences in drug use, cross-country comparisons clearly show that the use of antidepressants and anxiolytics is higher among women than men [248]. The results in papers III and IV were in line with those findings, which might indicate that the threshold for initiating such therapy is lower among females. On the other hand, none of the regression models accounted for diagnoses other than major NCD. In this regard, epidemiological studies show that the frequencies of depression and anxiety disorders are in most contexts and settings notably higher among women [249].

Contrary to the other classes of psychotropics addressed in paper III, the odds of using antidementia drugs were higher among males than females when adjusting for covariates. One explanation might be that AChEIs may interact with several drugs that are commonly used by older women; for example, there are potentially clinically significant interactions between donepezil and SSRIs, both of which can result in QT prolongation, and antidepressants were, as seen in Table 9, associated with female sex. Of note, the association was seemingly opposite to the one found by Sönnerstam et al. [250] in a study largely based on the same dataset but focusing on drug use before and after major NCD diagnosis. One cautious interpretation of these conflicting findings is that AChEIs are initiated in similar amounts in both sexes when the diagnosis of major NCD is confirmed but for some reason discontinued earlier among females; future studies could perhaps further elucidate this relationship to assess the need for potential pharmaceutical interventions that focus on the continuation and/or deprescribing of antidementia drugs. In conclusion, the results in papers III and IV indicate that sex differences in prescribing patterns, at least in Western societies, should be considered when developing new strategies to mitigate and optimize psychotropic drug use among older people with cognitive impairment.
Methods and methodology

Definitions and measurements of drug use

How to define and measure drug use is vital in pharmacoepidemiology and drug utilization research. For the study populations of papers III and IV, dispensation data were utilized since the main intention was to describe drug use in terms of potentially harmful exposures. Since pillbox monitors and similar devices naturally become unfeasible in such large datasets, dispensation records get as close as possible to measuring actual drug use. Dispensation data are also a more exact measure of actual exposure than are medical records and prescriptions. Nevertheless, neither of the registry-based studies could fully capture adherence and the exact dosage regimens, two highly relevant factors in terms of risk, as higher exposure presumably increases the probability of ADRs. The Swedish subsidiary system allows prescription fills for a maximum of three months at a time, and most prescriptions for long-term treatments are adjusted accordingly. The six-month time window applied to define psychotropic drug users thus covered such prescriptions. Still, dichotomizing drug use is an oversimplification of a very complex concept that differs considerably between individuals using the same drug.

Some other limitations were the lack of information regarding indications and treatment durations. However, the principal aim of the registry-based studies was to describe exposure to psychotropics, not to evaluate physicians’ treatment guideline adherence or to confirm inappropriate prescribing. The NPS aspect of major NCD is problematic, and utilization of psychotropics can, as mentioned, be fully warranted under certain circumstances. Finally, including nursing home placement as a covariate in paper III might have improved the regression analysis in terms of prediction, or at least indicated whether it is the diagnosis itself or a higher prevalence of major NCD within nursing home settings that creates the associations. Nevertheless, the regression models were still considered sufficient to account for disease progression, which is a relevant aspect when comparing major NCD subtypes in relation to drug use.

The complexity and causality of hospital admissions

Even though MRPs appear to be common in this population, it is not a given that resolving those issues automatically affects readmissions and other hard clinical outcomes, not even if the endpoint is limited to medication-related events only. People aged 75 years or older and encountered in acute medical wards are on average multimorbid and frail; hence, it is difficult to address this population in research because of the
competing risk of readmission arising from deterioration or symptoms related to the underlying conditions themselves. The complex circumstances of an emergency hospital admission are generally difficult to fully comprehend, and even though the probability of MRAs seems to be high, there could still be other important factors that add up or interact. One illustrative example of the complexity of assessing the causality of admissions is HF, a condition in which there is often a need to balance the need for increased diuretics, beta-blockers and ARBs/ACHIs against the risk of excessive hypertensive treatment resulting in orthostatic hypotension, dizziness and falls, combined with an overall negative prognosis. Therefore, although the results in paper II and previous findings confirm a high prevalence of MRPs that might be prevented or managed, it is still likely that other factors, whether medication related, disease related or a combination of both, may result in early readmission despite close follow-up and early intervention by clinical pharmacists or other healthcare professionals. Moreover, despite the use of standardized tools and criteria, the assessments were probably highly subjective in some cases since there is no uniform answer regarding the most optimal treatment for each individual patient.

Proxy screening cognitive impairment

Readmission rates appear to be especially high among patients with major NCD [36], and even milder cognitive deficits can have drastic effects on the ability to cope with medication regimens [189]. Cognitive impairment might therefore, at least in theory, be highly decisive for the primary outcome of the intervention study. The level of cognitive function is also considered important for the ability to successfully interact with the pharmacist performing the intervention. The short four-item version of the Gottfries’ test provided a fast and feasible way to screen for cognitively impaired individuals even in the absence of a clinically documented major NCD diagnosis. The rationale for the specific cut-off for cognitive impairment chosen in the intervention study (i.e. more than one negative answer) was the fear of missing individuals in early stages of disease progression with significant risk of further deterioration during the follow-up time. Still, it is uncertain whether dichotomizing such a complex concept as cognitive impairment will be meaningful in practice, but based on the difference in all-cause readmissions based on Gottfries’ four-item test scores (Figure 8), there are at least vague indications that adjusting for cognitive impairment may increase the statistical efficiency of the endpoint analysis. Raising the cut-off for cognitive impairment to more than two negative answers, thereby increasing specificity from 92.5% to 98.6%, might in hindsight have been an alternative, since the population
likely included a considerable number of cases with temporary episodes of sudden and fluctuating confusion, probably related to the principal or primary diagnosis of the index admission or to stressors emerging from the hospitalization itself. That was at least the perception of the clinical pharmacists who interacted with the participants during the first months after they were discharged from hospital. The fact that delirium, in some cases drug induced, was confirmed in several participants’ hospital records further supports that suspicion. At the same time, underlying cognitive impairment is the leading risk factor for delirium [200, 218], so the study population may nonetheless be considered representative in the context of cognitive impairment and MRPs.

Since Gottfries’ four-item test was carried out as a proxy screening, it is possible that the person who filled in the questionnaire may not have perceived all instances in which the patient was simply guessing the correct answers. Furthermore, increased specificity would probably not have affected the allocation of the participants with the most pronounced cognitive deficits, i.e. the ones who theoretically might have the biggest impact on the outcome. Taken together, designing a screening tool is always a trade-off between specificity and sensitivity. Based on the results in paper II, a 0/4 cut-off might better distinguish groups with varying susceptibilities to MRA, but it must once again be stressed that longitudinal approaches are needed to determine whether those with the lowest test scores are at lower risk of such events; the results of the clinical trial presented in paper I may provide valuable feedback on that matter.

Neuropsychiatric disorders versus neuropsychiatric symptoms

An important factor to acknowledge in studies of psychotropic drugs and older people, especially cognitively impaired ones, is the occurrence of chronic neuropsychiatric disorders outside the NPS spectrum of major NCD. For example, both schizophrenia [251] and depression [85, 86] can be considered risk factors for the development of major NCD later in life. Unfortunately, dispensing data from the Swedish Prescribed Drug Register provide no clue as to whether antipsychotics and antidepressants were prescribed as a rational long-term treatment of chronic disease or utilized as in the management of the NPS emerging because of the underlying NCD. As seen in paper IV, the study population included a substantial proportion of individuals with earlier records of schizophrenia, much more than in the reference group. In that context, it must therefore be emphasized that neither of the registry-based studies was designed and conducted with the primary intention to describe and assess medication appropriateness.
Sampling and study populations

Inference and generalizability

As with most clinical trials, the study participants recruited to the intervention study should not be considered a true random sample, but rather a selected population of acutely admitted patients who met the eligibility criteria and consented to participate. Due to the working schedules of the research group, there might have been some systematic differences arising from the weekdays when the recruitment took place, so the sampling procedure is a potential source of bias that inevitably affects the external validity of both paper II and the final trial results. Furthermore, people who did not consent to participate in the trial could have had different MRPs or other types of health-related issues than those who were enrolled, problems that even might have been the direct cause of their unwillingness to consent.

The recruitment process of the intervention study was limited to the working hours of those involved in the trial. Consequently, many patients were probably admitted and discharged on short notice before they had been screened for eligibility. There are basically two major reasons for such sudden care transitions: 1) the patient is managing well enough to recuperate at home or, conversely, 2) the patient is in critical condition and requires intensive or other forms of specialized care. The generalizability is thus limited to people who fall somewhere between those two extremes. As a routine measure, the whole clinical ward was screened for eligible patients every time recruitment took place, and all these individuals were given the opportunity to participate, unless they were sleeping or occupied with clinical procedures. In summary, there are no obvious sources of ascertainment bias, i.e. when those being studied are systematically different from the intended study population, and the sample in paper II should, except for nursing home residents, on average be representative of the older patients typically encountered in emergency care.

In the registry-based papers, the concept of study population was chosen in preference to sample since the people analysed basically comprised all persons of interest during the specified time periods. At first glance, it may be reasonable to question the need for inferential statistical tests in relation to such extensive datasets when the whole intended study population can be analysed. Inference was perhaps of minor importance, but the reference group in paper IV was nonetheless only a large sample from the total older population. Second, even though a cross-sectional presentation more or less encompasses all individuals in the population
on a specified date, it can to some extent be regarded as a sample over time, so, as concluded by Thygesen and Ersbøll [252], inferential statistics are still applicable but should perhaps be given less weight than in other types of epidemiological studies. In any case, it is probably more interesting to consider the extent to which the study populations are truly representative of major NCD in Sweden. First, despite the relatively even distribution of affiliated primary care and specialized care units among the SveDem-affiliated care providers (totalling more than 900 units scattered across the country) [192], there are still considerable regional discrepancies in the number of SveDem registrations [253].

It is also necessary to clarify the distinction between data from SveDem and from national health databases such as the National Patient Register and the Swedish Prescribed Drug Register. Since SveDem is a voluntary registry, in terms of both affiliated units and individual patient consent, there might be clinically relevant differences between those registered in SveDem and those who are not. The generalizability is therefore less certain in paper III than in paper IV, since the study population of the latter paper only omitted potential individuals exclusively diagnosed with major NCD in primary care but who had never filled any prescription for antidementia drugs at the pharmacy. When comparing diagnoses registered in SveDem versus the National Patient Register, the degree of coverage was only 32%, and Table 8 shows that individuals registered in SveDem were both older and more likely to be female than those included from the National Patient Register. As a final note on representativity, the proportion of individuals with AD (including mixed AD and VaD) reported in paper III was slightly above 50% and thus similar to worldwide prevalence estimates [59].

An important difference between the study populations in papers III and IV is that the latter also included a reference group. The main purpose of matching individuals instead of making a random sample from the total population was to minimize potential selection bias arising from a hypothetical scenario in which individuals with major NCD would be compared against individuals sampled from the same year. Because of the data extraction method and cross-sectional approach of the study, a random sample of references would only have included people still alive by the end of 2019 and therefore less representative of older people in terms of overall health.

**Quality of registry data**

Registry data are validated to improve and assess their quality. The data from SveDem are continuously validated against both medical records
and external registries (e.g. the National Patient Register) and through adjudication by clinical specialists. Nevertheless, not all reporting units had undertaken those activities, and the exact degree to which SveDem data have been validated is uncertain. However, this issue should not be a major limitation in papers III and IV, since the registry was primarily used to identify the study population, whereas all information regarding medications and social services came from other registries. Potential issues regarding the quality of SveDem data should mainly concern the classification of major NCD subtypes, especially regarding the relatively large proportion of unspecified dementia. Using follow-up registrations from SveDem could have been a way to improve the quality of the data, but this information was only available for approximately half of the population in paper III and would not necessarily have enhanced the representativity, since those subject to more intense follow-up could differ in meaningful ways from those with basal registrations only. Furthermore, according to the annual SveDem report from 2017, approximately 5% of registrations have their diagnoses changed during follow-up, and most commonly among those classified as unspecified at baseline registration [254]. That information confirms the suspicion that the notably large number of unspecified dementia cases was due to uncertainties during the basal examination, but at the same time implies that this issue should be of little relevance to the overall interpretation of the findings. Regarding potential misclassification, there could also be hidden numbers of mixed-type AD and VaD among those labelled as AD or VaD since these pathologies often coexist and share a complex and partly unexplored relationship in terms of cause and effect [255]. The separate categories of AD and VaD, as well as mixed AD and VaD, might therefore probably best be regarded as clinical descriptions of the dominant pathology, or the lack of such, as they are generally not fully distinguishable disorders with a single cause. For example, a 2004 review by Fernando and Ince found the prevalence of ‘pure AD’ to be only 21% [256] and thus far below the 34.8% found in paper III. On the other hand, most patients with some clinical features of AD are still considered potential recipients of most antidementia drugs, even if they present with cerebrovascular pathologies, so this should not have had much impact on the dispensing data analysed. The same arguments also apply to the National Patient Register but are perhaps of less concern since the diagnoses recorded there are exclusively documented by specialist care. There are fewer quality issues regarding data from the Swedish Prescribed Drug Register, which is managed by the Swedish eHealth Agency and not reliant on manual inputting.
Statistical aspects and assumptions

**Logistic regression**

In papers II and III, multiple logistic regression was the principal statistical analysis method. Logistic regression models are based on several assumptions that need to be considered when analysing and interpreting the results [257]: 1) dichotomous outcome; 2) independent observations; 3) linearity between continuous independent variables and the logit function of the odds, for example, when age is treated as a continuous variable; 4) minimal multicollinearity between continuous independent variables; and 5) minimizing the influence of outliers. In addition, there should ideally be at least around 10–20 observations for each individual variable; however, that last assumption was not an issue for any of the relatively extensive datasets presented in this thesis. The above prerequisites were mainly assessed through visual inspection instead of statistical tests and cut-offs, entailing a degree of subjectivity.

**Generalized estimating equations**

In brief, the GEE approach applied in paper IV built on similar assumptions as does conventional logistic regression [203] but had an additional potential advantage in that the method also considered correlation within each matched pair. However, since major NCD was much more common among nursing home residents than among people living in ordinary private homes, many of the matching pairs were disrupted in the subgroup analyses, meaning that less weight was given to the initial matching procedure. Accounting for the matching sequences in the analysis was perhaps not a key factor given such extensive datasets as those in question, similar to previous conclusions regarding matching in case-control studies [258].

**Survival analysis and Cox regression**

The motives for choosing a time-to-event measure as the primary outcome of the intervention study instead of studying cumulative incidence or incidence rates were the advantages of minimizing missing data and of permitting more detailed and nuanced group comparisons. In the end, it is probably more realistic to focus on delaying rather than totally preventing readmission in this frail patient group. Cox proportional hazard models are based on several important assumptions; for example, the reason for censoring must be unrelated to prognosis [259]. Since a hospital admission can obviously not occur after death, survival analysis is a logical and valid method since it accounts for the whole period that
the participants were under observation. Still, it cannot be discounted that some fatalities might be medication related, contradicting the assumption mentioned above. However, unless the death is sudden (e.g. severe brain haemorrhage or coronary infarct), such individuals may presumably be acutely hospitalized, reaching the primary outcome of interest before succumbing to their medication-related illness in the hospital. Second, individuals in nursing homes who are too frail to be transferred to the hospital are excluded from the study in the first place and thus not an issue in terms of outcome assessment. Finally, mortality is a pre-specified secondary outcome of the study and can indicate unbalanced death rates between the groups. Another important assumption in Cox regression is that the hazards are proportional over time \[^{[260]}\], which is far from certain given the intended study population of older multimorbid individuals with various conditions that could deteriorate rapidly. Like logistic regression models, Cox regression models also assume a linear relationship between continuous covariates and the hazard ratio. All assumptions outlined above should therefore be tested once the collection of trial data has been completed.

Subgroup analyses of heart failure and cognitive impairment

Cognitive impairment and HF were two baseline covariates that in themselves seemed to be important prognostic factors regarding unplanned hospitalization and readmission among acutely admitted older patients \[^{[18, 26, 27, 36, 261]}\]. However, those two conditions also distinguished two potentially relevant subgroups of older people in relation to the intervention model being investigated. As described in paper I, there are planned subgroup analyses regarding both cognitive impairment and HF. In a previous study at Umeå University Hospital among older people diagnosed with major NCD, medication reviews conducted during ward stay significantly reduced the risk of medication-related readmission in the group without diagnosed HF, whereas no effect could be confirmed in the other subgroup with HF patients \[^{[36]}\]. Those results were somewhat in conflict with earlier conclusions that pharmacist care could reduce the risk of HF-associated hospital admissions \[^{[262]}\], and might have been due to poor adherence among the individuals with HF during the vulnerable post-discharge phase. The close pharmacist–participant interaction in the intervention model described in paper I might detect and address potential adherence issues. Consequently, the intervention may be more effective in groups in which the MRA rates are expected to be higher.

As for the other planned subgroup analysis, cognitive impairment can have a significant impact on adherence \[^{[189]}\] and was considered both an
important prognostic factor and a potential determinant of the effectiveness of the intervention. Moreover, people with concomitant cognitive impairment and HF seem to be at risk of undertreatment in terms of cardiovascular medicines [263], in turn adding further complexity to the anticipated effect in the overlap between the two subgroups. However, analyses of subgroups are controversial and often entail a considerable danger of type-I and type-II errors [264-267], but the rationale for including and pre-specifying analyses of subgroups and interaction effects in the study protocol was nonetheless considered important. Although the potential lack of sufficient statistical power for subgroup analyses should be acknowledged, an indication of a subgroup effect might provide useful indications for choosing proper eligibility criteria in upcoming post-discharge interventions.

Inter-rater agreement and reliability

Since paper II relied on classification by different assessors, the concepts of inter-rater reliability and inter-rater agreement are important to address. The Cohen’s kappa statistic is an established measure of inter-rater reliability, which in this context can be described as the degree to which different responders can consistently distinguish between unlikely MRAs and possible MRAs [268]. Although the kappa value is relevant and accounts for agreement/disagreement due to randomness, it is hard to fully evaluate and interpret the statistic. Considering that AT-HARM10 is primarily intended as an initial screening tool to efficiently select hospital admissions for a second and more thorough evaluation, it is probably not justified to apply the same kappa value acceptance criteria as applied, for example, in an expensive clinical procedure that directly impacts the subsequent treatment and outcome of the patient. Given that AT-HARM10 automatically defines admissions that cannot be classified as unlikely MRAs as possible MRAs, most of the utility probably lies in the ability to relatively quickly exclude hospital admissions that are unlikely to be medication related, thereby saving time by not having personnel conduct more thorough assessments. Therefore, the 68% inter-rater agreement regarding unlikely MRAs among the admissions that at least one assessor considered unlikely to be medication related is perhaps the most informative inter-rater statistic. Together with the initial validation of AT-HARM10 [39], paper II shows that AT-HARM10 may be a feasible and valuable instrument in research contexts; however, its utility in clinical practice needs further evaluation.
Ethical considerations

Ageism in research

As mentioned, older people comprise the most disease-burdened age group in our society; they thus represent the typical patients encountered in hospital and primary care settings and, ultimately, are also the most probable recipients of medicines. Despite this clinical reality, older people are far too often excluded from drug trials for a variety of reasons that appear to be both intentional and unintentional [269, 270]. In addition to clear age cut-offs as inclusion criteria, co-morbidities and polypharmacy are common reasons for exclusion since they may confound the results and in other ways impede the interpretation of findings. This dilemma ultimately affects generalizability, and studies of effect and safety profiles among older patients are instead left for post-marketing settings, so-called phase IV trials [271]. Here, research in pharmacoepidemiology and drug utilization fulfil an important role in the observation and evaluation of ‘real-world’ medication use, especially among older people with mental disorders for whom trial data are lacking or completely absent [272]. This thesis applies methods within the framework of pharmacoepidemiology and drug utilization research to study older populations with a focus on two especially vulnerable subgroups, namely, individuals diagnosed with major NCD and people 75 years of age or older who are acutely admitted to hospital.

Cognitive impairment and informed consent

Informed consent is generally a prerequisite for involving participants in clinical trials according to Swedish ethics regulations [197] and the Helsinki Declaration [273]. However, there are circumstances in which obtaining informed consent is problematic, for example, in research involving cognitively impaired individuals [274]. That was the case for all the papers included in this thesis, which necessitated important ethical considerations. All studies involved varying proportions of individuals with confirmed diagnoses of major NCD. Because of the nature and scale of the registry-based study populations, informed consent was not obtained; instead, the rights and interests of the study participants were represented by the Swedish Ethical Review Authority during the application for ethical approval.

Based on paper II, the prevalence of major NCD among acute hospital admissions of people aged 75 years or older appears to be in the vicinity of 10%, which is a similar percentage and what could be expected based on the estimated prevalence of approximately 13% in that age group in
general [59] when considering the exclusion of nursing home residents. For people with a diagnosis of major NCD documented in the medical chart, the next of kin was given the opportunity to decline participation on the study participant’s behalf. Applying this principle was disputable since cognitive impairment is challenging to assess and affect many different cognitive domains. For example, Jefferson et al. found that people with mild cognitive impairment also differ in decisional capacity from controls with normal cognition [275]. With these aspects in mind, truly informed consent may not have been obtainable from all study participants, particularly those who got a negative result on Gottfries’ four-item test, but such judgements always entail a delicate balance between enrolling non-informed participants and the risk of violating older people’s autonomy. To be included and enrolled in the intervention study, all participants had to express willingness to participate, regardless of their cognitive capacity. Moreover, for a non-pharmacological intervention focusing on implementing and reinforcing the physician’s instructions, there was a clear potential benefit for the study participant. The counteracting risk was estimated to be very low since the physician was still in control of all decision-making regarding treatment alterations. In summary, the integrity of study participants as well as the need for a simple and feasible method for assessing each person’s ability to provide informed consent ultimately outweighed the possibility of enrolling individuals unable to fully comprehend all aspects of participating in the trial.

Impact of the coronavirus disease

In early 2020, outbreaks of the coronavirus disease 2019 (COVID-19) emerged rapidly worldwide and quickly turned into a long-lasting pandemic. The disease had a noticeable impact on the organizational structure, decision-making and priorities of the Swedish healthcare system. Region Västerbotten was no exception, which resulted in many patients in the recruitment ward at Umeå University Hospital being relocated to other wards to prevent spread of the infection, while other potential study participants could not be seen in person until the suspicion of incipient or ongoing COVID-19 infection had been assessed and dismissed through testing. Moreover, it was also a concern that meeting potential study participants in person could facilitate the spread of the disease to, from and within the medical ward. Those worries led to an official six-month pause in the recruitment of study participants, and the inclusion rate for the intervention study described in paper I was severely affected for a long time afterwards. Consequently, the data collection and
analyses could not be completed in due time, and the original intention to publish the complete trial results in this thesis was inevitably discarded. There was less negative impact, if any, on the registry-based studies since they were based on data that had been registered before the pandemic accelerated.
Clinical significance

The aim of this thesis was to describe medication use in the older population and to identify potential means of managing MRPs in certain vulnerable subgroups of older people. It is therefore interesting to reflect on how the results could be useful for clinical practice, from both the shorter- and longer-term perspectives. The study outlined in paper I is conducted in a clinical setting and is almost fully integrated with standard care. The protocol thus provides a concrete example of how MRPs and associated hospital admissions can be managed in the context of transitional care. Although it remains to be determined whether the intervention may be effective, the experiences and process evaluations of the trial will nonetheless be important for the development of subsequent clinical trials.

Regarding papers II–IV, knowledge based on cross-sectional data is not enough to directly affect treatment guidelines but can nonetheless be clinically relevant for several reasons. First, the large proportion of possible MRAs among older people in the emergency care setting indicates that this is a relevant patient group in the management of MRPs. Considering the multifactorial nature of hospital admissions, the large proportions of possible MRAs detected using AT-HARM10 among acutely admitted older people do not automatically mean that all those admissions were preventable, but it is nonetheless an important indicator that there are many clinically relevant MRPs that could be paid more attention in this specific group of older people. Even if such efforts are not enough to significantly reduce readmission rates, it could still be of great value for the individual patient’s situation as well as for relatives and caregivers if issues related to medication use were identified and resolved.

Second, this thesis does not treat older people as a single homogenous group; rather, it considers that medication use as well as MRPs seem to differ depending on cognitive function, and that such differences should be acknowledged, further explored and finally accounted for when developing future interventions or other means of improving drug use and preventing emergency hospital admissions and similar undesired clinical outcomes. Third, although the risk association between cognitive impairment and MRAs remains ambiguous, the results still suggest that it might be more time efficient to identify and manage MRAs in hospitalized older people with higher scores on Gottfries’ four-item test. It is also noteworthy that those four simple questions regarding orientation to time seem predicative of all-cause readmission.
Concerning psychotropic drug utilization among older people, both with and without cognitive impairment, none of the studies had information on indications for treatment; hence, it is difficult to identify clear and direct implications of the results for psychotropic medication use among older individuals. However, the proportions of psychotropic drug users, especially in cases of major NCD and/or nursing home care, may themselves be considered a sign that a more restrictive utilization and targeted pharmaceutical approach is warranted. The results also stress that people with LBD as a group are especially exposed to antipsychotics, despite the well-documented risks associated with those drugs, and could function as an important additional reminder to consider other medicines or non-pharmacological approaches before initiating antipsychotics in cases of confirmed or suspected LBD.
Implications for future research

This thesis is largely based on descriptive data and cross-sectional comparisons; hence, the findings are not confirmatory, but nonetheless provide an interesting and solid basis for further exploration and investigation in different subgroups of vulnerable older people. The results highlight the danger of treating older people as a homogenous study population. Future pharmaceutical intervention studies should thoroughly define the intended target population and design the activities accordingly. For example, interventions that involve the management of NPS and the deprescribing of psychotropic drug use seem relevant in the nursing home context.

Importantly, none of the registry-based papers confirms inappropriate drug utilization due to limitations in the registry data; rather, the proportions of drug users are worrying in themselves and indicate that a substantial proportion of the older population is exposed to potentially harmful drugs. One way to take the results one step further would be to focus on long-term exposure to antipsychotics, since those drugs should be utilized as temporarily as possible and only if non-pharmacological strategies have proven insufficient. Furthermore, people with LBD had notably higher odds of psychotropic drug exposure than did people with AD despite being more vulnerable to such drugs, and future studies concerning non-pharmacological treatment and AChEIs as alternatives to antipsychotics seem warranted. Importantly, such studies can be conducted even in the absence of indications for treatment, since both antipsychotics and AChEIs have relatively narrow therapeutic areas. In terms of individual psychotropic drugs, mirtazapine has emerged as a popular option in the management of various NPS. Given its extensive utilization in the older population, more data on long-term effects and safety could offer an interesting perspective for pharmacoepidemiological studies.

A secondary finding when comparing the different data sources used in paper IV was the notable differences in both population characteristics and psychotropic drug use between people registered in SveDem and those not found in SveDem but registered as having major NCD in the National Patient Register. It is relevant to investigate those discrepancies further, for example, using a cohort design based on diagnosis/registration dates coupled with time-to-event data regarding prescription fills for specific psychotropic drugs, to determine whether being served by a SveDem-affiliated care provider actually increases the risk of more pharmacological treatment over time. Likewise, it would be interesting to investigate how the cross-sectional association found in
paper II translates to a longitudinal risk association regarding cognitive impairment and MRA using different cohorts based on the index-test score from Gottfries’ four-item test or other relevant screening tools for cognitive impairment.
Conclusion

This thesis highlights the heterogeneity of subgroups of older people, who in different respects can be considered especially vulnerable to drugs. Issues regarding medication use may be at least partly involved in about one third of acute hospital admissions among people aged 75 years or older living in independent households. Therefore, the intervention model described in paper I seems relevant in terms of setting and study population. Moreover, although MRAs were less common among study participants who had been graded with lower cognitive test scores, cognitive impairment still seems to increase the risk readmission to hospital, and could thus be an important factor to consider during the development of any novel interventions or other initiatives intended to manage MRPs and reduce the risk of MRAs. Relatively few of the investigated hospital admissions involved psychotropics, and the emergency care setting is therefore not ideal for approaches that focus primarily on psychotropic drug utilization. Psychotropic drugs are extensively used in the older population in general, especially antidepressants and hypnotic drugs, but people with major NCD and/or in nursing homes have significantly higher odds of such drug exposure. Targeting psychotropic drug utilization is therefore probably more relevant among people with more severe forms of cognitive impairment, especially in the nursing home setting. In the context of cognitive impairment and major NCD, older people with LBD were especially exposed to potentially harmful antipsychotic drug utilization, and further efforts to identify these individuals as early as possible and initiate appropriate drug therapy should be of the highest priority.
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111. Socialtjänstlag (SFS 2001:453) 5 kap 5 §.


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