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DRUG USE IN INSTITUTIONALIZED AND HOME-DWELLING ELDERLY PERSONS

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Till Tove och Wilhelm

"Change is the essential process of all existence"

Spock, Star Trek

ABSTRACT

ENGLISH

The overall aim of this thesis is to investigate drug use in institutionalized and home-dwelling elderly, with a special focus on dementia. The major findings from the separate studies are summarized below.

Study I. In this register-based study of 1 260 843 home-dwelling and 86 721 institutionalized persons aged ≥ 65 years, 30% of the institutionalized and 12% of the home-dwelling elderly were exposed to potentially inappropriate drug use (PIDU). Institutionalization was associated with overall PIDU (OR 2.36, 95% CI 2.29-2.44), after adjustment for age, sex and number of drugs (i.e. a proxy for overall co-morbidity).

Study II. We studied the use of analgesics and psychotropics in 2 610 persons aged ≥ 66 years who participated in the baseline examination in the Swedish National Study on Aging and Care-Kungsholmen (SNAC-K). About 46% of the persons with dementia and 25% of those without dementia used analgesics. Also, 63% of the persons with dementia compared to 32% of those without dementia used psychotropics. The prevalence of pain-related diagnoses was similar in persons with and without dementia. However, having a pain-related diagnosis was associated with use of psychotropics in persons with dementia, but not in those without dementia.

Study III. In this study based on data from SNAC-K and the National Patient Register, persons with dementia had a higher prevalence of osteoporotic fractures in the previous four years than persons without dementia (i.e. 25% compared to 7%). Persons with dementia were, however, less likely to use osteoporosis drugs (OR 0.34, 95% CI 0.19-0.59), after controlling for age, sex, osteoporotic fractures and type of housing (own home or institution).

Study IV. In this nationwide register-based study, we analyzed use of antibiotics commonly used to treat lower urinary tract infection (UTI). We found that use of trimethoprim in institutionalized women was more than twice as common as the recommended level. Also, the use of quinolones, in women treated with UTI antibiotics, was high in women aged 65-79 years (i.e. used by 20% and 21% of institutionalized and home-dwelling women, respectively), which is not in line with the national recommendations. In men, we found that institutionalized men aged ≥ 80 years were less commonly treated with the recommended drugs (i.e. quinolones and trimethoprim) compared to home-dwelling men in the same age group (74% compared to 83%).

Conclusions: Our results indicate that 1) institutionalization is a potential risk factor for PIDU, 2) although persons with dementia do not receive less analgesics than persons without dementia, they may be inappropriately treated with psychotropics for their pain, 3) persons with dementia are undertreated for osteoporosis, and 4) the treatment recommendations for lower UTI are not adequately followed. In order to improve the quality of drug therapy in older people, time and resources should be allocated to facilitate the implementation of regular medication reviews in this population and the cooperation between different health care professionals should be encouraged.

Det övergripande syftet med det här doktorandprojektet är att studera läkemedelsanvändning hos äldre personer i ordinärt och särskilt boende (SÄBO), med särskilt fokus på demens. En kort summering av de viktigaste resultaten från de ingående delstudierna ges nedan.

Studie I. I denna registerbaserade studie av 1 260 843 hemmaboende och 86 721 personer i SÄBO ≥ 65 år, fann vi att 30% av personerna i SÄBO och 12% i ordinärt boende var exponerade för potentiellt olämplig läkemedelsanvändning. Att bo i SÄBO var associerat med en ökad total risk för olämplig läkemedelsanvändning (OR 2.36, 95% CI 2.29-2.44), även när vi justerat analyserna för ålder, kön och antal läkemedel (användes som en proxy för sjuklighet).

Studie II. Vi studerade användningen av analgetika (smärtstillande läkemedel) och psykofarmaka hos 2 610 personer (≥ 66 år) som deltog i the Swedish National Study on Aging and Care-Kungsholmen (SNAC-K). Vi fann att 46% av personerna med demens och 25% av övriga deltagare använde analgetika. Vidare använde 63% av personerna med demens psykofarmaka jämfört med 32% av personerna utan demens. Det var ingen skillnad i förekomst av smärtrelaterade diagnoser. Att ha en smärtrelaterad diagnos var associerat med användning av psykofarmaka hos personer med demenssjukdom, men inte hos dem utan demens.

Studie III. I denna studie baserad på data från SNAC-K och patientregistret, hade personer med demens fler osteoporosrelaterade frakturer de föregående fyra åren än personer utan demens (dvs. 25% jämfört med 7%). Trots detta hade personer med demens en lägre sannolikhet att få behandling med osteoporosläkemedel (OR 0.34, 95% CI 0.19-0.59), när vi justerat analyserna för ålder, kön, osteoporosrelaterade frakturer och typ av boende.

Studie IV. I denna registerbaserade studie, analyserade vi användningen av antibiotika som används för att behandla nedre urinvägsinfektion (UVI). Vi fann att kvinnor i SÄBO använde mer än dubbelt så mycket trimetoprim som den rekommenderade nivån. Vi fann också att yngre kvinnor (65-79 år) som behandlades med UVI-antibiotika ofta använde kinoloner (dvs. 20% och 21% av kvinnorna i SÄBO respektive eget boende), vilket inte stämmer överens med de nationella rekommendationerna. Hos män fann vi att de i SÄBO (≥ 80 år) mer sällan fick de rekommenderade läkemedlen för UTI (dvs. för män trimetoprim eller kinoloner) jämfört med hemmaboende män i samma ålder (dvs. 74% jämfört med 83%).

Slutsatser: Våra resultat tyder på att 1) att bo i SÄBO är en möjlig riskfaktor för olämplig läkemedelsanvändning, 2) att personer med demens visserligen inte får analgetika i mindre omfattning än andra äldre, men att deras smärta riskerar att bli olämpligt behandlad med psykofarmaka, 3) att personer med demens är underbehandlade för osteoporos, och 4) att behandlingsrekommendationerna för behandling av nedre UVI inte följs i sin helhet. För att förbättra läkemedelsanvändningen hos äldre måste tid och resurser avsättas för att möjliggöra genomförandet av regelbundna läkemedelsgenomgångar. Även samarbetet mellan olika professioner inom vården bör uppmuntras.

LIST OF PUBLICATIONS

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LIST OF ABBREVIATIONS

ABU	Asymptomatic Bacteriuria
AD	Alzheimer's Disease
ADR	Adverse Drug Reaction
ATC	Anatomic Therapeutic Chemical (classification system)
BPSD	Behavioral and Psychological Symptoms in Dementia
BZ	Benzodiazepines
CI	Confidence Interval
CNS	Central Nervous System
DDD	Defined Daily Dose
DDI	Drug-Drug Interaction
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
MMSE	Mini Mental State Examination
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	Odds Ratio
OTC	Over-the-counter (i.e. OTC drugs are drugs that can be bought without a prescription)
PIDU	Potentially Inappropriate Drug Use
PRN	“Pro Re Nata”; PRN use of drugs refers to drugs used as needed
SBU	The Swedish Council of Health Technology Assessment
SPDR	Swedish Prescribed Drug Register
STOPP/START	Screening Tool of Older Persons potentially inappropriate Prescriptions/Screening Tool to Alert doctors to Right Treatment
STRAMA	The Swedish Strategic Programme against Antibiotic Resistance
UTI	Urinary Tract Infection
WHO	World Health Organization

1 INTRODUCTION

1.1 DRUGS AND AGING

1.1.1 Drug utilization in the elderly population

The percentage of elderly people is increasing in the world. Increased life expectancy together with lower birth rates leads to this demographic change, which is expected to continue (Figure 1).¹

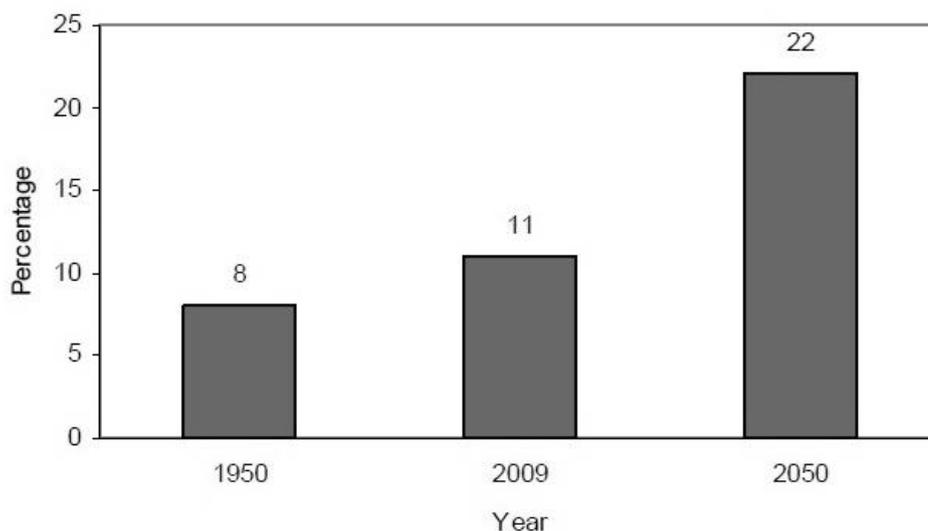


Figure 1. Proportion of the world population, 60 years and older year 1950-2050. Source: United Nations, World population aging 2009. Reprinted with permission.

In Sweden, 18% of the population was 65 years and older in 2010.² According to Statistics Sweden, life expectancy was 83 years for girls and 79 years for boys born in 2010.² One important factor for the increased life expectancy is that many diseases are today treatable with pharmacological drugs. Thus, many elderly persons live with multiple diseases and medications. In Sweden, people 75 years and older consume on average 5.4 prescription drugs per person.³ This corresponds to more than one fourth of all prescription drugs used in Sweden.⁴⁻⁵ Moreover, drug use in the elderly population has increased over time.⁶⁻⁷

Drug therapy in the elderly population is complicated by age-related changes in the body (see the sections below about pharmacokinetics and pharmacodynamics), which make older people more sensitive to drugs than younger people. Also, use of many drugs simultaneously, i.e. polypharmacy, is associated with several adverse outcomes, such as increased risk of adverse drug reactions,⁸ inappropriate drug use³ and drug-drug interactions,⁸⁻⁹ which may cause hospitalizations.¹⁰⁻¹¹ Taken together, older people have the greatest risks of adverse outcomes of drugs.

Although elderly people on average consume many drugs, some conditions may be undertreated, e.g. osteoporosis, pain, depression and cardiovascular diseases.¹²⁻¹⁵

Therefore, continuous monitoring of elderly persons' health and drug therapy is essential in order to optimize drug treatment and improve health status and quality of life.

1.1.2 Age-related changes in pharmacokinetics

Pharmacokinetics is often described as “what the body does to the drug”. It includes absorption, distribution, metabolism and excretion of the drug.¹⁶ Below are examples of age-related changes in the body which may affect the pharmacokinetics of drugs. The result is often a prolonged action and increased effects of the drug.

1.1.2.1 Absorption

The absorption of most drugs is not affected by old age *per se*. However, some diseases, surgery or use of certain drugs (i.e. opioids and anticholinergic drugs) may delay the absorption.¹⁷

1.1.2.2 Distribution

The relation between body fat and water changes in older people since the total amount of body water decrease.¹⁸ Therefore, fat-soluble drugs (e.g. the benzodiazepine diazepam), have a larger volume of distribution, which may lead to prolonged effect and accumulation of the drug which may in turn cause adverse side effects (e.g. excessive sedation).^{17, 19}

1.1.2.3 Metabolism

The function of several liver enzyme systems is reduced in elderly people.²⁰ This affects both the bioavailability (the fraction of the actual dose of the drug that reaches the bloodstream) and elimination of some drugs.

Reduced function of enzymes involved in the first-pass metabolism may lead to an increased effect of certain drugs (e.g. propranolol) due to increased bioavailability.²¹ Conversely, some drugs that are pro-drugs (i.e. drugs that are administered in an inactive form but are metabolized into an active form in the body) and activated via first pass-metabolism, e.g. enalapril, may have a decreased effect.²²

Fat-soluble drugs, in particular, undergo hepatic metabolism. Some of these drugs are eliminated slower in old age, e.g. diazepam, whereas the elimination of oxazepam is unchanged. Examples of other drugs that undergo hepatic metabolism, and may be eliminated slower in older people, are tramadol, citalopram and propranolol.²²⁻²³

1.1.2.4 Excretion

The most important age-dependent change in pharmacokinetics is the reduced renal function. As a consequence, water soluble drugs or metabolites, which undergo renal excretion, may be accumulated. This may lead to increased plasma concentrations and an increased risk for adverse side effects. Therefore, it is important to measure renal function in older people. Examples of drugs that need to be dose-adjusted according to renal function are atenolol, quinolones, digoxin and gabapentin.²³⁻²⁵

1.1.3 Age-related changes in pharmacodynamics

Pharmacodynamics is often describes as “what the drug does to the body”.¹⁶ Several organ systems are changed in old age which may increase the risk for adverse effects of many drugs. Below are examples of important organ systems that may change with age.

First, the brain becomes more sensitive to adverse side effects of many drugs that act on the central nervous system. This can lead to an increased sensitivity to sedative drugs.¹⁹ Opioids may cause confusion and are associated with an increased risk of falls in elderly people.²⁶ Due to changes in the central cholinergic pathways, older people are also particularly sensitive to anticholinergic drugs that may cause cognitive impairment and confusion in this population.²⁷

Second, the function of the baroreflex may be impaired. This can lead to an increased sensitivity of blood pressure lowering drugs and orthostatic reactions.¹⁷

Third, the gastrointestinal mucosa becomes more sensitive with aging, which leads to an increased risk of non-steroidal anti-inflammatory drug (NSAID)-induced gastrointestinal bleeding.²⁸

1.1.4 Polypharmacy

There are several definitions of polypharmacy. Some researchers have used a qualitative measure, such as use of drugs that are not clinically indicated.¹⁰ Others have defined polypharmacy quantitatively and a common definition is the use of five or more drugs.²⁹ Over 60% of Swedes aged 70-79 years are exposed to polypharmacy according to that definition, and the prevalence of polypharmacy increases further with age.³⁰ Polypharmacy has been associated with increased risk of adverse side effects, drug-drug interactions, hospitalization, medication errors, inappropriate drug use and decreased compliance.^{3,31} Polypharmacy also leads to increased healthcare costs.³² There is a linear relationship between number of used drugs and drug related problems (e.g. inappropriate drug use).³³

However, polypharmacy does not necessarily lead to adverse outcomes.³⁴ It is possible to maintain a high quality even when the patient uses several drugs if there is a continuous monitoring of the drug therapy. The challenge is to recognize problems related to polypharmacy without denying elderly people valuable drug therapy.

1.1.5 Geriatric pharmacoepidemiology

1.1.5.1 Definition

Epidemiology has been described as “the study of the determinants, occurrence, and distribution of health and disease in a defined population”.³⁵ In pharmacoepidemiology, the outcome measure is usually drug use or an effect/consequence of drug use. Pharmacoepidemiology has been defined as the study of drug use in large populations

in order to promote a rational, safe and cost-effective use of drugs.³⁶ In geriatric pharmacoepidemiology, the study population consists of elderly people.

1.1.5.2 Geriatric pharmacoepidemiology in Sweden

Sweden has a long tradition of collecting individual based health care information, including information about drug use. Drug use information has been collected in several population-based studies of elderly persons in Sweden. Information about all dispensed prescribed drugs is also collected in the nationwide Swedish Prescribed Drug Register (SDPR). Due to the unique personal identification number of each citizen in Sweden, it is possible to record link data about drug use to other registers, e.g. other health registers at the National Board of Health and Welfare (Table 1) or registers kept by Statistics Sweden, such as the Integrated Database for Labor Market Research (LISA), which includes information about, for example, education and profession.³⁷

1.1.5.3 The Swedish Prescribed Drug Register

During the recent years, many pharmacoepidemiological studies in Sweden have been based on the SPDR. The register contains, since July 2005, individual based information on all prescription drugs dispensed at Swedish pharmacies to the entire Swedish population (about 9 million inhabitants).³⁸ The register contains information primarily about age, sex and dispensed drugs (i.e. amount of prescribed drugs, when the prescription was filled and prescribed dosage), costs, place of residence and data about the prescriber (e.g. profession).³⁸ The Pharmacies Service Company (Apotekens Service AB) is responsible for administer the data collection which is mandatory for each pharmacy. The data is then transferred to the Swedish National Board of Health and Welfare, which is hosting the SPDR. The register is updated monthly. Only few other European countries, e.g. the Nordic countries³⁹ and the Netherlands,⁴⁰ have similar possibilities of studying individual-based drug use on a national level. Studying drug use in a large nationwide population has many advantages, including analysis of rare outcomes and exposures, such as individual drugs, and subpopulations (e.g. centenarians⁴¹) with high statistical precision.

Table 1. A selection of Swedish registers of health and social services at the Swedish National Board of Health and Welfare

Register	Year	Main information
The Swedish Prescribed Drug Register	2002/ 2005	Information about prescribed drugs dispensed at pharmacies. Since 2005, the register contains individual-based information, such as age, sex and personal identification number.
The National Patient Register	1987	Information about all inpatient care for Sweden since 1987 (for parts of Sweden since 1964). Since 2001, the register also contains information about specialized out-patient care.
The Swedish Medical Birth Register	1973	Information about all births in Sweden. It is compulsory for each health care provider to report births to the register.
The Swedish Cancer Register	1958	Covers the whole Swedish population. It is mandatory for all health care providers to report all newly diagnosed cancers to the register.
The Cause of Death Register	1961	Contains information about all deaths of people who are registered in Sweden.
The Social Service Register	2007	All municipalities in Sweden report individual-based information about social services granted by the municipality to the register, including institutional care for elderly people.

1.1.5.4 The Kungsholmen study and SNAC-K

Many Swedish studies on drug use in the elderly have been based on data from the Kungsholmen project.^{27, 42-49} The Kungsholmen project was conducted in Kungsholmen, which is a central part of Stockholm, the capital of Sweden, between year 1987-2000. The main aim of the project was to study aging and dementia, but numerous studies were also published about other health related topics in the elderly.⁵⁰

In 1999, a longitudinal research project named The Swedish National Study on Aging and Care (SNAC) was initiated, aimed to study health and care in the aging population. SNAC consists of 4 research centers in different parts of Sweden. One of the research centers is Kungsholmen, Stockholm (SNAC-K). Similar to the Kungsholmen project, researchers from the Stockholm Gerontology Research Center and Aging Research Center, Karolinska Institutet, are responsible for the project. SNAC-K consists of a population-based part and a care system part.⁵¹ SNAC-K is an ongoing longitudinal project. In the population-based part, information about for instance drug use, diseases, cognition and socio-demographics are collected, which makes SNAC-K suitable for studies of drug use in the elderly population.

1.1.6 Dementia

Dementia leads to a decline in cognitive functions, e.g. memory and other intellectual abilities.⁵² According to the WHO, the symptoms of dementia can include: "memory loss, difficulties with language, judgment, and insight, failure to recognize people, disorientation, mood changes, hallucinations, delusions, and the gradual loss of ability

to perform all tasks of daily living”.⁵³ The personality and the emotional functions may also be affected.⁵² Dementia is uncommon below the age of 60, but after the age of 65, both the prevalence and incidence doubles every five years.⁵⁴ In Sweden, more than 140 000 persons have a dementia disorder.⁵⁵ Institutionalization is common as the dementia disease progresses. As the main risk factor for dementia is old age, the number of persons with dementia is expected to increase in the future due to the increased life expectancy.⁵⁶ The most common type of dementia is Alzheimer’s disease (AD), which accounts for about 60% of the dementia cases.⁵⁴

Persons with dementia are at particular risk of drug related problems. First, persons with dementia use more psychotropic drugs than other elderly persons.^{44, 57} This may be problematic since these persons are sensitive to adverse side effects of these drugs, such as confusion and falls.⁵⁸ Second, persons with dementia are particularly sensitive to adverse side effects of drugs with anticholinergic properties (e.g. antipsychotics, tricyclic antidepressants and urinary antispasmodics). These drugs may affect cognitive functions negatively in persons with dementia.⁵⁹ Third, dementia patients may be undertreated for several conditions, such as pain, osteoporosis and cardiovascular diseases,⁶⁰⁻⁶⁶ because these patients often have difficulties in verbally communicating physical discomfort or pain.^{52, 67} Instead they may show behavioral symptoms, such as increased agitation, aggression, depression and anxiety.⁶⁸⁻⁶⁹ These behavioral symptoms can be misunderstood, which may lead to undertreatment of the somatic disorder or inappropriate treatment with psychotropics.^{52, 70-71}

1.2 DRUG USE AND TYPE OF HOUSING

1.2.1 Institutions

In Sweden, about 6% of persons aged 65 years and older live in different types of institutions,⁷² i.e. old people’s homes, group dwelling (small housing collectives where the residents have their own apartment but also have access to shared spaces, care and supervision),⁷³ nursing homes and sheltered accommodations. Some settings are specialized in care for persons with dementia, i.e. special care units for dementia.⁵⁷ Although some institutions in Sweden are organized in private regime, almost all public elderly care is financed and organized within the municipality system.

About 80% of the institutionalized elderly in Sweden have some degree of cognitive impairment and 60% have dementia.^{55, 74} In addition, institutionalized elderly often suffer from other diseases/conditions. Functional dependence, dementia, cerebrovascular disease and hip fractures have been associated with living in an institution.⁷⁵ It has also been shown that institutionalized elderly more commonly suffer from physical disabilities, urinary incontinence, anxiety and depressive symptoms compared to home-dwelling elderly.⁷⁴

Drug use in institutions is often extensive and use of 10 or more different drugs is common.⁷⁶⁻⁷⁸ Co-morbidities and polypharmacy are factors that complicate drug use in

this population of frail, vulnerable persons. Bergman et al⁷⁸ have showed that 70% of the elderly in these settings are exposed to potentially inappropriate drug use (PIDU).

1.2.2 Home-dwelling elderly

Home-dwelling elderly is a heterogeneous group of people. It includes both newly retired or still working healthy persons and elderly persons with multimorbidity with a great need for home-care services (e.g. assistance with households' tasks, personal hygiene and help with administration of their medications). It has been estimated that home-dwelling elderly persons in Sweden use on average 4.3 drugs per person.⁷⁹ However, use of 10 different drugs and low quality of drug therapy are also common among home-dwelling elderly.⁴ Concerns have been raised about inappropriate drug use in this setting because drug therapy among home-dwelling elderly is usually less well monitored than among institutionalized elderly.⁸⁰

1.2.3 Comparing institutionalized and home-dwelling elderly

Few previous studies have compared drug use between institutionalized and home-dwelling elderly. However, Jyrkkä et al⁶ followed a random sample of elderly people aged 75 years and older in Kuopio, Finland, from 1998 to 2003. In 2003, institutionalized elderly used on average 11 drugs per persons compared to 7.5 among home-dwellers.⁶ The three most commonly used drug classes in home-dwelling elderly were then antithrombotic agents, cardiac therapy and beta blocking agents (used by 68, 57 and 53%, respectively), whereas psycholeptics, analgesics and laxatives were the three most commonly used drugs classes in institutions (used by 86, 76 and 60%, respectively).⁶ The institutionalized elderly often suffered from multimorbidity, dementia and cardiovascular diseases in the Finnish study, which has also been found for Swedish institutions.⁷⁵ Many patients were bedpatients, which may explain the high use of laxatives. However, the authors also discuss that the use of laxatives for constipation could be caused by side effects of anticholinergic drugs.⁶

Table 2 shows the 20 most commonly dispensed drug classes in institutionalized and home-dwelling elderly according to a recent study by Johnell et al (in press). In this study, the three most commonly used drug classes among home-dwelling elderly were antithrombotic agents, beta blocking agents and lipid modifying agents, whereas the institutionalized elderly most frequently used antithrombotic agents, minor analgesics and antidepressants. This study was based on the same database as Study I and IV in this thesis. Although there are different disease patterns between institutionalized and home-dwelling elderly, other factors, such as different prescribing traditions in the two settings, may also play a role in explaining the differences in drug therapy. Further, as discussed by Johnell et al (in press), the high use of psychotropics in institutions may reflect an attempt to manage Behavioral and Psychological Symptoms of Dementia (BPSD) instead of using non-pharmacological methods, e.g. due to lack of staffing.

Table 2. The 20 most commonly dispensed drug classes in 1 347 564 persons aged ≥ 65 years by residential setting, 2008, according to Johnell et al (paper in press)¹
Values are % (n).

ATC-code	Drug class	Community-dwelling (n=1 260 843)	Institutionalized (n=86 721)
B01A	Antithrombotic agents	36.6 (461 049)	48.3 (41 853)
C07A	Beta blocking agents	33.2 (418 905)	28.1 (24 411)
C10A	Lipid modifying agents	25.8 (324 942)	9.0 (7 800)
C09A	ACE inhibitors	16.2 (204 751)	14.6 (12 679)
C08C	Selective calcium channel blockers, mainly vascular effects	16.6 (208 964)	9.7 (8 448)
N05C	Hypnotics/sedatives	14.6 (183 472)	33.8 (29 286)
C03C	High-ceiling diuretics	13.4 (168 798)	38.4 (33 260)
N02B	Minor analgesics	11.8 (149 000)	46.5 (40 296)
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux	13.0 (163 996)	23.9 (20 746)
B03B	Vitamin B12 and folic acid	11.2 (140 705)	29.6 (25 712)
N06A	Antidepressants	10.1 (127 676)	43.9 (38 074)
H03A	Thyroid preparations	9.1 (114 951)	11.5 (9 977)
C09C	Angiotensin II antagonists	9.2 (116 110)	4.5 (3 937)
A12A	Calcium	7.7 (96 907)	12.5 (10 815)
A06A	Laxatives	6.2 (77 787)	33.9 (29 374)
A10B	Blood glucose lowering drugs, excl. insulins	8.0 (100 606)	7.0 (6 061)
M01A	Non-steroid antiinflammatory and antirheumatic products	8.1 (102 687)	3.7 (3 206)
N02A	Opioids	6.7 (84 032)	17.9 (15 484)
G03C	Estrogens	7.3 (91 844)	8.1 (7 065)
C03A	Thiazide diuretics	7.5 (94 457)	4.6 (3 947)

¹ The table is reproduced from Johnell K, Fastbom J. Comparison of drug use between community-dwelling and institutionalised elderly. A nationwide study. *Drugs & Aging*: 2012, *in press*, with permission from Adis, a Springer business (© Adis Data Information BV 2012. All rights reserved).

1.3 POTENTIALLY INAPPROPRIATE DRUG USE

1.3.1 Definition

Potentially inappropriate drug use (PIDU) has been defined as use of medications for which the risks outweigh the benefits.⁸¹ PIDU in the elderly population can be use of drugs that due to age-related changes are less well tolerated than in younger people. PIDU also includes the use of drugs with wrong dosages or duration for the indication⁸²⁻⁸³ or use of drugs without evidence-based indication.⁸⁴ Also, undertreatment of potentially treatable diseases is a form of PIDU.⁸⁴

Many adverse drugs reactions in elderly people are caused by poor prescribing and are at least partly preventable by better knowledge and practice.⁸⁵

1.3.2 Occurrence and consequences

PIDU is a common health problem in the elderly population. Studies of PIDU have reported prevalences between 3-70% in older people.^{3, 29, 78, 86-90} The wide range is explained by the use of different criteria for the definition of PIDU and different settings. The lowest prevalence has been found among elderly in ambulatory care⁸¹ and the highest in institutions.⁷⁸ Table 3 shows important studies of PIDU published in the previous 10 years.

PIDU has been associated with adverse drug reactions, hospitalization, admittance to nursing home and mortality.⁹¹⁻⁹⁴ There is also a risk that side effects caused by PIDU are misinterpreted as disease symptoms and treated with additional drugs, which leads to a “prescribing cascade” with possible harmful consequences.⁹⁵

Table 3. A selection of important studies of PIDU in institutionalized and home-dwelling elderly published in the past 10 years.

Author, year	Participants	Measure of PIDU	Main finding
Leikola et al. 2011 ⁹⁶	N=841 509, age: ≥ 65 years, register-based Finnish study of non-institutionalized elderly, year: 2007.	Modified Beers 2003 criteria ⁹⁷	Prevalence of PIDU was 14.7% in home-dwelling elderly.
Barnett et al. 2011 ⁹⁸	N=70 299, age: 66-99 years, institutionalized and home-dwelling elderly residing in Tayside, Scotland, year: 2005-2006.	Modified Beers criteria 2003 ⁹⁷	Prevalence of PIDU was 31%. No overall association between institutionalization and PIDU was found.
Ghadimi et al. 2011 ⁹⁹	N=2 041, age: ≥ 65 years, older persons visiting the General Practitioner, Iran, year: 2005 and 2006.	Modified Beers 2003 ⁹⁷	Prevalence of PIDU was 30%.
Ruggiero et al. 2010 ¹⁰⁰	N=1 716, age: ≥ 65 years, nursing home residents, ULISSE project, Italy, year: 2004-2005	Modified Beers 2003 ⁹⁷	Prevalence of PIDU was 48%.
Cahir et al. 2010 ¹⁰¹	N=338 801, age: ≥ 70 years, national population study, Ireland, year: 2007	European criteria ¹⁰²	Prevalence of PIDU was 36%.
Hosia-Randell et al. 2008 ¹⁰³	N=1 987, age ≥ 65 years, institutionalized elderly, Helsinki, Finland, year: 2003.	Modified Beers 2003 ⁹⁷	Prevalence of PIDU was 34.9%.
Johnell et al. 2007 ³	N=732 228, age: ≥ 75 years, register-based nationwide study, Sweden, year: 2005.	National indicators for rational drug use in the elderly population ¹⁰⁴	Prevalence of PIDU was 17% (both institutionalized and home-dwelling elderly included).
Bergman et al. 2007 ⁷⁸	N=7 904, age: ≥ 65 years, multi-dose users residing in nursing homes, Gothenburg, Sweden, year: 2003.	National indicators for rational drug use in the elderly population ¹⁰⁴	Prevalence of PIDU in nursing homes was 74%.
Goulding et al. 2004 ¹⁰⁵	N=22 031, age: ≥ 65 years, ambulatory care, U.S. year: 1995 and 2000.	Beers 1997 criteria ¹⁰⁶	Prevalence of PIDU in ambulatory care was 7.8% in both 1995 and 2000.
Lane et al. 2004 ¹⁰⁷	N=1 275 619, age ≥ 66 years, home-dwelling and institutionalized elderly, Ontario, Canada, year: 2001.	Modified Beers, potentially inappropriate drugs in the always avoid or rarely appropriate category were studied ¹⁰⁸	The prevalence of PIDU was 2.3% in institutionalized elderly and 3.3% in home-dwelling elderly.
Dhalla et al. 2002 ⁸⁰	N=19 911, age: ≥ 66 years, persons newly admitted to nursing homes, Ontario, Canada, year: 1997- 1999.	Modified Beers criteria, a subset ¹⁰⁶	The prevalence of PIDU declined from 25.4% to 20.8% after nursing home admission.

1.3.3 Measures of inappropriate drug use

1.3.3.1 Beers criteria (United States)

The most commonly used measure of PIDU in the elderly population is probably the Beers criteria, which were originally developed in the United States in 1991 for use in the nursing home setting.¹⁰⁹ The Beers criteria have been continuously updated and the later versions are more applicable also for home-dwelling elderly persons.^{97, 106} The version from 2003 includes 48 individual drugs or classes of drugs considered as inappropriate to use in older people.⁹⁷ In addition, it includes drugs that should be avoided in 20 diseases/conditions.⁹⁷ Some of the drugs in the Beers criteria are dependent on the prescribed dosage. The Beers criteria, including modified versions, have been widely used in studies of PIDU in both the U.S. and in Europe.^{80-81, 98, 103, 105, 107, 110-112} However, since these criteria were developed for use in the U.S., they are not a completely accurate measure when applied to data from other countries. For instance, several drugs that are approved in the U.S. are not available in European countries. In addition, DDIs are not included in the Beers criteria.¹⁰¹ The Beers full list of criteria has also been criticized for being a too rough measure in a recent study that found no significant impact on mortality in patients exposed to PIDU, as defined by the Beers criteria, compared to non-exposed elderly persons.⁹⁸

1.3.3.2 STOPP/START (Europe)

In order to create a measure of inappropriate drug use more suitable for the European situation, the STOPP/START criteria were developed by experts in Ireland and the United Kingdom in 2008. The STOPP (Screening Tool of Older Persons potentially inappropriate Prescriptions) criteria contain 65 criteria for inappropriate prescribing in elderly people and the START (Screening Tool to Alert doctors to Right Treatment) criteria contains 22 prescribing indicators for common diseases in older people.¹⁰²

1.3.3.3 National indicators

Several countries, such as Sweden, Norway, Finland and France, have developed national indicators for evaluation of the quality of drug therapy in older people.^{83, 104, 113-115} An advantage is that such indicators may be a more appropriate measure of PIDU since they are developed for national conditions.

In Sweden, the National Board of Health and Welfare has developed both disease- and drug specific indicators for evaluation of the quality of drug therapy in older people. The first version was launched in 2003 and a revised version in 2010.^{83, 104} Several of the drug-specific indicators have successfully been applied to register-based data, i.e. use of anticholinergic drugs, long-acting benzodiazepines, concurrent use of three or more psychotropics and potentially serious drug-drug interactions (DDIs).^{3, 29, 87-88}

1.4 TREATMENT OF SOME COMMON CONDITIONS IN THE ELDERLY

1.4.1 Pain

Pain is common in the elderly population. It has been estimated that about 50% of home-dwelling elderly and up to 80% of nursing home residents suffer from pain.¹³ In the elderly population, chronic pain is often experienced in major joints, the back, legs and feet, and underlying diseases are often osteoarthritis, fractures and cancer.¹¹⁶

Several previous studies have reported an undertreatment of pain in the elderly. For instance, a recent U.S. study of 14 017 nursing home residents found that 44% of the residents with pain did not receive standing orders for pain medication or appropriate pain management.¹¹⁷ Several reasons for the undertreatment have been suggested, e.g. fear of adverse side effects of analgesics, polypharmacy and communication problems between the patients and the health care staff.¹¹⁸

Cognitive impairment is probably the major reason for communication problems, which may lead to undertreatment of pain. Numerous studies have shown that persons with dementia receive less pain treatment than other elderly, although some recent studies have not found that persons with dementia receive fewer analgesics (Table 4). Unrelieved pain may have severe consequences in everyday function and quality of life and may lead to increased agitation, depression and anxiety in older people.¹¹⁹⁻¹²²

There are several pain-assessment tools available for assessment of pain in patients with dementia.¹²³ In patients with mild dementia, self-report may be an adequate measure of pain. For patients with more severe dementia, however, it is more suitable to use a behavior-observation tool. For instance, Horgas et al¹²⁴ showed that persons with dementia self-reported less pain compared to cognitively intact persons, but they found no difference in behavioral pain indicators.

1.4.1.1 *Pain medications*

Analgesics are usually divided into peripherally acting (paracetamol, acetylsalicylic acid and NSAIDs) and centrally acting (e.g. opioids). Mild to moderate pain can usually be treated successfully with paracetamol (acetaminophen). In more severe pain conditions, it can be combined with a minor opioid (codeine or tramadol) or a major opioid (e.g. morphine).¹²⁵ NSAIDs are mainly used for treatment of inflammatory pain.

Paracetamol is considered to be safe when used in recommended doses. NSAIDs need to be prescribed with caution in older patients since they can cause gastrointestinal and renal complications.^{28, 126} In addition, use of NSAIDs have been associated with increased risk of myocardial infarction and death.¹²⁷ Opioids may cause constipation and sedation and have been associated with an increased risk of falls in older people.^{26, 125} On the other hand, poorly treated pain has also been associated with increased risk of falls in elderly women.¹²⁸

In neuropathic pain, which is a special form of pain caused by damages in the peripheral or central neurons, traditional analgesics are generally ineffective. Tricyclic antidepressants and anti-epileptic drugs may be used instead.¹²⁹

Table 4. A selection of important studies of pain treatment in older persons with dementia or cognitive impairment

Author, year	Study participants	Main finding
Horgas et al. 2009 ¹²⁴	N=126, age: ≥65 years, institutionalized elderly in Florida, year: not specified	Cognitively impaired elderly self-reported less movement-related pain, but there was no difference in pain behavioral indicators. Cognitively impaired elderly received on average 500 paracetamol equivalents more than cognitively intact elderly.
Husebo et al. 2008 ⁶⁰	N=181, age: ≥65 years, nursing home residents in Norway, year: not specified	Patients with severe dementia and mixed dementia who were treated with opioids had a higher pain intensity score than persons without dementia who were treated with these drugs.
Lövheim et al. 2008 ¹³⁰	N=546, age: ≥85 years, home-dwelling and institutionalized elderly, in northern Sweden and Finland, year: 2005-2006	Persons with dementia received significantly more paracetamol. There was no difference in use of opioids or NSAIDs.
Reynolds et al. 2008 ⁶²	N=551, age: range 22-103 years, nursing home residents in North Carolina, U.S., year: 2001-2004	56% of the patients with severe cognitive impairment received analgesics compared to 85% of the cognitively intact. There was no difference in the presence of pain-related conditions.
Nygaard et al. 2005 ⁶¹	N=125, age: ≥65 years, nursing home residents in Norway, year: 2000-2001	Elderly with a dementia diagnosis were less likely to receive PRN analgesics, but there was no difference in use of scheduled medications.
Balfour et al. 2003 ⁷⁰	N=460, age: ≥65 years, institutionalized and home-dwelling Alzheimer patients in Canada, year: 1991	Less than half of the arthritis patients received no pain treatment. Alzheimer patients with arthritis/rheumatoid arthritis received more benzodiazepines than the other Alzheimer patients.
Morrison et al. 2000 ⁶³	N=98, age: ≥70 years, hip-fracture patients admitted to a U.S. hospital, year: 1996-1998	Hip-fracture patients with severe dementia received 1/3 the amount of opioid analgesics than those without dementia.

1.4.2 Osteoporosis

Osteoporosis is a bone disease that is common in the elderly population. The bones become porous and the risk for fractures increases. Sweden has one of the highest prevalences of osteoporosis in the world and the occurrence increases with age.¹³¹ It has been estimated that about 50% of the institutionalized men and up to 85% of the institutionalized women have osteoporosis.¹³²⁻¹³³ A Swedish study has even suggested that almost all institutionalized women have osteoporosis.¹³⁴

Osteoporosis causes approximately 70 000 fractures per year in Sweden.¹³⁵ Common sites for osteoporotic fractures are the hip, spine and forearm.¹³⁶ The lifetime risk for a fracture in one of these sites is 46% for a 50 year old Swedish woman.¹³⁶ For a man, the risk is 22%.¹³⁶ Hip fractures, one of the most severe consequences of osteoporosis, have been associated with increased morbidity and mortality.^{131, 137}

Several previous studies have reported an undertreatment of osteoporosis in older people, i.e. in the oldest old,¹² in nursing homes,¹³⁸ for prevention of a secondary osteoporotic fracture,¹³⁹⁻¹⁴⁰ among low educated elderly¹⁴¹ and in persons with dementia.⁶⁵

Persons with dementia are considered as a high risk group for osteoporotic fractures because dementia is associated with an increased risk of falls and hip fractures.^{135, 142-143}

1.4.2.1 Osteoporosis medications

The Swedish Council of Health Technology Assessment (SBU) has concluded that enough evidence is available to support use of calcium/vitamin D combinations, bisphosphonates and raloxifene in order to prevent osteoporotic fractures in older people.¹³⁵

Bisphosphonates and raloxifene are antiresorptive drugs that increase the bone strength. Raloxifene is a selective estrogen receptor modulator that is approved for use in post-menopausal women.^{135, 144}

Calcium/vitamin D combinations are considered as a less potent osteoporosis treatment, but may reduce the risk for hip- and other non-spinal fractures in the elderly.¹³⁵

1.4.3 Urinary Tract Infection

In institutions, urinary tract infection (UTI) is the most common indication for antibiotic prescriptions, accounting for up to 60% of such prescriptions in this setting.¹⁴⁵ In home-dwelling elderly, it is the second most common infection.¹⁴⁶ UTI is most common in women, but also fairly common in elderly men, as the prevalence increases with age.¹⁴⁷ Concerns have been raised about the quality of use of UTI antibiotics in the institutional setting, as only 50% of the prescribed antibiotics are used according to recommendations.¹⁴⁸ Less is known about the quality of use of these drugs among home-dwelling elderly. However, the Swedish recommendations has been reported to be inadequately followed in a study of women >18 years who visited primary health care.¹⁴⁹

The most common type of UTI is lower uncomplicated UTI (cystitis).¹⁴⁵ Lower UTI is usually a harmless disease although it can be painful.¹⁵⁰ There is a low risk that it progresses to pyelonephritis, a more severe disease where the kidneys are involved in the infection.¹⁵⁰ Asymptomatic bacteriuria (ABU) is when bacteria are present in the urine but the patient has no clinical symptoms. Among the institutionalized elderly,

the prevalence of ABU is up to 50% in women and 40% in men.¹⁵¹ Treatment with antibiotics in ABU is not recommended, yet it occurs frequently.¹⁵¹

1.4.3.1 Antibiotics

1.4.3.1.1 Women

New Swedish national guidelines for treatment of lower UTI in adult women were published in 2007 by the Swedish Medical Product Agency in collaboration with the Swedish strategic program against antibiotic resistance (STRAMA).¹⁴⁵ According to these recommendations, pivmecillinam and nitrofurantoin should be considered as first line treatment. Due to increased resistance levels, trimethoprim is now considered as secondary choice and the use of quinolones should be minimized.^{104, 145} The treatment of lower UTI can be empirical, which means that no urine cultivation is necessary if the symptoms are typical.¹⁴⁵

Figure 2 shows the sales of the most commonly used UTI antibiotics in women year 2000-2010. In recent years, the sales of trimethoprim and quinolones have decreased in favor for pivmecillinam and nitrofurantoin, as recommended by the national guidelines.

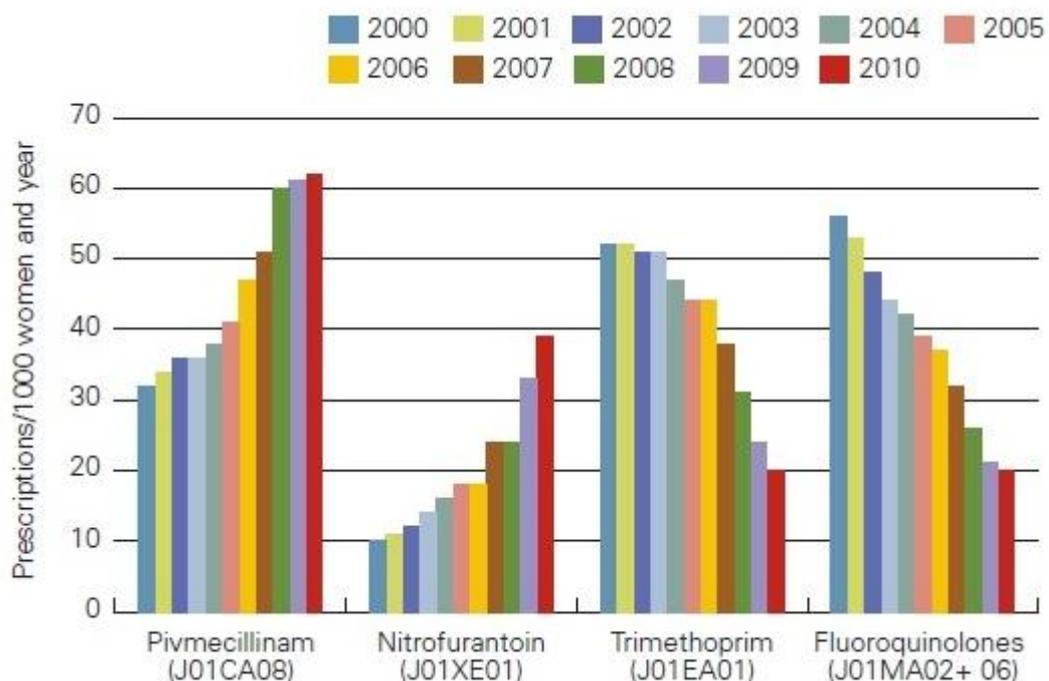


Figure 2. Antibiotics commonly used to treat UTI in Swedish women year 2000-2010. Source: Swedish Institute for Communicable Disease Control, SWEDRES 2010. Reprinted with permission.

1.4.3.1.2 Men

The National Board of Health and Welfare has published indicators for treatment of UTI in elderly men.¹⁰⁴ Since the prostate is often involved in the infection in men, the treatment recommendations for UTI differ from that in women. In men, quinolones or trimethoprim are recommended because these drugs penetrate prostatic tissue and secretions.

1.4.3.2 Antibiotic resistance

Antibiotic resistance is considered as a global health concern by the WHO.¹⁵²

Widespread use of antibiotics is a risk factor for antibiotic resistance.¹⁵³

Although Sweden has low resistance levels compared to other European countries, the problem is increasing.¹⁵⁴ To keep the resistance levels as low as possible, it is important with continuous monitoring of the use of antibiotics and the actual situation of resistance. It is also important that national guidelines regarding antibiotic prescribing are continuously updated to guide the prescriber to choose antibiotics with a favorable resistance profile.

The most common uro-pathogen is *Escherichia Coli*.¹⁴⁵ The resistance levels varies between regions in Sweden, but is overall 1-3% for pivmecillinam and nitrofurantoin, which are the first line antibiotics.¹⁴⁵ For trimethoprim, the resistance level has almost doubled since 1996, and is now about 19% in *Escherichia Coli* isolates.¹⁵⁴⁻¹⁵⁶ Also, the resistance levels for quinolones have increased in Sweden in recent years, from 8% in 2002 to 13% in 2010.¹⁵⁶ Figure 3 illustrates the resistance levels to quinolones in Sweden and in other European countries.

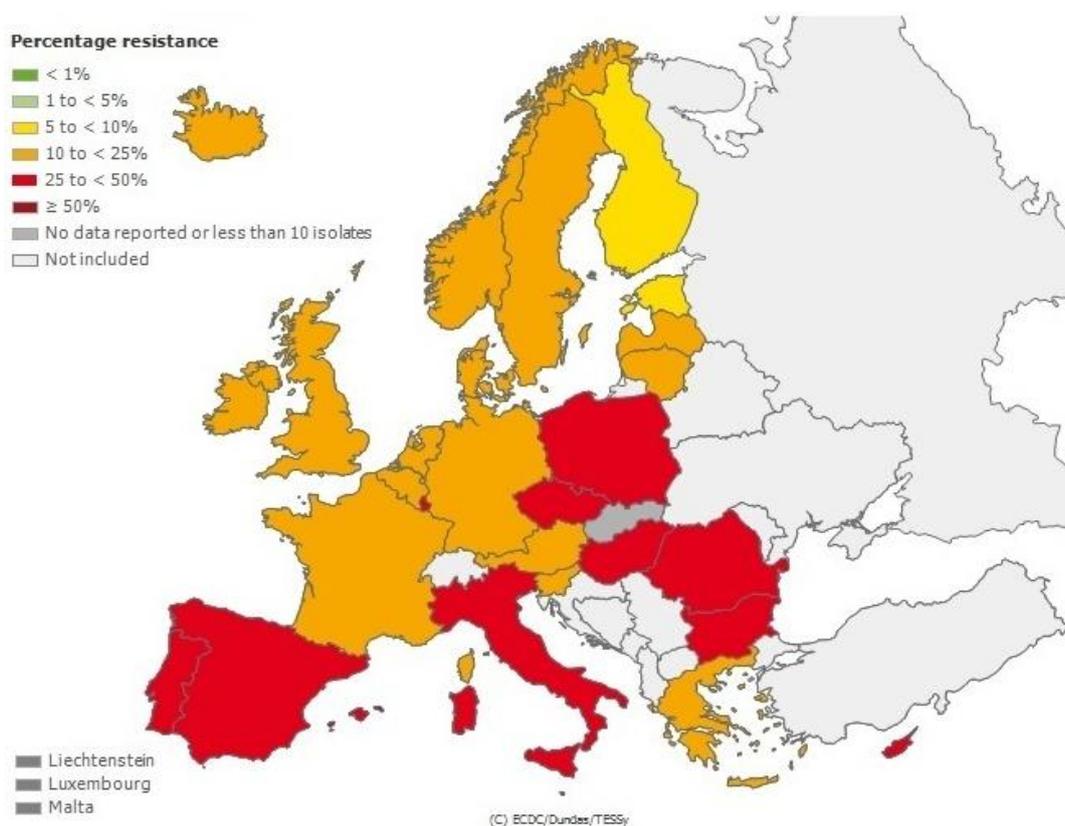


Figure 3. Proportion of Quinolone resistant (R + I) *Escherichia coli* isolates in European countries 2010. Source: EARS-Net²

² Map generated by the European Antimicrobial Resistance Surveillance Network (EARS-Net) online database, European Centre for Disease Prevention and Control, 16 February 2012.

http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/map_reports.aspx

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2 AIMS

2.1 GENERAL AIM

The general aim of this thesis is to investigate drug use in institutionalized and home-dwelling elderly persons, with a special focus on dementia.

2.2 SPECIFIC AIMS

2.2.1 Study I

The aim was to compare potentially inappropriate drug use (PIDU) in institutionalized versus home-dwelling elderly persons in Sweden.

2.2.2 Study II

The aim was to investigate if persons with dementia were as likely as persons without dementia to receive pharmacological pain treatment. We also aimed to investigate whether use of psychotropics was related to pain in persons with and without dementia.

2.2.3 Study III

The aim was to investigate and compare use of osteoporosis drugs among nursing home residents and home-dwelling elderly with and without dementia.

2.2.4 Study IV

The aim was to compare the quality and pattern of use of urinary tract infection (UTI) antibiotics (i.e. quinolones, pivmecillinam, trimethoprim and nitrofurantoin) between institutionalized and home-dwelling elderly persons.

3 MATERIALS AND METHODS

3.1 DATA SOURCES

3.1.1 The Swedish Prescribed Drug Register (Study I and IV)

The SPDR contains, since July 2005, individual based information on all prescription drugs dispensed at Swedish pharmacies to the entire Swedish population (about 9 million inhabitants).³⁸

3.1.1.1 Measurement of drug use (SPDR)

We analyzed use of dispensed, prescribed drugs on the date of 30 September 2008 in 1 260 843 home-dwelling and 86 721 institutionalized elderly persons. In Sweden, prescription drugs are prescribed for use for at most three months. Therefore, our computerized analyses employed an algorithm based on information about when the prescription was filled, the amount of drugs dispensed and the prescribed dosage, from the previous three-month period, to construct a list of concurrently used drugs on a given date, in this case September 30, 2008. When data on prescribed dosage were incomplete or missing (9.9%), the daily dose for the actual drug was looked up in a table derived from the same dataset with mean daily doses from prescriptions with known dosage information. For drugs prescribed as needed we assumed a dosage of 50% of that for regular drugs. Moreover, we assumed a daily dose of 1 defined daily dose (DDD)¹⁵⁷ for eye preparations and dermatological drugs.³ If the same drug was dispensed more than once during the period, it was counted as one drug.

Information about over-the-counter (OTC) drugs, drugs used in hospitals and drugs supplied from drug store rooms in institutions are not included in the SPDR.

3.1.2 The Swedish Social Services Register (Study I and IV)

Since 2007, all municipalities in Sweden report individual-based information about granted institutional care and home-help for older people to the Swedish Social Services Register.⁷² We collected information from the register about type of housing (i.e. home dwelling/institution) on 30 June 2008. By that date, all Swedish municipalities had reported to the register.⁷² Only a small fraction of the institutional care is organized outside the municipality system in Sweden.

3.1.3 The National Patient Register (Study III)

The National Patient Register contains, since 1987, information about all hospital discharges for the entire Swedish population. The register was recently validated and, today, more than 99% of all somatic and psychiatric hospital discharges are recorded in the register.¹⁵⁸ Since 2001, the register also contains information about specialized out-patient care.

3.1.4 SNAC-K (Study II and III)

3.1.4.1 Data collection

SNAC-K is an ongoing longitudinal study. However, we used data from the baseline examination collected in 2001-2004. At baseline, each participant met a team consisting of a physician, a registered nurse and a psychologist, for interviews and examination.⁵¹ Data about pain, diseases and drug use were collected during the interview by the physician. The full protocol is available at www.snac-k.se. When the older person could not provide information, a relative was asked instead. However, relatives or caregivers were not asked about the participants' experience of pain. If the person was living in an institution, the information was most often collected from medical records.

3.1.4.2 Study population

Study II and III are based on data from the population based part of the SNAC-K study. SNAC-K consists of a sample of older persons from different age cohorts (age 60, 66, 72, 78, 81, 84, 87, 90, 93, 96, and 99 years and older), who live in Kungsholmen / Essingeöarna, a central part of Stockholm, the capital of Sweden.

For the baseline examination, 5 111 persons were invited to participate and of these 4 590 were alive and eligible for participation (200 dead, 262 not able to contact, 4 deaf, 23 did not speak Swedish and 32 had moved), and of the eligible, 3 363 (73%) participated in the baseline examination. We only analyzed persons aged 66 years and older who had completed the interview with the physician (n=2 610). Of these, 305 had a dementia disorder. Five persons with missing information about drug use were excluded.

3.1.4.3 Measurement of drug use (SNAC-K)

In contrast to the SPDR, drug use in SNAC-K was based on self-report and included information about use of both prescribed and OTC drugs. During the baseline interview, the physician asked the participant about current drug use, including both regularly and as needed used drugs. Participants were asked in advance to bring a list of currently used drugs to the interview. If possible, e.g. when the interview was performed in the participant's own home, also drug prescriptions and medical containers were inspected. If the participant resided in an institution, information about drugs was most often retrieved from medical records.

The drug use analysis was performed by the custom designed software Monitor (Quality Pharma AB, Västerås, Sweden), which automatically classifies the drugs according to the Anatomical Therapeutic Chemical (ATC) classification system.

3.2 OUTCOME MEASURES AND EXPLANATORY VARIABLES

3.2.1 Outcome variables

All studies in this thesis have drug use as outcome variable. Drugs were classified according to the ATC classification system, as recommended by the WHO.¹⁵⁷

3.2.1.1 PIDU (Study I)

The Swedish National Board of Health and Welfare has developed indicators for evaluation of the quality of drug therapy in older people.¹⁰⁴ The indicators consist of both disease specific and drug-specific indicators. We analyzed four of the drug specific indicators, which have previously been applied to register-based data.^{3, 78, 87} Table 5 shows the analyzed indicators with examples and possible consequences.

Table 5. Indicators developed by the Swedish National Board of Health and Welfare in 2010 for analyses of PIDU in elderly persons (Study I)

Indicator	Example of drug/combination	May cause (examples)
Use of anticholinergic drugs	Antihistamines, urinary antispasmodics, older types of antipsychotics	Cognitive impairment, confusion and impaired functional status ¹⁵⁹⁻¹⁶⁰
Long-acting benzodiazepines	Diazepam, flunitrazepam, nitrazepam	Excessive sedation, cognitive impairment and falls ^{83, 159}
Concurrent use of 3 or more psychotropic drugs	Antipsychotics, anxiolytics, hypnotics/sedatives and antidepressants	Refined measure of polypharmacy, may cause cognitive side effects ¹⁶¹
Potentially serious drug-drug interactions	Concurrent use of aspirin and warfarin	Attenuated/abolished therapeutic effects or severe side effects ¹⁶²

3.2.1.2 Analgesics and psychotropics (Study II)

We analyzed use of the following analgesics: any analgesic (ATC-code N02), paracetamol (N02BE01) and opioids (N02A). We also analyzed the use of NSAIDs (M01A), excluding glucosamine (M01AX05). Use of psychotropics was classified into use of at least one psychotropic drug (i.e. antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C) or antidepressants (N06A)).

3.2.1.3 Osteoporosis drugs (Study III)

We analyzed use of the following osteoporosis drugs: calcium/vitamin D combinations (ATC-code A12AX), raloxifene (G03XC01) and bisphosphonates (M05BA and M05BB). We also analyzed the use of “any osteoporosis drug”, which referred to the use of at least one drug in the ATC-classes A12AX, G03XC01, M05BA or M05BB.

3.2.1.4 *UTI antibiotics (Study IV)*

We investigated use of the following antibiotics commonly used for treatment of lower UTI:¹⁶³ quinolones (ciprofloxacin (ATC-code J01MA02) and norfloxacin (J01MA06)), pivmecillinam (J01CA08), trimethoprim (J01EA01) and nitrofurantoin (J01XE01).

The National Board of Health and Welfare has developed indicators for treatment of UTI in elderly women and men.¹⁰⁴ We analyzed several of these indicators, which could be applied to register-based data. We also analyzed one of the quality indicators for treatment of lower UTI in adult women developed by The Swedish Association of General Practice:¹⁵⁰ Women: 1) The proportion women treated with UTI antibiotics for lower UTI, who used quinolones (should be as low as possible);¹⁰⁴ 2) The proportion women treated with the recommended drugs, pivmecillinam, nitrofurantoin or trimethoprim (should be about 40%, 40% and 15-20%, respectively)¹⁵⁰; Men: 1) The proportion men of all men treated with UTI antibiotics who used either quinolones or trimethoprim (should be as high as possible).¹⁰⁴

3.2.2 **Main explanatory variables**

3.2.2.1 *Type of housing*

Type of housing was classified into home-dwelling (living in own home) or institutionalized (e.g. sheltered accommodation, old people's home, group dwelling or nursing home).^{79, 164} This definition was made because it is not possible to distinguish between different types of institutional care in the Social Services Register (Study I and IV).⁷² We therefore classified the type of housing variable in a similar way also in Study II and III, which are based on SNAC-K data.

3.2.2.2 *Dementia*

In SNAC-K (Study II and III), two physicians set the dementia diagnosis independent of each other according to the DSM-IV criteria.¹⁶⁵ In case of disagreement, a third expert was consulted to make the final diagnosis.¹⁶⁶ Persons with questionable dementia (the criteria of memory impairment was fulfilled, whereas a second cognitive dysfunction was questionable) were included in the dementia group.⁴²

In study I and IV, we used treatment with anti-dementia drugs (ATC code N06D, i.e. cholinesterase inhibitors and memantine) as a proxy for dementia diagnosis.¹⁰¹

3.2.2.3 *Age*

Age was introduced in the statistical models as a continuous variable. We also performed analyses stratified into younger elderly (<80 years of age) and older elderly (≥80 years of age) in Study I, III and IV.

3.2.2.4 *Co-morbidities*

In Study I and IV, we used number of drugs (continuous variable) as a proxy for overall co-morbidity.¹⁶⁷

In Study II, we constructed a dichotomous variable based on presence of pain-related diagnoses.⁶⁰⁻⁶² We included the following diseases/conditions available in the SNAC-K questionnaire and commonly associated with pain: hip fracture the present or previous year, vertebral compression, rheumatic disorders (including rheumatoid arthritis, polymyalgia rheumatica, SLE and vasculitis,), osteoporosis, osteoarthritis, cancer the present or previous year and headache/migraine.

In Study III, we analyzed the occurrence of osteoporotic fractures in the previous four years. Information about these fractures was obtained from the National Patient Register.¹⁶⁸ We included the following fractures (with ICD-10 codes), commonly related to osteoporosis:^{136, 169} fractures of femur (S72), rib(s), sternum and thoracic spine (S22), lumbar spine and pelvis (S32), shoulder and upper arm (S42), forearm (S52) and lower leg, including ankle (S82). We also analyzed the occurrence of “any osteoporotic fracture”, defined as at least one of the above mentioned fractures.

3.3 STATISTICAL ANALYSIS

All statistical analysis was performed by using SPSS statistical packages, version 17.0 or later (SPSS Inc., Chicago, IL, USA).

3.3.1 Specific analysis

3.3.1.1 Study I

We performed crude and adjusted logistic regression analysis in order to study the association between institutionalization and PIDU. In the crude model, only type of housing was entered as explanatory variable. In model 1, adjustment was made for age (continuous variable) and sex. In model 2, additional adjustment was made for number of drugs (continuous variable) and the interactions between age and type of housing and between number of drugs and type of housing. We also made a separate analysis of younger elderly (<80 years of age) and older elderly (≥ 80 years of age). To study PIDU in persons with dementia, we used treatment with anti-dementia drugs (ATC code N06D, i.e. cholinesterase inhibitors and memantine) as a proxy for dementia diagnosis.¹⁰¹

3.3.1.2 Study II

We used logistic regression analysis to study the association between dementia status and use of analgesics and psychotropics in the study population. We used both crude and adjusted analysis. In model 1, adjustment was made for age (continuous variable) and sex. In model 2, additional adjustment was made for pain-related diagnosis and the interactions between sex and dementia, age and dementia, and pain-related diagnosis and dementia. In model 3, further adjustment was made for type of housing (own home or institution) and the interaction between pain-related diagnosis and type of housing. All variables involved in the interaction terms were effect-coded (also called deviance coding).¹⁷⁰ Hence, all results obtained were for the average person. Second, we analyzed persons with and without dementia separately in order to investigate how the different explanatory variables were associated with the use of analgesics and

psychotropics. The Mini Mental State Examination (MMSE)¹⁷¹ was used to control for dementia severity.

Exclusively for this thesis, we also made an analysis stratified by type of housing, to explore how dementia status and pain-related disorders were associated with use of analgesics and psychotropics in the different settings.

3.3.1.3 Study III

We used logistic regression analysis to investigate the association between dementia status and use of osteoporosis drugs. We used both crude and adjusted analysis. First, we analyzed the whole dataset. In model 1, adjustment was made for age (continuous variable) and sex. In model 2, additional adjustment was made for type of housing (own home or institution) and osteoporotic fractures. There was no interaction between dementia status and type of housing. Second, we excluded the severely demented cases, in order to investigate if our results were influenced by low use of osteoporosis drugs in patients with severe dementia. We used the MMSE¹⁷¹ as a measure of dementia severity and only included subjects with MMSE ≥ 10 in this analysis.

3.3.1.4 Study IV

We analyzed men and women separately. We also stratified the data into younger elderly (<80 years of age) and older elderly (≥ 80 years of age). Both crude and adjusted logistic regression analysis was used to study whether institutionalization was associated with use of UTI antibiotics. In the adjusted model, we controlled for age and number of other drugs (continuous variable). There were no significant interaction terms. Similar to Study I, we also studied the use of UTI antibiotics in persons who concurrently used anti-dementia drugs (ATC code N06D).

3.3.1.5 Weighting the SNAC-K data (Study II and III)

As the sampling fractions in the different age groups were different in SNAC-K, i.e. a proportionally larger group of the youngest and oldest age groups were sampled, data from the examined population was weighted against the total population in Kungsholmen / Essingeöarna by age group and sex. In Study II, we chose to present all figures and proportions weighted, whereas in Study III, we chose to report the weighted proportions.

4 ETHICAL CONSIDERATIONS

4.1 REGISTER DATA

Study I and *IV* were based on non-identifiable register-based data and were approved by the ethical board in Stockholm (Dnr 2009/477-31/3).

4.2 SNAC-K

Study II and *III* were based on SNAC-Kungsholmen base-line data and were approved by the ethical board in Stockholm (Dnr 01-114). Informed consent was obtained for each participant. If the participant was unable to make an informed decision, a proxy consent was requested from a close relative. We only analyzed non-identifiable data. SNAC-K follows the ethical guidelines of the Swedish Council for Research in the Humanities and Social Sciences.

5 MAIN RESULTS

5.1 STUDY I

Institutionalized elderly used on average more drugs than home-dwelling elderly, i.e. 7.2 compared to 4.3 drugs per person. PIDU was common in this nationwide study of 1 260 843 home-dwelling and 86 721 institutionalized elderly. Thirty percent of the institutionalized and 12% of the home-dwelling elderly was exposed to at least one PIDU (Figure 4). The most common type of PIDU in institutions was concurrent use of three or more psychotropics. Among home-dwelling elderly, the most common type of PIDU was use of anticholinergic drugs.

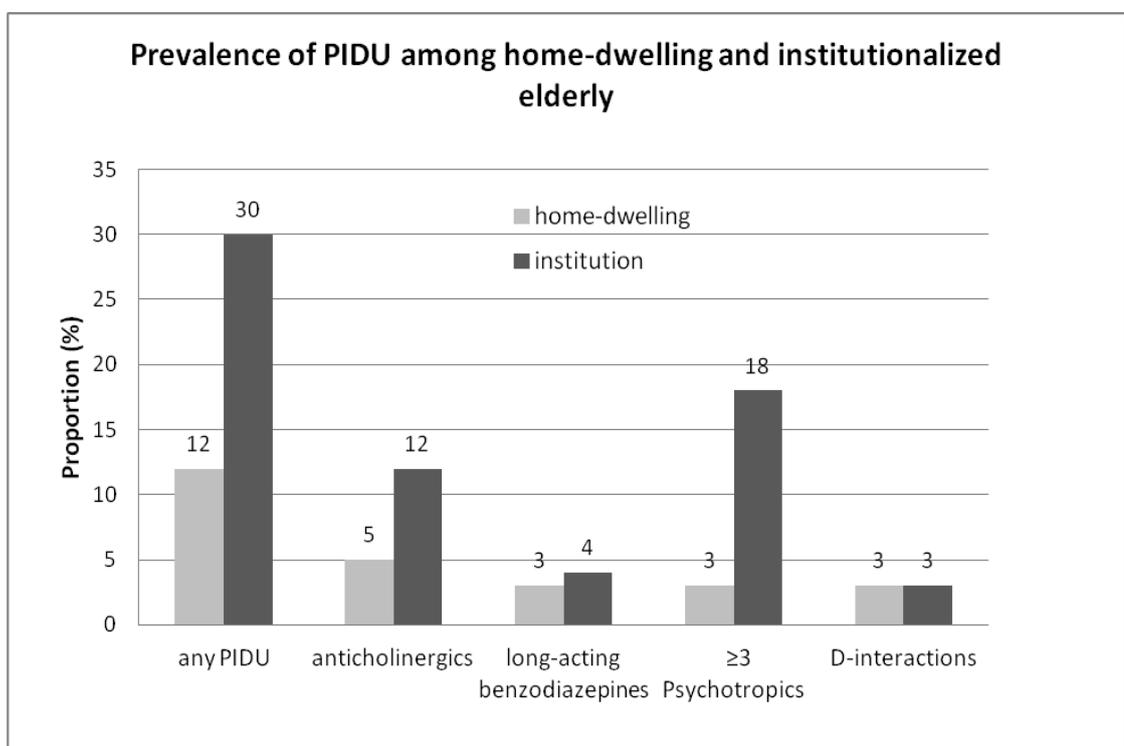


Figure 4 The prevalence of PIDU in 1 260 843 home-dwelling and 86 721 institutionalized elderly in Sweden 2008.

The crude logistic regression analysis revealed that institutionalization was associated with an increased likelihood of being exposed to overall PIDU. The association remained significant after adjustment for age and sex (data not shown) and after additional adjustment for number of drugs and the interaction terms (Table 6). Analyses of the individual indicators revealed that living in an institution was strongly associated with concurrent use of three or more psychotropic drugs, followed by anticholinergic drugs and long-acting benzodiazepines. On the contrary, institutionalization was associated with a lower probability of potentially serious DDIs, after adjustment for age, sex, number of drugs and the interaction terms.

Table 6. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) for potentially inappropriate drug use, overall, and stratified by age, 2008

	Potentially Inappropriate drug use^a	Anticholinergic drugs	Long-acting benzodiazepines	≥3 Psychotropics	Potentially serious DDIs
	OR_{adj}^b (95% CI)	OR_{adj}^b (95% CI)	OR_{adj}^b (95% CI)	OR_{adj}^b (95% CI)	OR_{adj}^b (95% CI)
Age ≥65 years (n=1 347 564)					
Type of housing					
Home-dwelling	Ref	Ref	Ref	Ref	Ref
Institution	2.36 (2.29-2.44)	2.58 (2.48-2.68)	1.50 (1.41-1.60)	7.26 (6.96-7.56)	0.60 (0.55-0.65)
Age < 80 years (n=885 430)					
Type of housing					
Home-dwelling	Ref	Ref	Ref	Ref	Ref
Institution	2.68 (2.54-2.83)	2.71 (2.53-2.90)	1.87 (1.68-2.08)	9.53 (8.89-10.21)	0.59 (0.51-0.68)
Age ≥80 years (n=462 134)					
Type of housing					
Home-dwelling	Ref	Ref	Ref	Ref	Ref
Institution	1.80 (1.70-1.91)	1.76 (1.62-1.90)	0.83 (0.73-0.94)	6.75 (6.21-7.33)	0.48 (0.41-0.55)

DDIs=drug-drug interactions; OR_{adj}=adjusted odds ratio; 95% CI= 95% confidence interval^aDefined as exposure to at least 1 of the following indicators: use of anticholinergic drugs, use of long-acting benzodiazepines, concurrent use of ≥3 psychotropics or potentially serious DDIs.^bAdjusted for age (continuous), sex, number of drugs (continuous) and the interactions between age and type of housing and between number of drugs and type of housing.

Analyses separated into younger elderly (aged <80 years) and older elderly (≥ 80 years) showed that institutionalization was positively associated with all types of PIDU in the younger elderly with the exception of potentially serious DDIs. In the older elderly, institutionalization was positively associated with overall PIDU, use of anticholinergic drugs and concurrent use of three or more psychotropics. However, institutionalization was associated with a lower likelihood of use of both long-acting benzodiazepines and potentially serious DDIs among the older elderly (Table 6).

Analysis of the persons using anti-dementia drugs (used as a proxy for dementia), revealed that use of these drugs was associated with a lower probability of exposure to overall PIDU compared to non-users of anti-dementia drugs (OR 0.89, 95% CI 0.86-0.92), after adjustment for age, sex, type of housing and number of drugs. Analyses of the individual indicators showed that use of anti-dementia drugs was negatively associated with use of anticholinergic drugs (OR 0.83, 95% CI 0.79-0.87), long-acting benzodiazepines (OR 0.49, 95% CI 0.45-0.53) and potentially serious DDIs (OR 0.61, 95% CI 0.56-0.66). However, use of anti-dementia drugs was positively associated with concurrent use of three or more psychotropic drugs (OR 1.45, 95% CI 1.38-1.51).

5.2 STUDY II

Of the persons with dementia, 46% used at least one analgesic drug compared to 25% of the persons without dementia. Sixty-three percent of the persons with dementia used at least one psychotropic drug compared to 32% of the persons without dementia. Persons with dementia used more opioids and paracetamol, but less NSAIDs than persons without dementia (Figure 5). In institutions, 49% used at least one analgesic, 39% used paracetamol, 28% opioids, 3% NSAIDs and 73% at least one psychotropic drug. Among the home-dwelling elderly, 25% used at least one analgesic, 16% paracetamol, 8% opioids, 12% NSAIDs and 30% at least one psychotropic drug. About 59% of the persons with dementia lived in institutions.

Further analysis with logistic regression showed that persons with dementia had a higher probability of use of paracetamol (OR 1.99, 95% CI 1.22-3.26) and psychotropics (OR 2.47, 95% CI 1.59-3.83), whereas there were no significant differences in use of any analgesic (OR 1.38, 95% CI 0.87-2.19), opioids (OR 1.37, 95% CI 0.73-2.56) and NSAIDs (OR 0.41, 95% CI 0.15-1.11), after controlling for age, sex, pain-related diagnosis, type of housing and the interactions between sex and dementia, age and dementia, pain-related diagnosis and dementia and between pain-related diagnosis and type of housing.

Results from the stratified analysis by dementia status showed that having at least one pain-related diagnosis was associated with a higher likelihood of use of analgesics in both persons with and without dementia (data not shown). Furthermore, having at least one pain-related diagnosis was significantly associated with use of any psychotropics, hypnotics and sedatives and antidepressants in persons with dementia but not in those without dementia (Table 7).

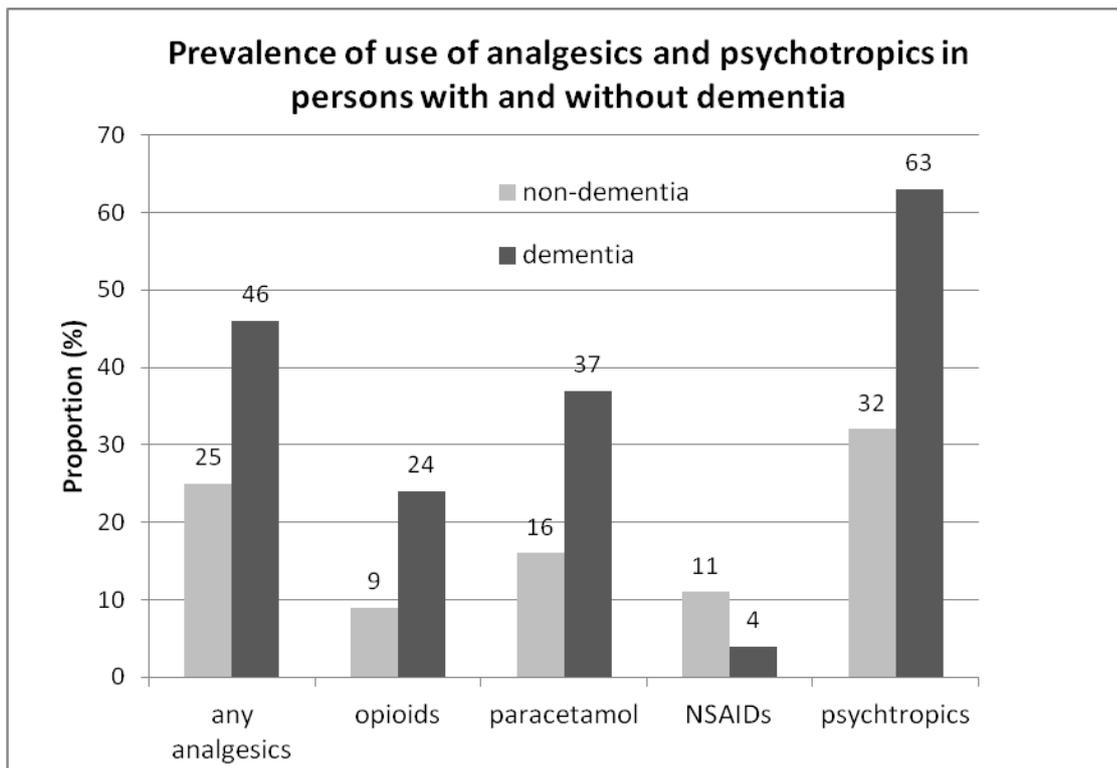


Figure 5. Use of analgesics and psychotropics in the study population (n=2 610), by dementia status.

Table 7. Logistic regression for use of psychotropics in patients having a pain-related diagnosis compared to not having a pain-related diagnosis, stratified by dementia status

Drug	OR _{adj} ^a (95% CI)
Dementia (n=304^b)	
Any psychotropic	1.93 (1.16-3.21)
Antipsychotics (N05A)	1.08 (0.48-2.43)
Anxiolytics (N05B)	1.82 (0.90-3.69)
Hypnotics and sedatives (N05C)	1.67 (1.02-2.74)
Antidepressants (N06A)	2.60 (1.45-4.65)
Non-dementia (n=2301^b)	
Any psychotropic	1.14 (0.77-1.69)
Antipsychotics (N05A)	0.60 (0.17-2.08)
Anxiolytics (N05B)	1.28 (0.78-2.10)
Hypnotics and sedatives N05C)	1.47 (1.00-2.16)
Antidepressants (N06A)	0.77 (0.48-1.25)

^aadjusted for age, sex, MMSE score, residential setting, pain-related diagnosis and the interaction between residential setting and pain-related diagnosis.

^bfive persons (1 with dementia and 4 without dementia) were not included in the analysis due to missing information about MMSE.

Table 8. Logistic regression for use of analgesics and psychotropic drugs, stratified by type of housing.

	Any analgesics	Opioids	Paracetamol	NSAIDs	Any psychotropic
	OR _{adj} ^a (95% CI)	OR _{adj} ^a (95% CI)	OR _{adj} ^a (95% CI)	OR _{adj} ^b (95% CI)	OR _{adj} ^a (95% CI)
<i>Home-dwelling (n=2 318)</i>					
Dementia status					
Non-demented	1	1	1	1	1
Demented	1.00 (0.55-1.83)	0.78 (0.25-2.42)	1.36 (0.73-2.53)	0.45 (0.21-0.96)	1.43 (0.89-2.31)
Pain-related diagnosis:					
No	1	1	1	1	1
Yes	3.31 (2.22-4.94)	3.69 (2.03-6.70)	3.56 (2.25-5.63)	2.86 (2.17-3.78)	2.17 (1.48-3.18)
<i>Institution (n=292)</i>					
Dementia status					
Non-demented	1	1	1	1	1
Demented	1.80 (0.98-3.31)	1.31 (0.63-2.76)	2.40 (1.28-4.51)	1.18 (0.31-4.44)	2.83 (1.39-5.73)
Pain-related diagnosis:					
No	1	1	1	1	1
Yes	1.84 (1.39-2.96)	1.45 (0.84-2.49)	1.74 (1.05-2.90)	3.15 (0.78-12.7)	1.04 (0.61-1.75)

^aadjusted for age, sex, dementia-status, pain-related diagnosis and the interactions between dementia and sex and dementia and pain related diagnosis.

^bfor NSAIDS the model were adjusted for the variables above except for sex among the institutionalized elderly and the interaction terms (since there were no mail NSAID users in the institutional setting and no non-demented NSAID users without pain-related diagnosis in the institutional setting).

Results from the stratified analysis by type of housing are presented in Table 8. There was no significant difference in the probability of use of any analgesics, opioids, paracetamol or any psychotropics among the home-dwelling elderly persons with and without dementia. However, dementia was associated with a lower use of NSAIDs in this setting. Among the institutionalized elderly, dementia was significantly associated with a higher use of paracetamol and any psychotropics. Having at least one pain-related diagnosis was associated with a higher use of any analgesics, opioids, paracetamol, NSAIDs and psychotropics among the home-dwelling elderly, but only with use of any analgesics and paracetamol among the institutionalized elderly.

5.3 STUDY III

Of the persons with dementia, about 5% used osteoporosis drugs compared to 12% of the persons without dementia (Figure 6). Calcium/vitamin D combinations were the most commonly used osteoporosis drug in both persons with and without dementia.

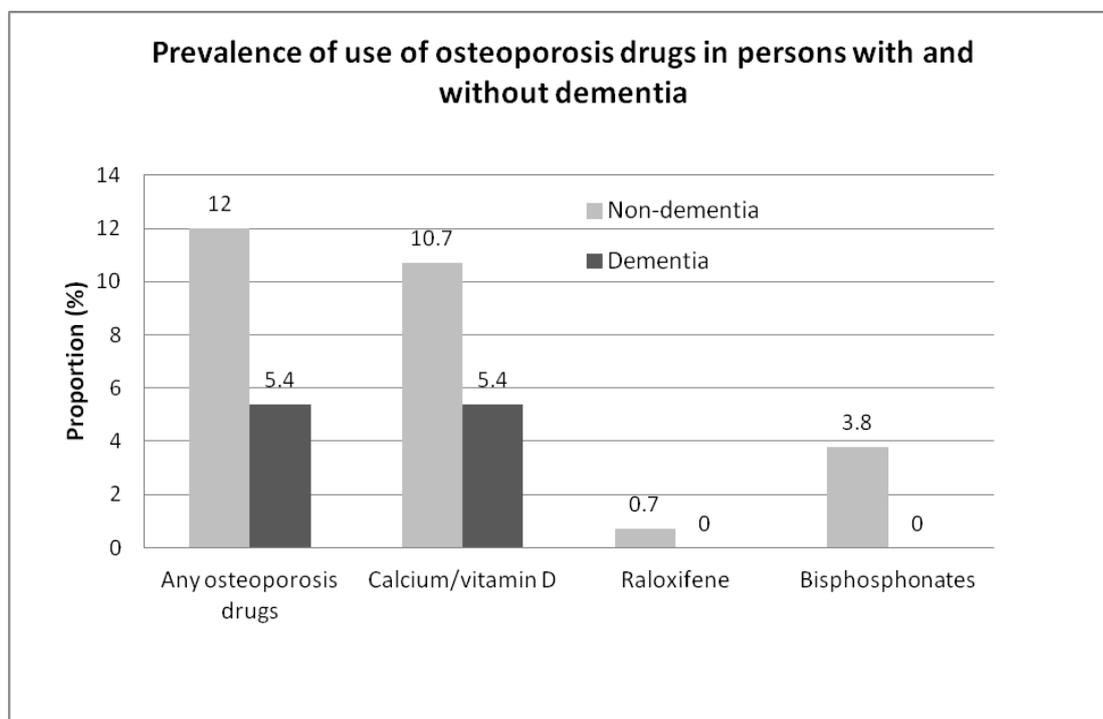


Figure 6. Use of osteoporosis drugs in the 305 persons with dementia and 2 305 persons without dementia in SNAC-K.

We found that persons with dementia were less likely to be treated with osteoporosis drugs, after controlling for age, sex, osteoporotic fractures and type of housing (own home or institution) (OR 0.34, 95% CI 0.19-0.59). Additional adjustment for educational level and use of glucocorticoids did not change the results.

The lower probability of use of osteoporosis drugs among persons with dementia was not explained by low use among the severely demented persons since the results changed only marginally when these persons (i.e. persons with MMSE score <10) were excluded from the analysis (OR 0.32, 95% CI 0.17-0.60).

Persons with dementia had a higher prevalence of osteoporotic fractures the previous four years than persons without dementia, i.e. 25% compared to 7% (Figure 7). The most common osteoporotic fracture was hip fracture. However, after controlling for age, sex and for type of housing, there was no significant association between dementia and osteoporotic fractures (OR 1.35, 95% CI 0.92-1.99). Living in an institution was associated with osteoporotic fractures after controlling for age, sex and dementia status (OR 3.53, 95% CI 2.43-5.13).

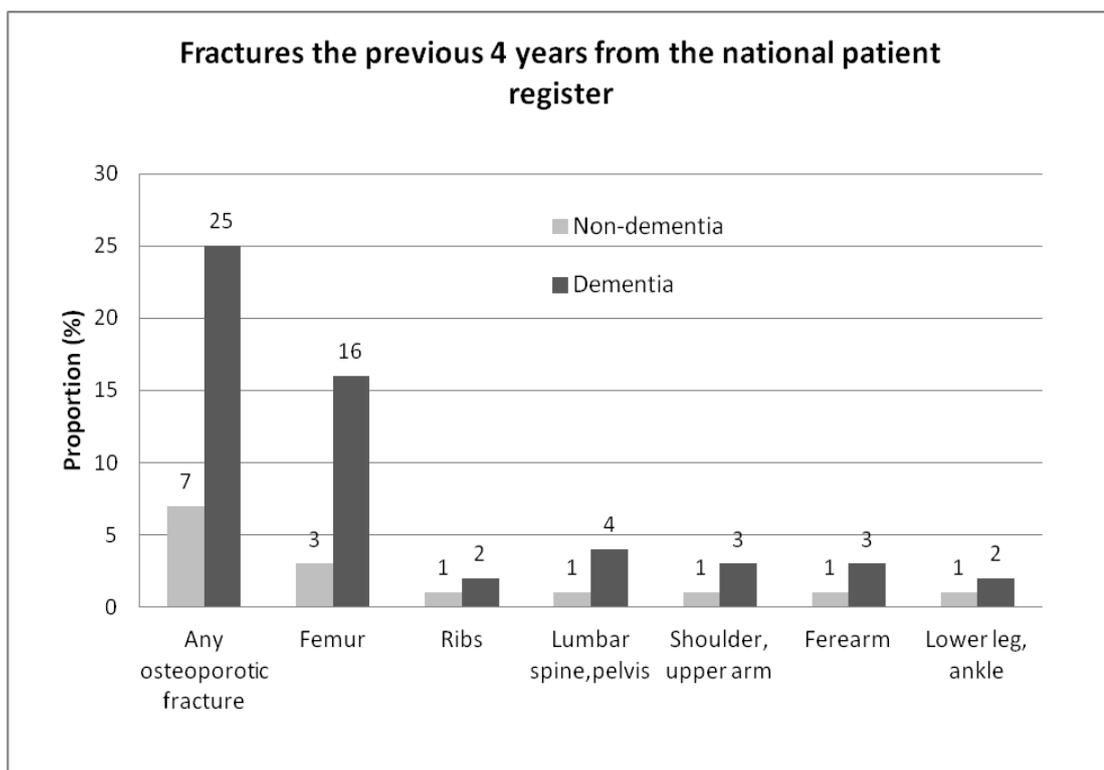


Figure 7. Prevalence of osteoporotic fractures the previous four years, by dementia status.

5.4 STUDY IV

By the date of 30 September 2008, 12 455 of the 1 347 564 analyzed individuals of age ≥ 65 years used UTI antibiotics. The 1-day point prevalence for use of UTI antibiotics in Sweden was 1.6% among institutionalized and 0.9% among home-dwelling elderly.

5.4.1 Women

Among the institutionalized women treated with UTI antibiotics, trimethoprim was the most commonly used UTI antibiotic in both the younger and older ages (used by 31% and 40%, respectively). Among the home-dwelling women, the most commonly used UTI antibiotic was pivmecillinam in both age groups (i.e. used by 32% of the younger and 35% of the older home-dwelling women).

The proportion of women treated with quinolones was higher in the younger ages, where 20% of the institutionalized women and 21% of the home-dwelling women used these drugs (Figure 8). According to the national indicators,¹⁰⁴ the proportion of women

using quinolones, of all women with lower UTI treated with UTI antibiotics, should be as low as possible.

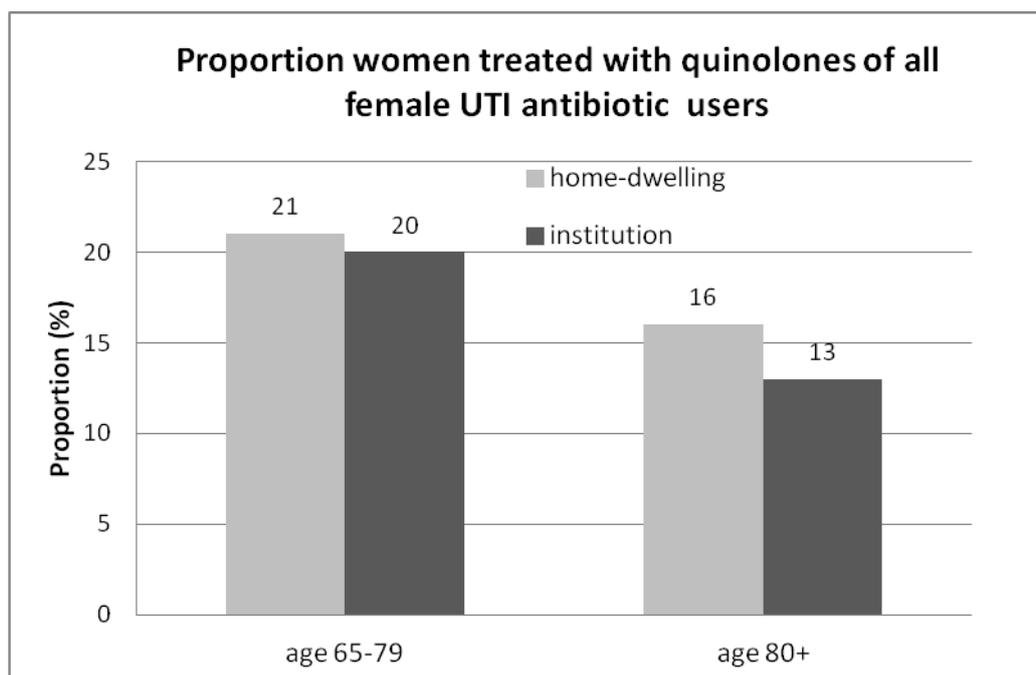


Figure 8. Proportion women treated with quinolones of all female UTI antibiotic users (n=8 538), 30 September 2008.

The proportion of women treated with the recommended UTI antibiotics, i.e. pivmecillinam, nitrofurantoin or trimethoprim was 29%, 27% and 45% in institutions and 40%, 28% and 34% for home-dwellers, which is not consistent with the national goal (Figure 9).

Of the women using UTI antibiotics, 2% (n=208) concurrently used anti-dementia drugs. Use of anti-dementia drugs (a proxy for dementia) was associated with a lower likelihood of use of quinolones (OR 0.57, 95% CI 0.36-0.89) after adjustment for age, type of housing and number of other drugs. There was no significant association between use of anti-dementia drugs and use of pivmecillinam (OR 1.15, 95% CI 0.85-1.55), nitrofurantoin (OR 0.95, 95% CI 0.68-1.34) or trimethoprim (OR 1.13, 95% CI 0.84-1.52).

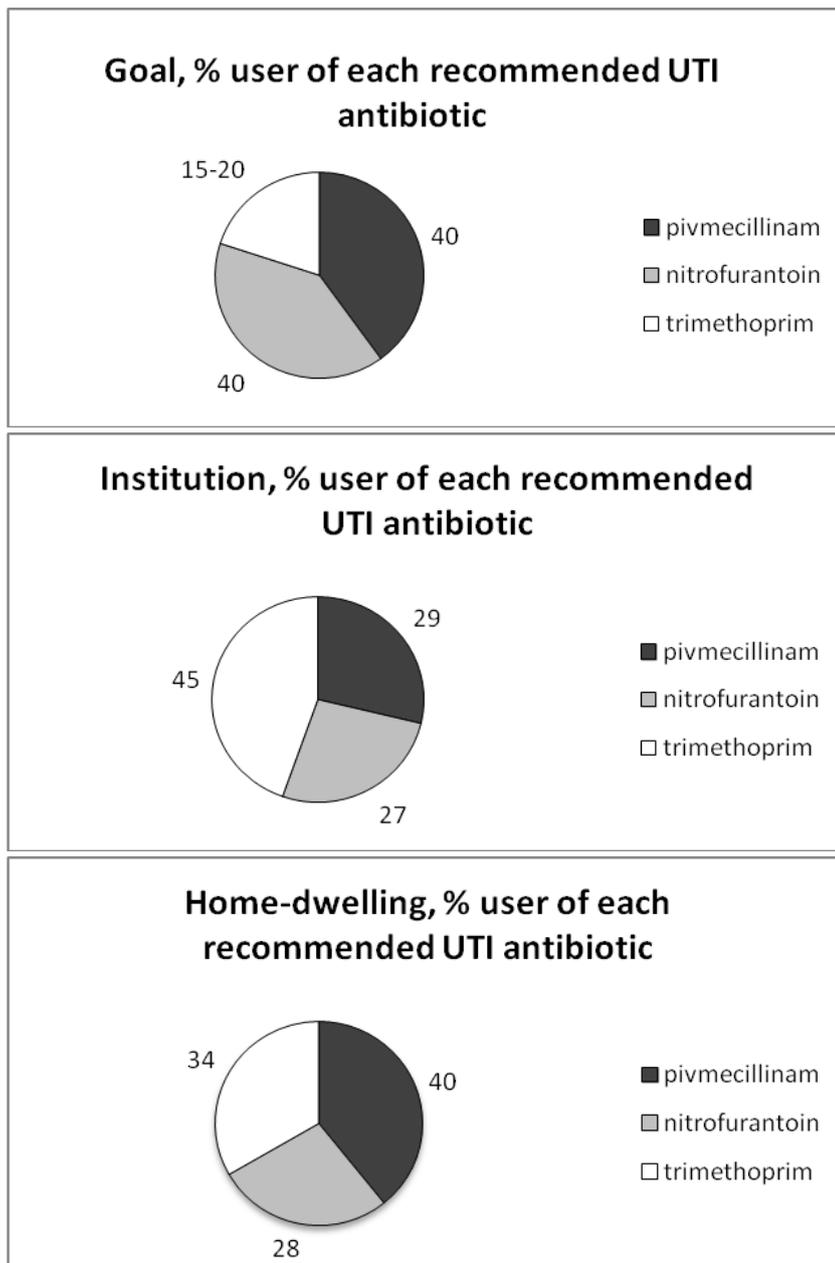


Figure 9. The proportion of women treated with the recommended UTI antibiotics, i.e. pivmecillinam, nitrofurantoin or trimethoprim; goal¹⁵⁰ and actual use in institutionalized and home-dwelling women, 30 September 2008.

5.4.2 Men

Among men, the most commonly used UTI antibiotic was a quinolone. This drug was used by 68% of the younger and 58% of the older home-dwelling men. In institutions, 49% of the younger and 45% of the older men used quinolones. Also, the proportion of men treated with either trimethoprim or quinolones (which currently are the recommended drugs for treatment of UTI in men) was higher among home-dwelling men in age ≥ 80 years, where 83% of the home-dwelling men compared to 74% of the institutionalized men in the same age-group used these drugs (Figure 10).

Among the male UTI antibiotic users, 2% (n=77) concurrently used anti-dementia drugs. There was no association between use of anti-dementia drugs and use of the UTI antibiotics (quinolones (OR 0.71, 95% CI 0.45-1.12), pivmecillinam (OR 1.19, 95% CI

0.56-2.51), nitrofurantoin (OR 0.96, 95% CI 0.45-2.02) or trimethoprim (OR 1.45, 95% CI 0.89-2.37).

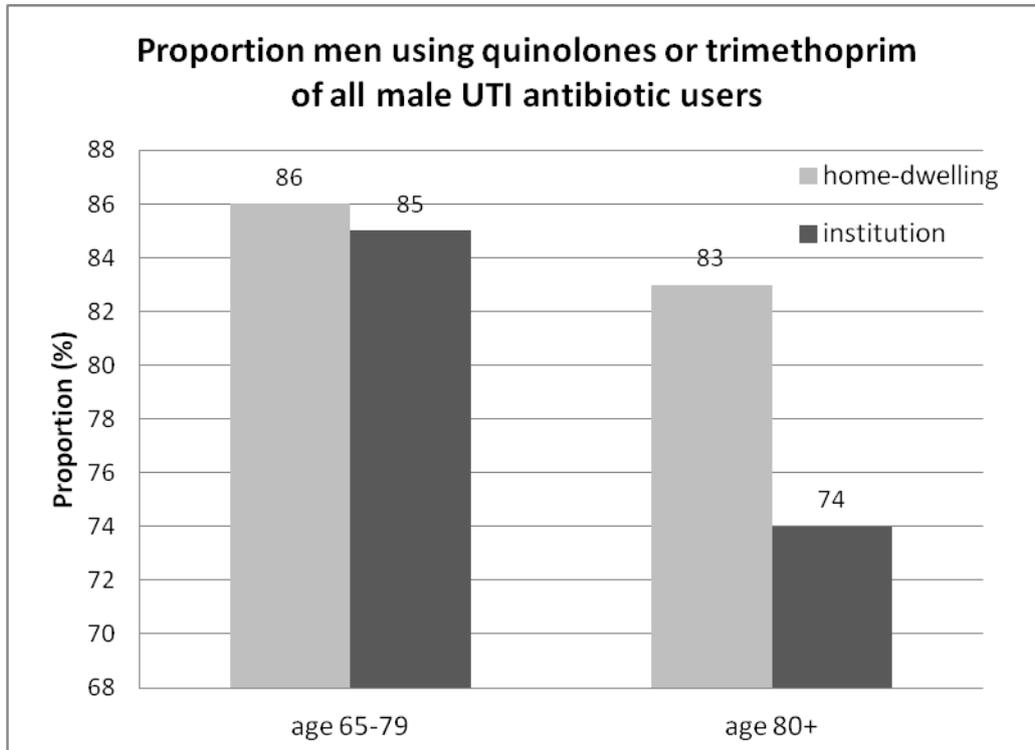


Figure 10. Proportion men treated with either quinolones or trimethoprim of all male UTI antibiotic users (n=3 917), 30 September 2008.

6 DISCUSSION

6.1 MAIN FINDINGS

6.1.1 Institutionalization and potentially inappropriate drug use

We found that PIDU was more common in institutions than among home-dwelling elderly, which is in line with previous research.^{78, 81, 96, 100, 103, 112, 172-173}

Institutionalization was associated with use of overall PIDU and the specific indicators use of three or more psychotropics, anticholinergic drugs and long-acting benzodiazepines, but with a lower prevalence of potentially serious DDIs, after adjusting for age, sex and number of drugs. Few studies have so far compared PIDU between institutionalized and home-dwelling elderly.^{80, 98, 107} A recent study found no association between type of housing and overall risk of PIDU, although institutionalization was associated with some individual indicators, such as use of long-acting benzodiazepines.⁹⁸ A Canadian study found that the prevalence of PIDU declined after admittance to nursing home, although the number of drugs increased.⁸⁰ Another Canadian study found that institutionalized elderly were close to half as likely as home-dwelling elderly to be exposed to PIDU, after controlling for age, sex and comorbidities.¹⁰⁷ Suggested explanations for these findings were mandatory service by clinical pharmacists in nursing homes in Canada¹⁰⁷ and monitoring by health care professionals with experience of caring for older people.⁸⁰ In Sweden, service by clinical pharmacists or other forms of medication reviews is currently not mandatory in institutions, which may affect the quality of drug use. However, we cannot exclude that the differences in findings are explained by differences in setting and criteria for PIDU.

Furthermore, institutionalization was more strongly associated with PIDU among the younger elderly, which is in line with previous studies that have suggested that the younger elderly are at a high risk of PIDU.^{57, 78, 87}

Analysis of elderly persons treated with anti-dementia drugs (used as a proxy for dementia disease) showed that these persons on average had a higher quality of drug use compared to other elderly, with the exception of the individual indicator concurrent use of three or more psychotropics, which is in line with previous findings.⁵⁷ A previous Swedish study reported that the quality of drug use was higher in nursing homes for dementia patients compared to other nursing homes, except for concurrent use of three or more psychotropic drugs.⁵⁷

6.1.2 Pain treatment and dementia

We found that persons with dementia had a higher probability of use of paracetamol whereas there were no significant differences in use of any analgesic, opioids and NSAIDs, after adjustment for individual factors and type of housing (own home/institution). Our results contradict many previous studies, which have reported a lower use of analgesics among people with dementia compared to other elderly.^{62, 174-175} However, Lövheim et al¹³⁰ found results similar to ours, i.e. that persons with dementia

use more analgesics overall, in particular paracetamol, whereas there is no difference in use of opioids and NSAIDs. Their study was based on data from the GERDA/Umeå 85+ study, which contain a sample of institutionalized and home-dwelling older people of age 85, 90 and 95 years and above living in Umeå, Sweden, and Vaasa and Mustaari, Finland. Also, a recent U.S. study measuring the use of analgesics in paracetamol equivalents, found that persons with dementia used significantly more analgesics than persons without dementia.¹²⁴ We found that paracetamol was the most commonly used analgesic in both persons with and without dementia, which seems reasonable given the high occurrence of musculoskeletal pain-related conditions in old people.¹²⁵ Also, the low use of NSAIDs in institutions and in persons with dementia may reflect a cautious prescribing of these drugs which are associated with an increased risk of gastrointestinal bleeding in older people.¹⁷⁶ Taken together, these findings may reflect a change in pain management and treatment in persons with dementia. It has indeed been an increased focus on pain in persons with dementia over the last decades.^{124, 177} Also, the year 2006-2007 was announced as the global year against pain in older people by the International Association for the Study of Pain (IASP),¹³ although this occurred after the data collection of our study.

However, many elderly persons may still lack adequate pain treatment.^{13, 130, 178} For example, Hartikainen et al¹⁷⁸ found that although most home-dwelling older persons used analgesics, they still experienced daily pain both after movement and at rest. Thus, not only the presence of analgesics, but also the quality of analgesic treatment is important. A recent Swedish study showed that the prescriptions of opioids differed largely in hip fracture patients between different health care districts.¹⁷⁹ Furthermore, persons in institutions and with dementia are often excluded from physical rehabilitation programs since they are often considered to be too frail to get beneficial effects,¹⁸⁰ even though some studies suggest that cognitively impaired patient may benefit in physical functioning as much as other patients.¹⁸⁰⁻¹⁸¹

We also found that having a pain-related diagnosis was associated with use of any psychotropics, sedatives and antidepressants in persons with dementia, but not in patients without dementia. This could indicate that symptoms caused by pain may be inappropriately treated with psychotropics in patients with dementia,⁶⁸⁻⁶⁹ something that needs to be further investigated. Balfour et al⁷⁰ found that AD patients with arthritis or rheumatism were undertreated with analgesics, whereas they were prescribed more benzodiazepines than AD patients without musculoskeletal conditions. However, in the treatment recommendations for BPSD published by the Swedish Medical Product Agency in 2008, pain is suggested as one factor that should be investigated before treatment with psychotropics are initiated.⁵² Also, a recent randomized clinical trial showed that treatment of pain in persons with dementia significantly reduced behavioral disturbances in these persons.¹⁸² Hopefully, further increased knowledge of pain behavior in persons with dementia will increase the appropriateness of pain treatment in this population.

Like others, we found that use of analgesics was common in institutions.^{6,43} However, having a pain related diagnosis was only associated with use of any analgesic and paracetamol in institutionalized elderly, but not with NSAIDs and opioids. This differed from the home-dwelling elderly, in that the presence of a pain-related diagnosis was also associated with use of opioids and NSAIDs in these persons. The associations were also weaker in the institutionalized elderly. It is possible that these results reflect an attempt to prevent pain, and eventually behavioral symptoms, in institutionalized elderly persons without a clear indication. If so, it is very important that the treatment effect is continuously monitored and evaluated, which is often not the case in practice in Swedish institutions.⁷⁴

6.1.3 Treatment of osteoporosis in persons with dementia

Although osteoporotic fractures were more common in persons with dementia, the use of osteoporosis drugs was lower among these persons. The difference remained significant also after controlling for age, sex, osteoporotic fractures and type of housing. Moreover, our results were not explained by low use among persons with severe dementia. Few other studies have so far investigated the use of osteoporosis drugs in persons with dementia. However, our findings are in concordance with other studies that found that dementia/cognitive impairment was negatively associated with use of osteoporosis drugs.⁶⁵⁻⁶⁶ In contrast, cognitive impairment in osteoporosis patients was associated with use of osteoporosis drugs among home-dwelling elderly in a Canadian study.¹⁸³

We also found that the pattern of use of osteoporosis drugs differed between persons with and without dementia. It appears that calcium/vitamin D combinations were chosen before the more potent alternatives bisphosphonates and raloxifene in patients with dementia. However, bisphosphonates and raloxifene were relatively new drugs when the data of this study was collected. It is possible that fear of adverse side effects made the physicians select the more “safe” alternative calcium/vitamin D combinations. For example, patients with dementia may be more sensitive to serious adverse side effects of bisphosphonates and these drugs may also be complicated to administer in this population.¹⁸⁴ Also, raloxifene is mainly used by postmenopausal women¹⁸⁵ and lacks documentation of hip fracture prevention.¹³⁵ Anyhow, our results suggests that persons with dementia are not only potentially undertreated for osteoporosis, but also that the treatment, when it occurs, is less potent.

6.1.4 Use of urinary tract infection antibiotics in the elderly

The analysis of indicators for treatment of lower UTI in women and men revealed that the Swedish national treatment recommendations were not adequately followed.

We found that the use of quinolones (which should be as low as possible¹⁰⁴) was high in both home-dwelling and institutionalized women, particularly in the younger ages (i.e. <80 years). The Swedish strategic program against antibiotic resistance (STRAMA) has, due to increased resistance levels, set the goal that the proportion of adult women treated for lower UTI with quinolones should not exceed 10% in ages <80

years.¹⁸⁶ We found that this type of drug was about twice as common as the recommended level in ages 65-79 years. This finding is in line with the reported prevalence in younger Swedish women (i.e. 18-65 years of age).¹⁶³ A high use in older ages may be of particular concern, since resistance levels may increase with age.¹⁸⁷ Quinolones are also frequently involved in adverse drug reactions and older people are in particular sensitive to adverse effects in the central nervous system.^{104, 156} Therefore, our finding that persons who used anti-dementia drugs were less likely to use quinolones seems reasonable given that dementia patients may be particularly sensitive to cognitive side effects. The use of quinolones in treatment of lower UTI may be overestimated in this study since quinolones also have other indications besides UTI, such as infected bedsores and pyelonephritis. However, if this is the case, it is surprising that the use of quinolones was less common in older ages, where such conditions are more common.^{163, 188}

Of the women treated with the recommended drugs, we found that the proportion of institutionalized women who used trimethoprim was 45%, i.e. much higher than the recommended 15-20%.¹⁵⁰ Although the prescriptions for trimethoprim have generally decreased over the past ten years in Sweden,¹⁵⁶ there was still a high use of trimethoprim in institutions in this study. In home-dwelling elderly, pivmecillinam was the most commonly used UTI antibiotic, which may reflect an implementation of the national guidelines for treatment of UTI in this group of women. Nitrofurantoin was used less commonly in both institutionalized and home-dwelling elderly than recommended by the Swedish guidelines (i.e. 27 and 28% of the institutionalized and home-dwelling women, respectively, were treated with this drug compared with the recommended level of 40%).¹⁵⁰ Nitrofurantoin causes few ecological side effects and the resistance rate in uro-pathogens is low.^{104, 189} However, in patients with reduced kidney function, nitrofurantoin may be ineffective and may cause adverse side effects, such as partially reversible neuropathy.¹⁹⁰ Therefore, our results may possibly reflect cautious prescribing of this drug in older people where reduced kidney function is common. However, a Swedish study found that nitrofurantoin accounted for only 14% of the prescriptions for UTI in women aged >18 years in outpatient care.¹⁴⁹ This suggests that the low rate of prescriptions for nitrofurantoin may be a general problem and not only related to impaired kidney function in old age.

In men, we found that quinolones, followed by trimethoprim, was the most commonly used UTI antibiotic, which is in concordance with Swedish guidelines.¹⁰⁴ However, the proportion treated with either quinolones or trimethoprim was lower in institutionalized men, in particular in age ≥ 80 years. In this age group, we instead found a higher use of nitrofurantoin. Nitrofurantoin is not a recommended treatment for UTI in men since this drug doesn't reach sufficient concentration in prostatic tissues and secretions.^{104, 191} However, it is an ongoing discussion whether the treatment recommendations for UTI in men should be updated due to the increased resistance levels to trimethoprim and quinolones.

Similar to others, we found that the prevalence of use of UTI antibiotics was higher in institutions than among home-dwelling elderly.^{148, 192} Institutions are considered as a high risk environment for the development and spread of antibiotic resistance.¹⁹³⁻¹⁹⁴ However, treating UTI in institutionalized elderly is often complicated by several factors. For instance, the symptoms may be diffuse and communication problems, mainly due to cognitive impairment, further complicates the diagnostics.¹⁹⁵ Analysis of urine samples only have limited value in this population,¹⁹⁶ since the prevalence of asymptomatic bacteriurea (ABU), which should not be treated with antibiotics, is high.¹⁴⁵ ABU is an important factor to take into account when studying the quality of UTI treatment in the elderly population.¹⁴⁵ Unfortunately, since we lack information about diagnoses, we cannot estimate the occurrence of inappropriate treatment in ABU. However, although this limitation may affect the prevalence of use of UTI antibiotics in institutions, it would not affect the pattern of treatment, which is the main outcome measure in Study IV.

6.1.5 Use of psychotropics in elderly people

The findings in this thesis suggest that drug use in institutions was extensive, and often inappropriate for older people. In particular, the use of psychotropics was extensive, i.e. 73% of the institutionalized elderly and 63% of the persons with dementia used at least one psychotropic drug (Study II). Almost one fifth of the residents in institutions were exposed to concurrent use of three or more psychotropics and persons with dementia were more likely to be exposed to this indicator (Study I). Extensive use of psychotropics in institutions and among persons with dementia has also been found in other studies.^{57, 130} This may be of concern as frail elderly people are particularly sensitive to adverse effects of these drugs, such as confusion and falls.^{27, 58} Moreover, the risk of adverse events increases when several of these drugs are combined.¹⁹⁷ For the individual patient, use of three or more psychotropics may sometimes be justified. However, use of psychotropics in BPSD is often of limited value.⁵² Still, behavioral problems may have a greater impact on prescription of psychotropics than a psychiatric diagnosis in institutions.¹⁹⁸ It is important that psychotropics are not prescribed in a routine-like manner due to insufficient elderly-care, including lack of staffing and education.⁷⁶

6.1.6 Undertreatment in elderly people

We found that patients with dementia may be undertreated for osteoporosis (Study III). This finding illustrates that persons with dementia may be at risk of being undertreated for somatic conditions. For instance, previous research has shown that persons with dementia also are at risk of being undertreated for cardiovascular diseases and pain.⁶⁰⁻⁶⁴ Efforts to avoid polypharmacy and adverse drug reactions, together with the risk that the dementia disease dominates the practitioner's attention at the expense of other disorders, may lead to an underprescription of potentially valuable drugs.^{34, 184, 199} Another important cause may be communication problems. Husebo et al⁶⁰ found that cognitively impaired institutionalized elderly receive fewer medications than cognitively intact persons. The authors suggested that this finding

may be due to cognitively impaired persons' reduced ability to communicate their symptoms.⁶⁰

However, undertreatment of osteoporosis, and other conditions (e.g. cardiovascular diseases), also occurs frequently in other elderly persons. Previous studies have suggested that both elderly persons treated with many drugs, and elderly people with other chronic diseases than dementia, may be undertreated.¹⁹⁹⁻²⁰² A Dutch study found that older people with polypharmacy were more commonly exposed to undertreatment than other elderly persons.²⁰² In that study, the most commonly underprescribed drugs were laxatives in patients treated with morphine followed by use of beta blocking agents in myocardial infarction and ACE-inhibitors in heart failure.²⁰²

6.1.7 Improving drug use in older people

Although undertreatment of several diseases is common among older persons, it is also common that drug therapies continue for a long time (many years) without a critical reevaluation of the effect.⁴

Already in 2001, the Swedish government emphasized the importance of medication reviews in patients treated with many drugs in a proposal to the parliament.⁴ Several studies have shown that clinical pharmacy services may reduce the number of drug related problems (e.g. inappropriate drug use, adverse drug reactions and non-adherence etc.),²⁰³ as well as morbidity and health care costs.²⁰⁴ Medication reviews are not currently mandatory in Swedish institutions, although it probably will be in the near future, according to a suggestion by the National Board of Health and Welfare.²⁰⁵ However, the proportion of residents in institutions that have their medications reviewed has been suggested as an indicator for the evaluation of care and services in the elderly persons.⁷⁴ According to a recent report from the National Board of Health and Welfare, 66% of the institutionalized elderly had their medications reviewed in 2010, although there were large differences between different municipalities ranging from 0-100%.⁷⁴ A stressful situation, lack of time, staff and resources has previously been suggested as factors that complicates the implementation of medication reviews in many institutions.⁴

Also, some practitioners may feel an uncertainty when treating frail elderly patients who use many drugs.^{200, 206} Practitioners may hesitate to follow evidence-based guidelines, since most guidelines are based on randomized controlled trials from which this population is excluded and which are not adapted for patients with multimorbidity.²⁰⁰ Therefore, there is a need for guidelines which also apply to frail elderly persons in institutions.²⁰⁰ However, since the disease pattern is often complex in these patients, an increased collaboration between general practitioners, specialist practitioners, nurses, clinical pharmacists and other health care professionals is necessary to keep the quality of drug use as high as possible. Also, time and resources should be allocated to facilitate the implementation of medication reviews in elderly people treated with many drugs.

6.2 LIMITATIONS

6.2.1 Methodological considerations

6.2.1.1 *Study design*

The cross-sectional design of the studies in this thesis does not allow us to draw conclusions about causality. However in Study III, we analyzed the occurrence of osteoporotic fractures during four years before the use of drugs was recorded.

6.2.1.2 *Generalizability*

Representativeness, i.e. how well the sample reflects the target population, is important for the generalizability of the results in epidemiological studies.

In Study I and IV, we analyzed the use of prescribed drugs in a large nationwide population of elderly persons. However, it is important to recognize that the study population only includes people who were dispensed at least one drug during the three-month study period. Hence, we do not have any data on the non-users of prescribed drugs. Therefore, the healthiest elderly may not be represented in our register-based studies. In order to estimate the drug use on 30 September 2008, we assumed that all currently used drugs would be dispensed during the prior three months, since drugs are dispensed for a maximum of 90 days' supply in Sweden. However, if the drugs were dispensed before the three-month period but used at a slower rate than intended, they would not be included in the analysis. Conversely, we might include drugs that were dispensed during the three-month period but discontinued prematurely.⁷⁹

The response rate in SNAC-K baseline (i.e. of those alive and eligible) was about 73%. The reason for non-participation is unknown; but some basic characteristics were collected. There was no difference in the sex distribution between participants and non-participants, but the non-participants were on average slightly older, and therefore, probably more disabled and more likely to live in institutions.⁵¹ This might have led to an underestimation of drug use and diseases, particularly in the oldest patients. On the other hand, some non-participants, particularly those of younger age, were probably healthy persons who were not motivated to participate in a study about aging and health.⁴⁶ Also, the participants in SNAC-K live in an urban area, a central part of Stockholm, and are on average relatively well educated.²⁰⁷ These factors may affect the generalizability of our results. In addition, the sampling proportions in the youngest and oldest age groups were larger than in the other age groups. However, since we weighed the data, this should not affect the generalizability of our results.

6.2.1.3 *Confounding*

In pharmacoepidemiological studies, it is important to consider confounding by indication, i.e. that the association between drug use and outcomes may be confounded by the underlying disease that the drug is indicated for.²⁰⁸ We have tried to handle this limitation in all of the studies. In study I and IV, we used number of drugs as a proxy for overall co-morbidity since we did not have information about diseases. In study II,

we analyzed the occurrence of pain-related diagnosis, and in study III, we analyzed osteoporotic fractures.

Further, we took into account other major confounding variables available in our datasets (i.e. age, sex, dementia and type of housing). Additional adjustment for multi-dose dispensing (i.e. ‘Apodos’) did not change the findings in Study I. Neither did adjustment for education or use of glucocorticoids in Study III. However, residual confounding due to unknown factors cannot be excluded.

6.2.1.4 *Other potential sources of bias*

6.2.1.4.1 Type of housing

In Study I and IV, data about type of housing were retrieved from the Social Services register by the date of 30 June, 2008. All Swedish municipalities reported data about institutional care at that time point.⁷² However, it cannot be excluded that some mistakes have occurred during the data collection, e.g. some municipalities may have failed to report information for some individuals.⁷²

SNAC-K (Study II and III) has information about the different types of institutions. However, since some groups were small and we wanted to have enough statistical power, we chose to analyze the type of housing variable in the same way as in Study I and IV.

6.2.1.4.2 Dementia

In SNAC-K, the dementia diagnosis was clinically based, as neuroimaging or biomarkers were not available for the complete sample. However, the dementia diagnosis was set and validated according to the Diagnostic and Statistical Manual of Mental Disorders (4th Edition) [DSM-IV] criteria¹⁶⁵ in a three-step procedure; two physicians set the diagnosis independent of each other and in case of disagreement, a third expert was consulted to make the final diagnosis.¹⁶⁶

In Study I and IV, we used anti-dementia drugs as a proxy for dementia.¹⁰¹ Most patients who use these drugs have a dementia disorder (in particular AD), but all persons with dementia do not receive anti-dementia drugs. This leads to an underestimation of dementia, particularly other forms than AD. Also, it has been shown that high education is associated with use of anti-dementia drugs.²⁰⁹ Therefore, it is possible that we capture the more highly educated dementia cases in these studies.

6.2.1.4.3 Other diseases/co-morbidities

In Study I and IV, we did not have information about co-morbidities or indications for drug use. However, we used number of drugs as a proxy for overall co-morbidity.¹⁶⁷

In Study II, we chose not to study the participants’ experience of pain further since a high proportion of the persons with dementia were not able to answer questions about their experience of pain. Therefore, we constructed a variable for the occurrence of pain-related diagnoses. Information about these diagnoses was based mainly on self-

report or information from a close relative. However, if the participant resided in an institution, this information was provided from medical records. The different sources of information could affect the reported prevalence of diseases in the different groups. For instance, the prevalence of pain-related disorders among home-dwelling elderly with dementia may have been underestimated, since relatives may not be aware of all the diseases/conditions of the participant.

In Study III, we analyzed the occurrence of osteoporotic fractures retrieved from the Patient Register. Almost all fractures in Sweden are treated in hospitals and are thereby included in the register. Although we analyzed fractures known to be related to osteoporosis,¹⁶⁹ some of them might have occurred in the absence of osteoporosis. However, due to the high age of the study population, we assume that most of the fractures were osteoporotic.

6.2.1.4.4 Drug use

The SPDR (Study I and IV) only contains information about prescription drugs dispensed at the pharmacy. Therefore, we lacked data on over-the-counter drugs, herbals, drugs used in hospitals and drugs supplied from drug store rooms in institutions, which may have led to an underestimation of drug use among home-dwelling and institutionalized elderly, respectively. Also, dispensed drugs do not necessarily reflect the actual drug use, as adherence rates may be low.

In Study II and III, information about drug use was retrieved from the participant or their relatives or from medical records, when the participant resided in an institution. The different sources of information could affect the reported prevalence of drugs in the different groups. Among the home-dwelling elderly, there is a risk of recall error. However, an advantage of using self-report is that the use of over the counter drugs (e.g. calcium/vitamin D combinations and minor analgesics) is taken into account.

6.2.2 Other concerns

The data about drug use in SNAC-K was collected in 2001-2004. Several new guidelines have been published since then, which may affect the use of drugs in older people. For instance, new recommendation about treatment of BPSD were published in 2008 by the Swedish Medical Product Agency,⁵² which may have changed the use psychotropics in persons with dementia.

6.3 CONCLUSION

We found that drug use was extensive among elderly Swedes, particularly among institutionalized elderly who used on average 7.2 prescribed drugs per person. About 30% of the institutionalized elderly and 12% of the home-dwelling elderly were exposed to at least one PIDU. Also, after controlling for age, sex and number of drugs (a proxy for co-morbidity), institutionalization was strongly associated with a higher probability of use of overall PIDU as well as the individual indicators use of anticholinergic drugs, long-acting benzodiazepines and concurrent use of three or more psychotropics. In particular, the high use of psychotropics may be of concern as frail elderly people are sensitive to adverse effects of these drugs e.g. confusion and falls. Therefore, there is a need for further research in order to investigate whether the higher occurrence of PIDU in institutions is explained by differences in disease patterns, different prescribing traditions or other underlying risk factors between these settings.

Unlike many previous studies, we did not find that persons with dementia used fewer analgesics than other elderly. However, our results suggest that patients with dementia may be inappropriately treated with psychotropics for their pain. In addition, it seems that institutionalized elderly may receive analgesics regardless of the presence of a pain-related diagnosis. Therefore, there is a need for further investigations of the appropriateness of pain treatment in persons with dementia and institutionalized elderly persons.

Although persons with dementia had a higher prevalence of osteoporotic fractures, they were less likely to use osteoporosis drugs than persons without dementia. Thus, our findings indicate an undertreatment of osteoporosis in persons with dementia.

We found a different pattern of use of UTI antibiotics in institutionalized and home-dwelling elderly persons. Our results indicate that the recommendations for treatment with UTI antibiotics were not adequately followed, which may lead to increased development of antibiotic resistance or unsuccessful treatment of the infection. In particular, the high use of trimethoprim (which is recommended as second line antibiotic for treatment of lower UTI in women) among institutionalized women and the low use of quinolones or trimethoprim (which currently are the recommended drugs in men) among institutionalized men need further investigation. Also the use of quinolones among the younger women was high.

Taken together, the studies in this thesis show that older people are often exposed to inappropriate drug use, that undertreatment of important somatic diseases occur in persons with dementia, and that treatment recommendations may not be adequately followed in elder care. Our results indicate that elderly in institutions and those with a dementia disorder are particularly at risk of having poor quality of their drug therapy. Therefore, it is important that treatment guidelines and indicators also apply to these vulnerable groups. More attention should be given to older people's drug therapy, both in research and in practice. In order to improve the quality of drug use in elderly

people, time and resources should be allocated to facilitate the implementation of regular medication reviews in this population and the cooperation between different health care professionals should be encouraged.

6.4 FUTURE DIRECTIONS

Studies of drug use in the elderly population should be a continuous process. In the future, the number of elderly people will increase, new drug therapy will emerge and, hence, drug use will be even more important in this population. Therefore, the development and changes in drug therapy among older people should be monitored on a regular basis. This is particularly important for frail elderly persons in institutions and those with dementia. However, as many elderly people today continue to live in their own homes despite poor health, also these patients' drug use needs to be regularly monitored and evaluated.

The introduction of the new Social Services Register makes it possible, via record linkage to the SPDR, to nationally study drug use in the most frail elderly persons in institutions. This unique opportunity was utilized in this thesis, and should be further employed in future research. However, since the register also contains information about home-care services, also studies about drug use in frail home-dwelling elderly persons should be encouraged.

Since the information about drug use in Study II and III in this thesis was collected in 2001-2004, it is important that the results of these studies are complemented by results of studies with more recent data.

Future studies of drug use should also aim to include diagnoses to limit the problem of confounding by indication. Then, it would be possible to observe actual differences in drug therapy between different groups (e.g. between institutionalized and home-dwelling elderly) without the concern that the results are confounded by differences in the underlying disease patterns.

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- 208** McMahon AD. Approaches to combat with confounding by indication in observational studies of intended drug effects. *Pharmacoepidemiol Drug Saf* 2003; 12: 551-8.
- 209** Johnell K, Weitoft GR, Fastbom J. Education and use of dementia drugs: a register-based study of over 600,000 older people. *Dement Geriatr Cogn Disord* 2008; 25: 54-9.

9 APPENDIX

List of dissertations from the Aging Research Center and the Stockholm Gerontology Research Center, 1991-2011.

2011

Schön Per. Gender matters. Differences and change in disability and health among our oldest women and men.

Rieckmann Anna. Human Aging, Dopamine, and Cognition: Molecular and functional imaging of executive functions and implicit learning.

Caracciolo Barbara. Cognitive Impairment in the nondemented elderly: Occurrence, risk factors, progression

2010

Fors Stefan. Blood on the tracks. Life-course perspectives on health inequalities in later life.

Keller Lina. Genetics in dementia. Impact of sequence variations for families and populations.

2009

Atti Anna-Rita. The effect of somatic disorders on brain aging and dementia: Findings from population-based studies.

Livner Åsa. Prospective and retrospective memory in normal and pathological aging.

Paillard-Borg Stephanie. Leisure activities at old age and their influence on dementia development.

Rana AKM Masud. The impact of health promotion on health in old age: results from community-based studies in rural Bangladesh.

Thilers Petra. The association between steroid hormones and cognitive performance in adulthood.

2008

Gavazzeni Joachim. Age differences in arousal, perception of affective pictures, and emotional memory enhancement. (Stockholm University)

Marengoni Alessandra. Prevalence and impact of chronic diseases and multimorbidity in the aging population: A clinical and epidemiological approach.

Rovio Suvi. The effect of physical activity and other lifestyle factors on dementia, Alzheimer's disease and structural brain changes.

Haider Syed Imran. Socioeconomic differences in drug use among older people. Trends, polypharmacy, quality and new drugs.

Agahi Neda. Leisure in late life. Patterns of participation and relationship with health.

Meinow Bettina. Capturing health in the elderly population. Complex health problems, mortality, and the allocation of home-help services.

Xu Weili. Diabetes mellitus and the risk of dementia. A population-based study.

2007

Ferdous Tamanna. Prevalence of malnutrition and determinants of nutritional status among elderly people. A population-based study of rural Bangladesh. (Licentiate thesis)

Westerbotn Margareta. Drug use among the very old living in ordinary household.

Rehman Jenny. The role of gender in face recognition. (Stockholm University)

Beckman Gyllenstrand Anna. Medication management and patient compliance in old age.

Nordberg Gunilla. Formal and informal care in an urban and a rural population. Who? When? What?

2006

Klarin Inga. Drug use in the elderly – are quantity and quality compatible.

Nilsson Erik. Diabetes and cognitive functioning: The role of age and comorbidity.

Ngandu Tiia. Lifestyle-related risk factors in dementia and mild cognitive impairment: A population-based study.

Jonsson Laukka Erika. Cognitive functioning during the transition from normal aging to dementia.

2005

Derwinger Anna. Develop your memory strategies! Self-generated versus mnemonic strategy training in old age: Maintenance, forgetting, transfer, and age differences.

De Ronchi Diana. Education and dementing disorders. The role of schooling in dementia and cognitive impairment.

Passare Galina. Drug use and side effects in the elderly. Findings from the Kungsholmen Project.

Jones Sari. Cognitive functioning in the preclinical stages of Alzheimer's disease and vascular dementia.

Karp Anita. Psychosocial factors in relation to development of dementia in late-life: a life course approach within the Kungsholmen Project.

Nilsson Jan. Understanding health-related quality of life in old age. A cross-sectional study of elderly people in rural Bangladesh.

2004

Berger Anna-Karin. Old age depression: Occurrence and influence on cognitive functioning in aging and Alzheimer's disease

Cornelius Christel. Drug use in the elderly - Risk or protection? Findings from the Kungsholmen project

Qiu Chengxuan. The relation of blood pressure to dementia in the elderly: A community-based longitudinal study

Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population. Results from the Kungsholmen Project.

Larsson Kristina. According to need? Predicting use of formal and informal care in a Swedish urban elderly population. (Stockholm University)

2003

Jönsson Linus. Economic evaluation of treatments for Alzheimer's disease.

2002

Fahlander Kjell. Cognitive functioning in aging and dementia: The role of psychiatric and somatic factors.

Giron Maria Stella T. The rational use of drugs in a population of very old persons.

2001

Jansson Wallis. Family-based dementia care. Experiences from the perspective of spouses and adult children.

Kabir Nahar Zarina. The emerging elderly population in Bangladesh: Aspects of their health and social situation.

Wang Hui-Xin. The impact of lifestyles on the occurrence of dementia.

2000

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (In collaboration with H. M. Queen Sophia University College of Nursing, Stockholm, Sweden)

von Strauss Eva. Being old in our society: Health, functional status, and effects of research.

1999

Almberg Britt. Family caregivers caring for relatives with dementia – Pre- and post-death experiences.

Robins Wahlin Tarja-Brita. Cognitive functioning in late senescence. Influences of age and health.

Zhu Li. Cerebrovascular disease and dementia. A population-based study.

1998

Agüero-Eklund Hedda. Natural history of Alzheimer's disease and other dementias. Findings from a population survey.

Guo Zhenchao. Blood pressure and dementia in the very old. An epidemiologic study.

Björk Hassing Linda. Episodic memory functioning in nonagenarians. Effects of demographic factors, vitamin status, depression and dementia. (In collaboration with the Department of Psychology, University of Gothenburg, Sweden)

Hillerås Pernilla. Well-being among the very old. A survey on a sample aged 90 years and above. (Licentiate thesis)

1997

Larsson Maria. Odor and source remembering in adulthood and aging: Influences of semantic activation and item richness.

Almberg Britt. Family caregivers experiences of strain in caring for a demented elderly person. (Licentiate thesis)

1996

Wahlin Åke. Episodic memory functioning in very old age: Individual differences and utilization of cognitive support.

Wills Philippa. Drug use in the elderly: Who? What? & Why? (Licentiate thesis)

Lipinska Terzis Beata. Memory and knowledge in mild Alzheimer's disease.

1995

Mattiasson Anne-Cathrine. Autonomy in nursing home settings.

Grut Michaela. Clinical aspects of cognitive functioning in aging and dementia: Data from a population-based study of very old adults.

1994

Grafström Margareta. The experience of burden in care of elderly persons with dementia. (Karolinska Institutet and Umeå University)

Holmén Karin. Loneliness among elderly - Implications for those with cognitive impairment.

Josephsson Staffan. Everyday activities as meeting-places in dementia.

Stigsdotter-Neely Anna. Memory training in late adulthood: Issues of maintenance, transfer and individual differences.

Forsell Yvonne. Depression and dementia in the elderly.

1993

Fratiglioni Laura. Epidemiology of Alzheimer's disease. Issues of etiology and validity.

Almkvist Ove. Alzheimer's disease and related dementia disorders: Neuropsychological identification, differentiation, and progression.

Basun Hans. Biological markers in Alzheimer's disease. Diagnostic implications.

1992

Borell Lena. The activity life of persons with a dementia disease.

1991

Herlitz Agneta. Remembering in Alzheimer's disease. Utilization of cognitive support.