

Psychotropic drugs, which include antipsychotics, anxiolytics, hypnotics, and antidepressants, are commonly utilised among the elderly. However, drug utilisation in this population is complex due to multiple morbidities, extensive drug utilisation and an increased sensitivity to drugs. Inappropriate utilisation of drugs among the elderly is an issue of great public health importance. The aim of this thesis is to assess and analyse potentially inappropriate utilisation of psychotropic drugs among the elderly in Sweden.

This thesis is based on data from individual-based registers on dispensed drugs and socioeconomic determinants, the Gothenburg 95+ Study, and aggregated drug sales statistics. Two indicators of inappropriate psychotropic drug utilisation were compared. Utilisation of psychotropic drugs and of inappropriate psychotropic drugs were analysed in relation to mental disorders and socioeconomic determinants. Trends over time in utilisation of inappropriate psychotropic drugs and recommended drugs were also assessed.

The findings emphasise the importance of choosing clinically relevant indicators to analyse inappropriate drug utilisation among the elderly. This thesis also identified socioeconomic inequities in psychotropic drug utilisation among the elderly, which is in conflict with the aims of equity in health care. Further, only a small proportion of the elderly with depression utilised antidepressants, while hypnotics and anxiolytics were considerably more common. This pattern could indicate symptomatic treatment and suggests a need for improvement in the diagnostics and treatment of depression among the elderly.

The findings in this thesis showed that there are substantial problems in the utilisation of psychotropic drugs among the elderly. However, there was a trend towards the utilisation of recommended rather than inappropriate psychotropic drugs among the elderly.

Eva Lesén

Psychotropic drugs among the elderly

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Population-based studies on indicators of inappropriate utilisation in relation to socioeconomic determinants and mental disorders

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ABSTRACT

Background: Drug utilisation among the elderly is complex due to multiple morbidities, extensive drug utilisation and an increased sensitivity to drugs. One of the most common drug groups utilised in this population is psychotropic drugs, which include antipsychotics, anxiolytics, hypnotics, and antidepressants. Inappropriate utilisation of drugs among the elderly is an issue of great public health importance.

Aims: The overall aim of this thesis is to assess and analyse potentially inappropriate utilisation of psychotropic drugs among the elderly in Sweden. The specific aims are to assess to what extent the indicator “concurrent use of three or more psychotropic drugs” captures the utilisation of Potentially Inappropriate Psychotropics (PIP) among the elderly, and to analyse potentially inappropriate utilisation of psychotropic drugs in relation to time, mental disorders, institutionalisation, and socioeconomic determinants among the elderly in Sweden.

Methods: Data from individual-based registers on dispensed drugs and socioeconomic determinants in 2006, the Gothenburg 95+ Study (1996-1998), and aggregated drug sales statistics from 2000-2008 were used. The agreement between the two indicators “concurrent use of three or more psychotropic drugs” and PIP was assessed. Utilisation of psychotropic drugs and PIP was assessed in relation to mental disorders and institutionalisation among the 95-year olds, and in relation to socioeconomic determinants among individuals aged 75 years and older. Further, trends over time in utilisation of PIP and recommended drugs were analysed.

Results: During 2006, about half of the elderly aged 75 years and older utilised psychotropic drugs and one fifth of all elderly utilised PIP. One fourth of individuals utilising PIP were captured by the indicator “concurrent use of three or more psychotropic drugs”. In 1996-1998, less than one tenth of the 95-year olds with depression utilised antidepressants, while hypnotics and anxiolytics were more common. Individuals with low income and the non-married were more likely to utilise PIP compared to those with high income and the married, respectively. During 2000-2008, utilisation of PIP decreased and utilisation of recommended psychotropic drugs increased.

Conclusions: There are substantial problems in the utilisation of psychotropic drugs among the elderly. This thesis found that the agreement between two indicators of inappropriate psychotropic drug utilisation was poor, which emphasises the importance of choosing relevant indicators. The findings also show socioeconomic inequities in psychotropic drug utilisation among the elderly, a low utilisation of antidepressants among 95-year olds diagnosed with depression, and a trend towards the utilisation of recommended rather than inappropriate psychotropic drugs among the elderly.

Key words: drug utilisation, psychotropic drugs, elderly, inappropriate drugs, quality indicators, mental disorders, socioeconomic determinants, Sweden

SVENSK SAMMANFATTNING

Bakgrund: Användning av läkemedel bland äldre är komplicerat på grund av multisjuklighet, användning av flera läkemedel och en ökad känslighet för läkemedel. En av de vanligaste läkemedelsgrupperna hos äldre är psykofarmaka, som inkluderar antipsykotika, ångestdämpande, sömnmedel och antidepressiva läkemedel. Olämplig användning av läkemedel bland äldre är ett betydande folkhälsoproblem.

Syfte: Det övergripande syftet med avhandlingen är att beskriva och analysera potentiellt olämplig användning av psykofarmaka bland äldre i Sverige. De specifika syftena är att undersöka i vilken utsträckning indikatorn ”samtidig användning av tre eller fler psykofarmaka” fångar användningen av potentiellt olämpliga psykofarmaka (PIP) bland äldre och att analysera potentiellt olämplig användning av psykofarmaka i relation till förändring över tid, psykiatriska diagnoser, boendeform och socioekonomiska determinanter bland äldre i Sverige.

Metod: Avhandlingen baseras på data från individbaserade register över läkemedelsköp och socioekonomiska determinanter under 2006, Göteborg 95+ studien (1996-1998) samt aggregerade data över läkemedelsförsäljning under 2000-2008. Överensstämmelsen mellan de två indikatorerna ”samtidig användning av tre eller fler psykofarmaka” och PIP undersöktes. Användning av psykofarmaka och PIP studerades i relation till psykiatriska diagnoser och boendeform hos 95-åringar och i relation till socioekonomiska determinanter hos de som var 75 år och äldre. Vidare analyserades förändring över tid i användning av PIP och rekommenderade psykofarmaka.

Resultat: Hälften av alla äldre som var 75 år och äldre använde psykofarmaka under 2006 och en femtedel av alla äldre använde PIP. En fjärdedel av individerna som använde PIP fångades av indikatorn ”samtidig användning av tre eller fler psykofarmaka”. Bland 95-åringarna med depression år 1996-1998 använde färre än en av tio antidepressiva läkemedel, medan sömnmedel och ångestdämpande läkemedel var vanligare. PIP var vanligare hos de äldre med låg inkomst och bland de som inte var gifta, jämfört med individer med hög inkomst och de gifta. Under 2000-2008 minskade användningen av PIP medan användningen av rekommenderade psykofarmaka ökade.

Slutsatser: Det finns fortfarande stora problem i äldres användning av psykofarmaka. Avhandlingen visar en låg överensstämmelse mellan två indikatorer för olämplig användning av psykofarmaka, vilket pekar på betydelsen av att välja relevanta indikatorer. Avhandlingen visar också på socioekonomiska ojämlikheter i användningen av psykofarmaka hos äldre, en låg användning av antidepressiva läkemedel bland 95-åringar med depression och en ökning i användningen av rekommenderade istället för olämpliga psykofarmaka bland äldre.

Nyckelord: läkemedelsanvändning, psykofarmaka, äldre, olämpliga läkemedel, kvalitetsindikatorer, psykiatriska diagnoser, socioekonomiska determinanter, Sverige

ORIGINAL PAPERS

The thesis is based on the following papers:

- I. Lesén E, Petzold M, Andersson K, Carlsten A. To what extent does the indicator “concurrent use of three or more psychotropic drugs” capture use of potentially inappropriate psychotropics among the elderly? *Eur J Clin Pharmacol* 2009;65:635-42.
- II. Lesén E, Carlsten A. There is a trend in the utilization of psychotropics among elderly towards recommended drugs. *Pharmacoepidemiol Drug Saf* 2010;19:1095-9.
- III. Lesén E, Carlsten A, Skoog I, Waern M, Petzold M, Börjesson-Hanson A. Psychotropic drug use in relation to mental disorders and institutionalisation among 95-year olds - a population-based study. *Int Psychogeriatr* (in press).
- IV. Lesén E, Andersson K, Petzold M, Carlsten A. Socioeconomic determinants of psychotropic drug utilisation among elderly: a national population-based cross-sectional study. *BMC Public Health* 2010;10:118.

The papers will be referred to in the text by their Roman numerals.

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CONTENTS

ABBREVIATIONS	11
DESCRIPTIONS OF KEY CONCEPTS	13
1 BACKGROUND	15
1.1 Public health science and pharmacoepidemiology	15
1.2 Trends in population structure and health status among the elderly	16
1.3 Trends in drug utilisation among the elderly	18
1.4 Psychotropic drug utilisation among the elderly	19
1.5 Challenges in drug utilisation among the elderly	20
1.6 Inappropriate drug utilisation among the elderly.....	21
1.7 Indicators of inappropriate drug utilisation among the elderly	23
1.8 Concluding remarks	25
2 AIMS OF THE THESIS.....	27
3 METHODS	29
3.1 Data sources	29
3.1.1 Individual-based drug utilisation data linked to socioeconomic information.....	29
3.1.2 Drug utilisation trends over time	30
3.1.3 Drug utilisation patterns in relation to mental disorders.....	30
3.2 Definition of potentially inappropriate psychotropic drugs	31
3.3 Description of the papers	33
3.3.1 Paper I: PIP versus the indicator “concurrent use of three or more psychotropic drugs”	33
3.3.2 Paper II: Trends in the utilisation of psychotropic drugs among the elderly.....	34
3.3.3 Paper III: Psychotropic drug utilisation in relation to mental disorders and institutionalisation among 95-year olds.....	34
3.3.4 Paper IV: Socioeconomic determinants of psychotropic drug utilisation among the elderly.....	35
4 ETHICAL CONSIDERATIONS	37
5 RESULTS	39
5.1 Paper I: PIP versus the indicator “concurrent use of three or more psychotropic drugs”	39
5.2 Paper II: Trends in the utilisation of psychotropic drugs among the elderly	41
5.3 Paper III: Psychotropic drug utilisation in relation to mental disorders and institutionalisation among 95-year olds	42

5.4 Paper IV: Socioeconomic determinants of psychotropic drug utilisation among the elderly.....	43
6 DISCUSSION.....	47
6.1 Main findings.....	47
6.2 General discussion	47
6.2.1 Utilisation of psychotropic drugs among the elderly	47
6.2.2 Indicators of inappropriate psychotropic drug utilisation among the elderly	50
6.2.3 Utilisation of PIP among the elderly	51
6.2.4 Efforts aimed at improving drug utilisation among the elderly	55
6.3 Methodological considerations	57
6.3.1 Classification of PIP	57
6.3.2 Information on drug utilisation	57
6.3.3 Diagnoses of mental disorders among the 95-year olds	59
6.3.4 Socioeconomic determinants	59
7 CONCLUSIONS AND IMPLICATIONS	61
8 FUTURE RESEARCH.....	63
9 ACKNOWLEDGEMENTS	65
10 REFERENCES	67

APPENDIX

Papers I-IV

NHV Reports

ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical classification system
CI	Confidence Interval
CPRS	Comprehensive Psychopathological Rating Scale
DDD	Defined Daily Dose
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, third edition, revised
DTC	Drug and Therapeutics Committee
LISA	Longitudinal integration database for health insurance and labour market studies (LISA by Swedish acronym)
OR	Odds Ratio
PDD	Prescribed Daily Dose
PICP	Potentially Inappropriate Combinations of Psychotropics
PIP	Potentially Inappropriate Psychotropics
PIPS	Potentially Inappropriate Psychotropic Substances
RCT	Randomised Controlled Trial
SALAR	Swedish Association of Local Authorities and Regions
SEK	Swedish Krona
SPDR	Swedish Prescribed Drug Register
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TID	Thousand Inhabitants and Day
WHO	World Health Organization

DESCRIPTIONS OF KEY CONCEPTS

ATC classification system	The Anatomical Therapeutic Chemical (ATC) classification system classifies drugs into different groups in five levels according to the organ or system on which they act and their chemical, pharmacological and therapeutic properties. The ATC classification system is administered by the World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology, Oslo, Norway. The example of diazepam is shown below: <table><tr><td>N</td><td>Nervous system</td></tr><tr><td>N05</td><td>Psycholeptics (antipsychotics, anxiolytics and hypnotics)</td></tr><tr><td>N05B</td><td>Anxiolytics</td></tr><tr><td>N05BA</td><td>Benzodiazepine derivatives</td></tr><tr><td>N05BA01</td><td>diazepam</td></tr></table>	N	Nervous system	N05	Psycholeptics (antipsychotics, anxiolytics and hypnotics)	N05B	Anxiolytics	N05BA	Benzodiazepine derivatives	N05BA01	diazepam
N	Nervous system										
N05	Psycholeptics (antipsychotics, anxiolytics and hypnotics)										
N05B	Anxiolytics										
N05BA	Benzodiazepine derivatives										
N05BA01	diazepam										
DDD	The Defined Daily Dose (DDD) is the assumed average daily maintenance dose for a drug utilised for its main indication in adults. The DDD system is administered by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway.										
Drug utilisation	Actual drug use is near impossible to examine in large populations, since it would require massive efforts to determine whether the drug was consumed or not. To emphasise this, the word “utilisation” is used as a collective term for drug prescribing, sales, dispensing, and actual consumption of drugs (1).										
Inappropriate drug utilisation	Inappropriate drug utilisation includes: a lack of drugs that are clinically indicated; utilisation of drugs without a clinical indication; and incorrect utilisation of a drug that is clinically indicated, e.g. utilisation of										

an inappropriate drug. Drugs are defined as inappropriate when the risks outweigh the potential benefits, or when safer and equally effective alternatives are available (2).

PIP	Potentially Inappropriate Psychotropics (PIP)
PICP	encompass psychotropic substances and combinations
PIPS	considered potentially inappropriate among the
	elderly, based on criteria from the Swedish National
	Board of Health and Welfare (3). PIP includes both
	Potentially Inappropriate Combinations of Psycho-
	tropics (PICP) and Potentially Inappropriate Psycho-
	tropic Substances (PIPS).

Psychotropic drugs	Psychotropic drugs include antipsychotics, anxiolytics,
	hypnotics, and antidepressants.

1 BACKGROUND

1.1 Public health science and pharmacoepidemiology

Three key concepts are generally included in definitions of public health science: 1) the population perspective, 2) the focus on determinants of health, and 3) the ambition to improve the health of the general population and reduce inequities in health (4, 5). Pharmacoepidemiology is a part of public health science that contributes to knowledge about patterns, determinants, quality, and outcomes of drug utilisation in a population perspective. Pharmacoepidemiology has been defined as “the study of the distribution and determinants of drug-related events in populations and the application of this study to efficacious drug treatment” (6) and “the study of the use and effects/side effects of drugs in large numbers of people with the purpose of supporting the rational and cost-effective use of drugs in the population thereby improving health outcomes” (1).

Drug therapy is a common intervention in clinical practise and the vast majority of the elderly population utilise drugs (7). Drugs are utilised to cure diseases, to reduce or eliminate symptoms, to arrest or slow down a disease progress, or to prevent diseases or symptoms, and ultimately to improve the patients’ quality of life (8). Rational drug utilisation has been defined by the WHO as “patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community” (9). Thus, if drugs are utilised appropriately, they can enable a high quality of life for many elderly, despite a declining health status.

Before a new drug is approved for utilisation in the general population, the drug has often only been assessed for efficacy and safety in small, selected populations for short treatment durations in randomised controlled trials (RCTs). RCTs rarely include elderly and very seldom elderly with multiple morbidities and multiple drugs (10, 11). Efficacy refers to effects under strict conditions, such as in RCTs. Effectiveness measures the outcomes achieved in real-life settings, where the individuals may be younger or older than the participants in RCTs, may utilise other drugs, have other morbidities or a lower adherence to the drug. Pharmacoepidemiology contributes to knowledge about drug effectiveness, safety and drug utilisation patterns in real-life settings and aims to improve rational utilisation of drugs and ultimately to improve public health.

The health care systems in all Nordic countries aim to provide health care for the entire population on equal terms, and the vision is health for all (12-16). Equity in health care implies that all individuals should be entitled to health care, including drugs, based on their needs, irrespective of their age, sex or status in society. It is thus of great public health importance to assess drug utilisation patterns in relation to socioeconomic determinants and morbidity. The process from the identification of a health problem by the individual, to a decision to seek health care and the health care professional's decision to utilise a drug for the patient is influenced by both medical and non-medical factors (17-25). There is thus a risk for inequities in drug utilisation in numerous steps of this process. Health care seeking behaviour varies between individuals. How individuals perceive their need for health care is influenced by their knowledge and beliefs about health issues as well as any stigma related to their health problems. Economic resources, social support and availability of health care resources may enable or hinder health care seeking. Further, once the individual is in contact with the health care, drug utilisation may be influenced by their knowledge about health issues, their socioeconomic and demographic characteristics and their communication abilities. Prescriber related factors, such as age, sex and personal prescribing preferences, may also influence drug utilisation. The elderly with low socioeconomic status utilise more drugs compared to those with higher socioeconomic status (26, 27), which could correspond to their higher morbidity (28, 29). However, this group is also more likely to utilise inappropriate drugs and less likely to utilise newly-marketed drugs (26, 30, 31), which could indicate socioeconomic inequities in drug utilisation.

1.2 Trends in population structure and health status among the elderly

The number and the proportion of elderly in the population are increasing, particularly in welfare states such as the Nordic countries (32-34). Sweden has the highest proportion of elderly among all the Nordic countries and one of the oldest populations in the world (34, 35). Over time, the life expectancy has increased. This change can partly be attributed to the shift in the primary cause of death from infectious diseases with a high mortality to non-communicable diseases with a lower mortality (33, 36, 37). Among men in Sweden, the average life expectancy at birth has increased from 74 years in 1983 to 79 years in 2009 (38). The corresponding increase among women was from 80 to 83 years during the same period. The elderly constitute the fastest growing segment of the population (33). During the last 40 years, the proportion of individuals aged 75 years and older in Sweden has almost doubled and was 9% in 2009 (39). The

number of individuals aged 75 years and older is expected to increase 83% between the years 2010 and 2050, while the corresponding increase for the entire population is estimated at 14% (40). Individuals surviving beyond 90 years of age represent a unique population, and the number of individuals aged 95 years and older in Sweden is expected to increase 165% between 2010 and 2050 (40, 41).

Health status declines with age, and a considerable proportion of the elderly suffer from multiple morbidities (34, 35, 42). Many of these morbidities could benefit from a rational pharmacological treatment. A decline in health status is associated with an increase in health care utilisation (33, 35). The proportion of elderly living in nursing homes and the utilisation of home care and home help services increase with age (43).

A considerable proportion of the disease burden among the elderly is attributed to mental disorders (44, 45), and the prevalence of many mental disorders increases with age (35, 44). The prevalence of dementia is about 14% among those aged 77-84 years and 48% among those aged 95 years and older (46-48). Dementia is more common among women than among men, at least in higher ages, which might be related to the higher survival among women. Depression is another major mental disorder among the elderly. The prevalence of major depression among the elderly varies substantially between different settings; from 1-42% (44, 49). Symptoms of depression that do not fulfil criteria for a depressive disorder, but still may be of clinical relevance, appear to be even more common. Many studies have found a higher prevalence of depression among elderly women than among elderly men (49). Furthermore, conflicting results have been reported regarding whether the prevalence of depression increases or decreases with age among the elderly. The prevalence of depression also appears to be elevated among nursing home residents and among the non-married. The prevalence of anxiety disorders varies between 1-28% (50). The wide distributions in prevalence rates of depression and anxiety are partly due to differences in study populations, e.g. whether they include nursing home residents or elderly living in community settings, and the use of different diagnostic criteria. Sleep problems are also common among the elderly, and these problems are often secondary to other disorders, such as depression (51).

The prevalence of chronic disease has been suggested to increase over time, while the prevalence of disability appears to decline or remain stable (36, 52). This trend could to some extent be due to increased and earlier diagnostics of diseases as well as improvements in medical treatments, resulting in less severe consequences of disease (35, 53). However, conflicting results regarding trends

over time in health status in relation to the increasing life expectancy among the elderly have been reported (33, 36, 52). The differences in trends between studies might be partly explained by variations in study population characteristics, for example whether or not nursing home residents are included, changes in participation rates over time and by the use of different indicators of health status. Several different theories that try to describe these trends have been proposed (33, 36, 52). The theory of expansion of morbidity suggests that the added life years consist of years with chronic diseases and disabilities, i.e. an increase in survival among those with poor health status. The theory of dynamic equilibrium proposes that the number of years with chronic disease and disability increase, but the disease severity decreases. The theory of compression of morbidity suggests that the age at onset of chronic disease and disability is postponed and the added life years consist of healthy years (33, 36, 52). Regardless of which theory or combination of theories that turns out to be most correct, the increasing number of elderly in the society will pose challenges for the health care.

1.3 Trends in drug utilisation among the elderly

The proportion of individuals utilising drugs and the average number of drugs utilised per individual increase with age (54-57). These figures are generally higher among women than men. In the Nordic countries, about 90% of individuals aged 75 years and older utilise at least one drug (54-57). Psychotropic drugs are one of the most common drug groups utilised among the elderly (54, 56, 58, 59). Central nervous system drugs (psychotropic drugs and analgesics) account for the largest expenditure in relation to total drug costs in all of the Nordic countries (60).

The average number of drugs per individual has increased over time among the elderly in the Nordic countries (54, 56, 58). This trend might have been influenced by the introduction of new drugs and broadening of indications (61). There has also been an increase in the preventive treatment of risk factors, access to medical care and consumer demand. Furthermore, medicalisation, i.e. that non-medical or socially constructed problems are redefined and treated as medical conditions, and that activities and care that were formerly non-medical are replaced by medical care, might also have influenced this trend (62).

Previous research from Europe and the United States indicate a decrease over time in the utilisation of inappropriate drugs among the elderly (63-65). However, the results have been presented only in large and aggregated age

groups (e.g. 65 years and older), and studies of trends in the Nordic countries are rare. The prevalence of inappropriate drug utilisation tends to increase with age (63, 66, 67), and since the proportion of the very old increases over time (32-34), such aggregated time trends in drug utilisation might be biased by the changes in population structure. There is thus a need for research where the influence of time is investigated more specifically and separated from the effects of ageing.

1.4 Psychotropic drug utilisation among the elderly

Psychotropic drugs include antipsychotics, anxiolytics, hypnotics, and antidepressants. These drugs are utilised for mental disorders such as depression, anxiety, psychotic and sleep disorders, but also for other indications (68-70). About 20-30% of elderly men and 30-50% of elderly women utilise psychotropic drugs, according to findings from the Nordic countries and other European countries (56, 70-72). As shown in Figure 1, utilisation of psychotropic drugs is more common among women than among men, and the prevalence increases with age among the elderly in Sweden (73). Hypnotics are most common among the psychotropic drugs.

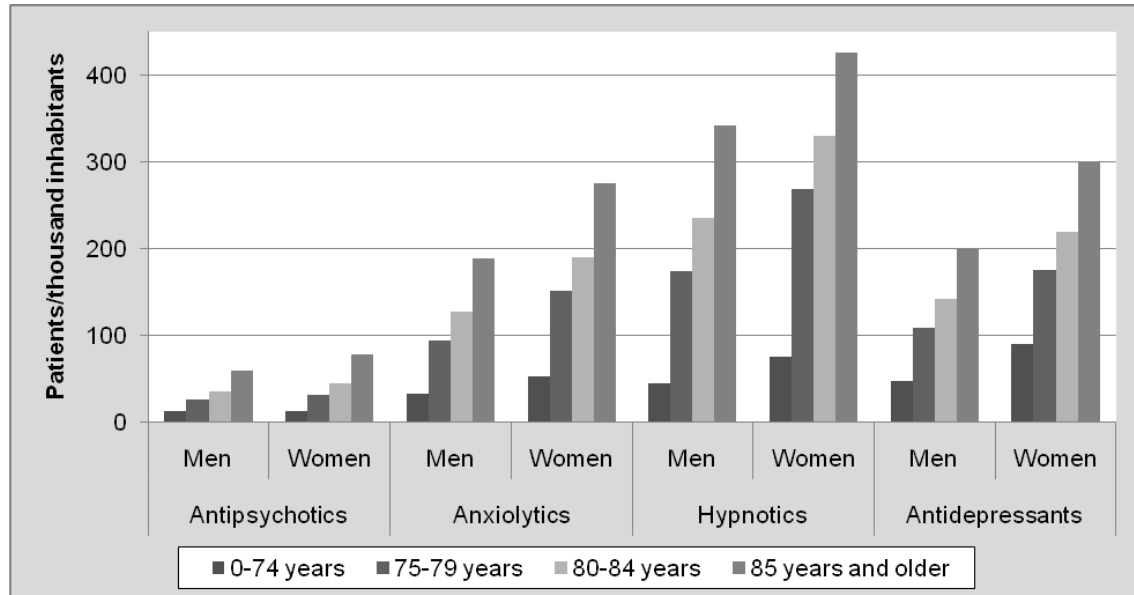


Figure 1 One-year prevalence of psychotropic drug utilisation in Sweden year 2009, measured as the number of individuals who at least once during 2009 purchased a psychotropic drug (“patients”) per thousand inhabitants, according to the Statistical database at the National Board of Health and Welfare (73).

The main recent changes among the psychotropic drugs include the introduction of the short-acting z-hypnotics (zopiclone, zolpidem and zaleplon), the new generation of antidepressants, e.g. the selective serotonin reuptake inhibitors (SSRIs), and the atypical antipsychotics in the early nineties (74). Findings from Europe and North America indicate that the utilisation of antipsychotics has increased among the elderly during the last decade (75, 76). The increase was primarily attributed to the introduction of the atypical antipsychotics. However, recent research suggests that their safety profile may not be superior than that of the conventional antipsychotics (77). Antidepressant utilisation has increased markedly in many western countries, including the Nordic countries, largely due to the introduction of the new generation antidepressants (71, 78-80). The SSRIs have a superior benefit-risk profile compared to the older generation of antidepressants, i.e. the tricyclic antidepressants (TCAs) (81). The more acceptable safety profile compared to the previously available alternatives has likely made antidepressant treatment more available in general practice, thereby reaching a larger and less severely depressed population than in specialised care. Other factors contributing to the increase in antidepressant utilisation include broadened treatment indications for antidepressants, an increased awareness of depression, and acceptance of its pharmacological treatment (82, 83). Regarding anxiolytics and hypnotics among the elderly, there have been no marked changes in overall prevalence, but a trend towards the utilisation of short-acting drugs, e.g. utilisation of z-hypnotics instead of the long-acting benzodiazepines (56, 71, 84).

1.5 Challenges in drug utilisation among the elderly

Drugs are an important component in the care of the elderly; however, drug utilisation in this population is complex due to multiple morbidities, extensive drug utilisation and age-related physiological changes. The age-related physiological changes among the elderly encompass pharmacokinetic and pharmacodynamic changes, and contribute to an increased sensitivity to adverse drug reactions. The pharmacokinetic changes include a relative decrease in body water, a relative increase in body fat and reduced kidney and liver functions (85). These changes contribute to an increased vulnerability for adverse drug reactions among the elderly and may for example prolong the effects of some hypnotics and anxiolytics (85). Changes in pharmacodynamics result in a higher sensitivity for the drug at the site of action (85). The sensitivity in the central nervous system increases for benzodiazepines and drugs with anticholinergic effects, such as the TCAs and the conventional antipsychotics, especially among individuals with dementia (85-87). Further, the regulatory functions become impaired and

this reduces the capacity to counteract drug effects. Reactions to drugs may thus be stronger among the elderly than among younger individuals. These age-related changes have important implications regarding the choice of drug and dose (88). There is limited evidence of effectiveness and safety of drugs among the elderly, since results from RCTs of drugs rarely are generalisable to the elderly population due to the exclusion of individuals from the general elderly population (10, 11). In relation to the high utilisation of drugs in this population, an important public health issue is therefore to assess effectiveness, safety and utilisation patterns of drugs among the elderly in real-life settings.

Individuals surviving beyond 90 years of age appear to have a better health status when they are 70-89 years old compared to those from the same birth cohort that do not survive to this high age (41). However, knowledge about health status and drug utilisation in this population group is limited. Not only are they excluded from RCTs, individuals aged 90 years and older are commonly underrepresented in pharmacoepidemiological studies focusing on elderly and results are rarely presented specifically for this age group (56, 70, 71). Study samples are seldom population-based and tend to focus on selected populations, such as nursing home residents (89). Furthermore, the variability in health status between individuals increases with age, and the variations are considerable among the elderly (90). It can therefore be problematic to extrapolate knowledge concerning younger elderly to this age group. Research on health status and drug utilisation patterns in this very old and growing age group is thus warranted.

1.6 Inappropriate drug utilisation among the elderly

As previously described, rational drug utilisation implies that the drug is appropriate for the patient's needs and administered in an individually adjusted dosage for an adequate period of time at the lowest cost to the patient and the community (9). To achieve quality in drug utilisation, it is crucial to balance benefits and risks, and to consider patient individuality and preferences as well as available health care resources (91, 92). Quality in drug utilisation is complex and involves several dimensions. One important aspect of quality in drug utilisation can be captured by analysing inappropriate drug utilisation, which includes a lack of drugs that are clinically indicated, utilisation of drugs without a clinical indication, and incorrect utilisation of a drug that is clinically indicated, e.g. utilisation of an inappropriate drug (91). Inappropriate drug utilisation among the elderly is acknowledged as an issue of great public health importance (91). A substantial part of the inappropriate drug utilisation among the elderly

concerns psychotropic drugs, and this drug group is therefore of particular public health interest (31, 50, 63, 93, 94).

The elderly commonly utilise multiple drugs. Between 42-77% of the elderly utilise five or more drugs and 9-28% utilise ten or more drugs (7, 26, 54, 56, 58). This might indicate inappropriate drug utilisation among the elderly. Although drug utilisation can lead to improvements in health, given that the drug is appropriately utilised for a clinically relevant indication, utilisation of several drugs may also increase the complexity and the risks of drug utilisation. Utilisation of a high number of drugs is associated with an increased probability for utilisation of inappropriate drugs, drug-drug interactions and adverse drug reactions (35, 66, 91). The utilisation of several drugs may have various explanations, e.g. a high number of morbidities or risk factors, and it is possible that such utilisation is appropriate. However, other possible contributory factors include a high number of prescribers, poor coordination between caregivers, and inadequate follow-up of treatment effects (95, 96). The term polypharmacy is often used in the context of multiple drug utilisation, but the definitions vary greatly and may focus on drug utilisation in relation to clinical indications or solely on number of drugs (97). The clinical relevance of a cut-off in the number of drugs as a marker of quality has been questioned (98). Utilisation of several drugs does not necessarily correspond to inappropriate utilisation if the patient has a need for all the drugs and if the benefits outweigh the risks. Further, utilisation of few drugs does not automatically correspond to appropriate utilisation; a drug may for example not be utilised despite that the patient could benefit from the drug (96).

A lack of drugs that are clinically indicated is an important aspect of inappropriate drug utilisation among the elderly. Depression and anxiety disorders are often underrecognised and undertreated among the elderly (50, 72, 93, 94, 99, 100). The availability of the new generation antidepressants with a more acceptable safety profile may in time result in an increase in the proportion of elderly individuals who utilise antidepressants (99).

Drugs are defined as inappropriate when the risks outweigh the potential benefits, or when safer and equally effective alternatives are available (2). The prevalence of utilisation of inappropriate drugs among the elderly ranges between 17-35% in Europe (31, 63, 66, 67, 101, 102). The variations in estimates between studies can be partly explained by differences in the characteristics of the study populations and in the criteria applied to define drugs as inappropriate. Utilisation of inappropriate drugs has been associated with mortality (103), hospitalisations (67, 103, 104), falls (105), self-reported adverse drug events

(106) and increased health care utilisation, and costs (107-109). However, some reports show no association between utilisation of inappropriate drugs and adverse outcomes (110). Psychotropic drugs are common among the inappropriate drugs utilised by the elderly, and the most common inappropriate psychotropics are the long-acting benzodiazepines and psychotropics with anticholinergic effects, such as the TCAs and the conventional antipsychotics (96, 111). Utilisation of long-acting benzodiazepines and drugs with anticholinergic effects may increase the risk for daytime sedation, cognitive decline, balance disorders and falls (86, 87, 96, 105, 112). Individuals with dementia are especially sensitive to drugs with anticholinergic effects. Another major public health concern is that there appears to be socioeconomic inequities in the utilisation of inappropriate drugs, where individuals with lower socioeconomic status are more likely to utilise inappropriate drugs compared to those with higher socioeconomic status (26, 31).

1.7 Indicators of inappropriate drug utilisation among the elderly

To measure the complex issue of quality in drug utilisation, some dimensions, such as patient individuality, often need to be excluded for practical reasons. Indicators can be used to assess quality in health care, and clinically relevant indicators of inappropriate drug utilisation among the elderly have a large potential to direct attention to areas in need of improvement (113). The ideal indicator should detect all cases of suboptimal care, and not classify optimal care as suboptimal. Indicators should have an association with relevant outcomes, i.e. indicators of inappropriate drug utilisation should be associated with adverse health-related outcomes (113). Inappropriate drug utilisation among the elderly can be assessed with explicit criteria (criterion-based) or implicit tools (judgement-based). Implicit tools are based on reviews and judgements of individual drugs by clinical expertise (114, 115). The use of such tools may provide more valid information on appropriateness, but the process may be time-consuming and give a low inter-rater reliability. This hampers their applicability and the comparability between studies.

Explicit criteria are commonly used to assess appropriateness in drug utilisation among the elderly. In general, such criteria focus on the choice of drug, dose, drug interactions, and duration of drug utilisation (91). These explicit methods are based on defined criteria, and are thus objective with a high inter-rater reliability. However, they generally omit factors such as patients' preferences, comorbidities, and lack of treatment for clinical indications. Explicit criteria for measuring utilisation of potentially inappropriate drugs among the elderly have

primarily been developed in North America (116-119), where Beers criteria are one of the most well-known examples. Explicit criteria have also developed in several European countries (3, 120-123).

Explicit criteria are not easily transferable between countries, since availability of drugs and utilisation patterns vary (31). Therefore, nationally adapted criteria are preferred. Swedish criteria have been developed by the National Board of Health and Welfare (3). These criteria were developed by a project group of clinical pharmacologists, pharmacists, geriatricians, and other experts. Systematic literature reviews, internationally published explicit criteria and Swedish guidelines and recommendations formed the basis for the development of the criteria. Expert groups commented the draft before it was finalised. The criteria includes specific drugs and combinations of drugs associated with an increased risk for adverse events among the elderly. Similar criteria have recently been developed in Norway, partly based on the Swedish criteria (123). Research on utilisation patterns of inappropriate drugs among representative samples of elderly is needed to better target future interventions aimed at improving drug utilisation among the elderly.

The indicator “concurrent use of three or more psychotropic drugs” is included among the explicit criteria published by the National Board of Health and Welfare (3). It is also used in annual national assessments of quality and efficiency in the Swedish health care (“Öppna jämförelser”) (124). The indicator is considered to indicate both poor quality in the treatment of psychiatric disorders and an increased risk of adverse outcomes and drug interactions (3). Utilisation of three or more psychotropics has been associated with an increased risk of falls (125), however with regards to mortality, other studies have found no increased risk (126). A shortfall of the indicator “concurrent use of three or more psychotropic drugs” is that it does not distinguish between types of psychotropic drugs. It is therefore important to assess the characteristics of this indicator in relation to indicators of specific inappropriate psychotropics, and to compare the distributions of individuals identified with each indicator. This can help guide the choice of indicator in future assessments of inappropriate drug utilisation among elderly.

To facilitate and enhance rational utilisation of drugs, there are lists of recommended drugs to complement the lists of drugs to be avoided. In Sweden, all 21 county councils and regions are required to have a Drug and Therapeutics Committee (DTC). This tradition is also strong in the other Nordic countries (127). The DTCs are independent from the pharmaceutical industry, and aim to enhance safe and cost-effective drug utilisation. They produce lists of

recommended drugs based on these aims. Some DTCs also produce lists specifically concerning the elderly. The recommendations are based on the scientific literature, and are developed in collaboration between prescribers, pharmacists, and clinical pharmacologists. Furthermore, the DTCs spread and argue for their recommendations among prescribers (127).

1.8 Concluding remarks

Drug utilisation among the elderly is complex due to multiple morbidities, extensive drug utilisation and an increased sensitivity to drugs. Psychotropic drugs are one of the most common drug groups utilised in this age group, and a large proportion of the inappropriate drugs utilised among the elderly are psychotropics. Therefore, an improvement in the utilisation of psychotropic drugs is likely to have a substantial and positive impact on a large proportion of the elderly population. To facilitate an improvement, it is crucial to increase the understanding of how utilisation of inappropriate psychotropic drugs can be measured and how these drugs are utilised among the elderly.

2 AIMS OF THE THESIS

The overall aim of this thesis is to assess and analyse potentially inappropriate utilisation of psychotropic drugs among the elderly in Sweden.

The specific aims are:

- To assess to what extent the indicator “concurrent use of three or more psychotropic drugs” captures utilisation of Potentially Inappropriate Psychotropics (PIP) among the elderly
- To analyse trends in utilisation of Potentially Inappropriate Psychotropic Substances (PIPS) in relation to drugs recommended by Drug and Therapeutics Committees (DTCs) among 75-year olds and among individuals born in 1925
- To assess the utilisation of psychotropic drugs in relation to mental disorders and institutionalisation among 95-year olds and to identify utilisation of PIP
- To analyse whether two socioeconomic determinants – income and marital status – are associated with differences in utilisation of psychotropic drugs and PIP among the elderly

3 METHODS

3.1 Data sources

3.1.1 Individual-based drug utilisation data linked to socioeconomic information

All Nordic countries have tax-supported health care systems that provide access for all citizens, irrespective of age or socioeconomic status (57). Prescription drugs within the reimbursement schemes are partially or completely subsidised. The Nordic countries have a long tradition of collecting national, population-based information on demography and health (57). The data collection is facilitated by the unique personal identification number available in all Nordic countries. In Sweden, the National Board of Health and Welfare has the overall responsibility for the collection of epidemiological data, and is in charge of keeping several health data registers, such as the Swedish Prescribed Drug Register (SPDR). The SPDR is a national, individual-based register with information on dispensed prescription drugs. Corresponding registers are available in all Nordic countries (57). Established in July 2005, the SPDR contains person-identifiable data on all prescription drugs dispensed in Swedish pharmacies (7). The SPDR includes information about the drug (type and amount), the patient (unique personal identification number, age, sex, and place of residence), date of purchase and drug costs. Drugs utilised in hospitals or purchased over-the-counter are not included. Data on dispensed drugs are included in the SPDR irrespective of reimbursement status, or whether the drugs are dispensed via ordinary prescriptions or via the multi-dose dispensed drug system (ApoDos). Multi-dose dispensed drugs are provided for individuals who cannot manage their own drugs in a safe and satisfactory manner (128). The drugs are delivered to the patients in small bags containing the drugs that should be consumed at each occasion. The patients' costs do not differ from those for ordinary prescriptions. The majority of nursing homes in Sweden supply drugs via ordinary prescriptions or via multi-dose, and information on these drugs is thus included in the SPDR (57). The corresponding drug registers in the other Nordic countries include similar information; however, there are some differences (57). The Finnish register includes reimbursed drugs only, and the coverage of drugs utilised in nursing homes varies between the countries. This hampers the possibility of conducting register-based Nordic comparative studies of drug utilisation among the elderly.

With data from such drug registers, it is possible to perform individual-based analyses, for example to study concurrent drug utilisation. Via the personal identification number, it is also possible to link the data to other individual-based registers, such as the longitudinal integration database for health insurance and labour market studies (the LISA database) at Statistics Sweden, with information on demographic and socioeconomic factors.

This thesis includes data from the SPDR on individuals aged 75 years and older in 2006 who purchased at least one prescribed psychotropic drug in a Swedish pharmacy. The age cut-off was based on the annual national assessment of quality and efficiency in the Swedish health care (“Öppna jämförelser”) published in 2006 (129). The data from the SPDR was linked to the LISA database for information on demographic and socioeconomic factors. In Sweden, the individuals’ co-payment for reimbursed drugs is independent of income. The maximum co-payment for prescription drugs within the reimbursement scheme is 1800 Swedish Krona (SEK) (1 SEK = €0.10 on 1 January 2006) per twelve month period (130).

3.1.2 Drug utilisation trends over time

Aggregated drug sales statistics include drugs sold on prescription by pharmacies. The data is however not person-identifiable, in contrast to the data from the SPDR. Aggregated drug sales statistics are available for a relatively long period of time, and are therefore suitable for analysing drug utilisation trends over time. Drug sales can be measured as the number of sold Defined Daily Doses (DDD) per Thousand Inhabitants and Day (DDD/TID). The DDD is a fixed measurement unit defined as the assumed average daily maintenance dose for a drug utilised on its main indication in adults. The DDD has the advantage of being comparable between countries and over time, but it may not correspond to the Prescribed Daily Dose (PDD), especially among the elderly (131, 132). For this thesis, total drug sales data from Sweden during years 2000-2008 was collected from Apoteket AB. Drug utilisation trends were analysed over time for 75-year olds and for those born in 1925.

3.1.3 Drug utilisation patterns in relation to mental disorders

Registers based on hospital care, such as the National Patient Register, are not necessarily suitable for population-based studies of drug utilisation in relation to mental disorders, since only about half of the mental health problems are identified in clinical practise (133). Further, the vast majority of patients with mental health problems are treated only in primary care, and are not referred to specialised care (133). Another limitation is the incomplete coverage of

psychiatric care in the National Patient Register (134). Therefore, population-based surveys where the participants are examined for mental health problems are more suitable for studies of drug utilisation in relation to mental disorders.

The Gothenburg 95+ Study is a population-based study of individuals aged 95 years and older in Gothenburg, Sweden, examined for mental disorders and drug utilisation (47). In 1996-1998, 589 95-year olds born 1 July 1901 - 31 December 1903 were identified via the Swedish population register, and were invited to participate. The sample included individuals living in nursing homes and in community settings. Forty seven individuals died before the investigation, 18 could not be traced, and 3 were excluded due to insufficient knowledge of the Swedish language. The response rate among the remaining 521 was 65%, thus 338 (263 women and 75 men) accepted participation. Respondents and non-respondents were similar regarding 3-year mortality and marital status. The response rate was however higher among men than among women (81% vs. 61%; Fisher's exact test $p < 0.001$).

3.2 Definition of potentially inappropriate psychotropic drugs

PIP is a collective term that covers the two subcategories Potentially Inappropriate Combinations of Psychotropics (PICP) and Potentially Inappropriate Psychotropic Substances (PIPS). PICP and PIPS were defined according to the explicit criteria from the Swedish National Board of Health and Welfare (3) and are described in Table 1. PIP refers to utilisation of PICP or PIPS. PICP are considered unnecessary and are associated with an increased risk for adverse drug reactions. PIPS are associated with an increased risk for daytime drowsiness, cognitive decline, balance disorders, and falls (3).

Table 1 Classification of Potentially Inappropriate Psychotropics (PIP), which include both Potentially Inappropriate Combinations of Psychotropics (PICP) and Potentially Inappropriate Psychotropic Substances (PIPS) (3).

PIP	
PICP	PIPS
Two or more benzodiazepines	<i>Long-acting benzodiazepines</i>
Two or more psychotropics in the same class	diazepam <i>anxiolytic</i>
Two or more antipsychotics	nitrazepam } <i>hypnotics</i>
Two or more anxiolytics	
Two or more hypnotics	flunitrazepam }
Two or more antidepressants	<i>Psychotropics with anticholinergic effects</i>
Two or more psychotropics with anticholinergic effects	chlorpromazine } <i>conventional</i>
	levomepromazine } <i>antipsychotics</i>
	prochlorperazine }
	chlorprothixene }
	hydroxyzine <i>anxiolytic</i>
	clomipramine } <i>tricyclic</i>
	trimipramine } <i>antidepressants</i>
	amitriptyline } <i>(TCAs)</i>
	nortriptyline }
	maprotiline }
	<i>Miscellaneous</i>
	propiomazine } <i>hypnotics</i>
	triazolam }

3.3 Description of the papers

Table 2 below provides an overview of the papers included in this thesis.

Table 2 Overview of the papers in this thesis.

Paper	Study focus	Age group	Study period	Geographical area	Data source
I	PIP versus the indicator “concurrent use of three or more psychotropic drugs”	75+ years	2006	Sweden	SPDR
II	Utilisation of PIPS in relation to drugs recommended by DTCs over time	75-year olds and individuals born in 1925	2000-2008	Sweden	Aggregated drug sales statistics
III	Utilisation of psychotropic drugs and PIP in relation to mental disorders and institutionalisation	95-year olds	1996-1998	Gothenburg, Sweden	The Gothenburg 95+ Study
IV	Utilisation of psychotropic drugs and PIP in relation to socioeconomic determinants	75+ years	2006	Sweden	SPDR linked to the LISA database

DTC: Drug and Therapeutics Committee

LISA database: the longitudinal integration database for health insurance and labour market studies

PIP: Potentially Inappropriate Psychotropic drugs

PIPS: Potentially Inappropriate Psychotropic Substances (a subcategory of PIP)

SPDR: the Swedish Prescribed Drug Register

3.3.1 Paper I: PIP versus the indicator “concurrent use of three or more psychotropic drugs”

PIP was defined in accordance with Table 1. The definition of PICP was based on concurrent utilisation of two or more different substances in the categories described in Table 1 for a total of 40 days during 2006. PIPS was defined as utilisation of at least one of the listed drugs during 2006. The indicator “concurrent use of three or more psychotropic drugs” was defined as concurrent utilisation of three or more different psychotropic drugs for a total of 40 days during 2006. Utilisation of PIP was classified as the reference against which the

indicator “concurrent use of three or more psychotropic drugs” was compared. Outcome measures were sensitivity, specificity, positive and negative predictive values and the likelihood ratio.

For the purpose of this study, treatment episodes needed to be estimated to study concurrent drug utilisation. However, information on prescribers’ dosage instructions is available only as a free text section in the SPDR. A review of PDDs was therefore performed for a random sample of dispensed prescriptions for each psychotropic substance. Substance-specific population average PDDs were estimated for each substance, thus enabling the calculation of theoretical treatment episodes based on the date of purchase and purchased amount.

3.3.2 Paper II: Trends in the utilisation of psychotropic drugs among the elderly

PIPS was defined according to Table 1. Drugs recommended by DTCs (DTC drugs) were defined based on guidelines from all 21 DTCs in Sweden. The guidelines were weighted in relation to the size of the 75-year old population in the county council or region which the DTC represented. Psychotropic drugs were classified as DTC drugs if they were recommended for at least half of the 75-year old population in Sweden. The antipsychotic DTC included risperidone, an atypical antipsychotic. The anxiolytic DTC included oxazepam, a short-acting benzodiazepine, and the hypnotic DTCs included the short-acting z-hypnotics zopiclone and zolpidem. The antidepressant DTCs included the new generation antidepressants citalopram, mirtazapine, and sertraline.

Utilisation was measured in DDD/TID among 75-year olds over time and among individuals born in 1925 over time. Outcome measures were utilisation of PIPS and DTC drugs, the ratio PIPS/DTC drugs, per cent change in utilisation between the years 2000 and 2008, and estimated change per year according to univariate linear regression. The statistical significance level was 0.05. In a sensitivity analysis not reported in the paper, trends in utilisation of all drugs recommended by DTCs, irrespective of the population size the DTCs represented, were assessed to analyse the stability of the findings.

3.3.3 Paper III: Psychotropic drug utilisation in relation to mental disorders and institutionalisation among 95-year olds

Information on regular and as-needed drug utilisation was primarily collected from multi-dose drug dispensing lists. When such lists were unavailable, information on drug utilisation was collected during home/nursing home visits where participants were asked to show the interviewer the drugs they utilised.

The participant was classified as utilising the drug if utilisation was documented by either the dispensing list or during the visit. PIP was classified according to Table 1.

Psychiatric examinations were performed in 1996-1998 by trained psychiatrists during home/nursing home visits. The Comprehensive Psychopathological Rating Scale (CPRS) (135) and a battery of cognitive tests were used (136). Dementia was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) (137), using information from personal examinations and close informant interviews. Interviews with a close informant, e.g. a spouse, child, sibling, close friend, or formal caregiver, were available for 283 participants (84%; 77% of those without dementia and 90% of those with dementia) and were conducted in 1999. Results regarding dementia diagnoses were published in 2004 (47). Depressive and anxiety disorders were diagnosed among participants without dementia according to DSM-III-R, with minor modifications due to the lack of information on symptom duration. These findings were published recently (136). Psychotropic drug utilisation in relation to psychotic disorders has been presented previously (138).

The outcome measures were utilisation of psychotropic drugs and PIP in relation to mental disorders and institutionalisation. A multiple logistic regression analysis was performed to analyse the associations between psychotropic drug utilisation and dementia, institutionalisation and sex. The results were presented as adjusted odds ratios (OR) and 95% confidence intervals (CI). P-values for comparisons between proportions were calculated with two-tailed Fisher's exact test. Binomial proportion 95% CI were calculated for proportions. The statistical significance level was 0.05.

3.3.4 Paper IV: Socioeconomic determinants of psychotropic drug utilisation among the elderly

PIP was defined according to Table 1. Concurrent drug utilisation in PICP was estimated as described in paper I above. Income was calculated using the square root scale: family disposable income during 2005 divided by the square root of the number of family members (139, 140). Study participants were categorised into income tertiles to focus on any differences between those with the lowest income compared to those with the highest income. For analyses stratified by sex, the income categorisations were performed separately for men and women. Marital status on 31 December 2006 was categorised as married, never married, divorced, or widowed. This information was missing for those who died or emigrated during 2006. Outcome measures were number of unique psychotropic drugs and number of PIP, as well as the corresponding binary measures,

utilisation of three or more psychotropic drugs and utilisation of PIP, in relation to socioeconomic determinants.

The associations with socioeconomic determinants were analysed with Poisson regression models for count outcomes (number of psychotropic drugs and number of PIP) and logistic regression models for binary outcomes (utilisation of three or more psychotropics and PIP). Besides age and sex, several potential confounders were included in the multiple regression models. In order to take time at risk for drug utilisation into account, the proportion of days during the study period when the individual was alive and resident in Sweden (the person-year proportion) was included. The person-year proportion was however not included in the regression models on marital status, since these analyses only included those who did not die or emigrate during 2006. The number of unique nonpsychotropic drug substances was included as a proxy for health care utilisation and comorbidity (141). Country of birth, categorised as Sweden, other Nordic countries, other European countries, and outside Europe, was also included as a potential confounder.

The results from the Poisson regression analyses were in agreement with the logistic regression analyses, and they are therefore not presented. Results from the adjusted logistic regression analyses are presented as OR and 95% CI. The level for statistical significance was 0.05.

4 ETHICAL CONSIDERATIONS

One of the most important ethical principles in research is that individuals should give informed consent before participating. This consent should be preceded by information about the research project, such as the aim and risks, and that participants can withdraw at any time without giving an explanation. In the registers used in this thesis, i.e. the SPDR and the LISA database, the collection of data is mandatory, and no informed consent is necessary (142). Further, individuals cannot withhold or withdraw data. This is in direct conflict with the ethical principle stated above. However, the benefits of these registers are substantial, and are believed to outweigh the risks. This is considered to motivate the lack of informed consent and the ability to withdraw (142). Withdrawal from the registers would likely be differential if it was allowed. The lack of informed consent in the registers therefore decreases the risk of selection bias. Further, the feasibility to perform large studies would be reduced if all participants were required to give informed consent.

The direct risks for the participants are minimal in the studies using individual-based register data and aggregated drug sales statistics, since the individuals are not contacted in any way. Linkage between the registers was enabled by the unique personal identification number, and was performed by those who are responsible for the registers. The personal identification number was replaced by a serial number before the data was delivered to the researchers, and the identification key was subsequently destroyed. Results were presented in aggregated form, ensuring anonymity. The register-based studies were approved by the regional ethics board in Gothenburg, Sweden. The drug sales statistics used in paper II could not be traced to individuals, and no ethical approval was needed. For the Gothenburg 95+ Study, written informed consent was obtained from all participants, or from a close relative in cases of dementia. Oral informed consent was given from blind participants. The regional ethics board in Gothenburg, Sweden approved the project. The funding received for the projects in this thesis was unrestricted, and the researchers were independent from the funders.

This thesis contributes to knowledge about how psychotropic drugs are utilised among the elderly, which can facilitate an improvement in drug utilisation. The benefits are therefore considered to outweigh the risks for the participants.

5 RESULTS

5.1 Paper I: PIP versus the indicator “concurrent use of three or more psychotropic drugs”

The study population included 384 904 individuals, which corresponds to a one-year prevalence of psychotropic drug utilisation of 48% among individuals aged 75 years and older in Sweden (N=800 129). The prevalence was 39% among men and 54% among women; 41% among those aged 75-84 years and 66% among those aged 85 years and older. The prevalence of PIP in the total population aged 75 years and older was 19%. The prevalence was 15% among men and 21% among women; 16% among those aged 75-84 years and 26% among those aged 85 years and older.

As presented in Table 3, 39% of those with psychotropic drugs utilised PIP. Long-acting benzodiazepines were utilised by 17%, and psychotropics with anticholinergic effects were utilised by 7%. The indicator “concurrent use of three or more psychotropic drugs” was observed among 15% among those who utilised psychotropic drugs. This proportion was higher among the group with only multi-dose dispensed drugs compared to those with only ordinary prescriptions (28 vs. 9%).

Figure 2 illustrates the agreement between PIP and the indicator “concurrent use of three or more psychotropic drugs”. The sensitivity was 27%, i.e. one fourth of individuals utilising PIP also had the indicator “concurrent use of three or more psychotropic drugs”. Among those without PIP, 93% did not have the indicator “concurrent use of three or more psychotropic drugs” (specificity). The positive predictive value was 72%, which means that about two thirds of all individuals with the indicator “concurrent use of three or more psychotropic drugs” also utilised PIP. The negative predictive value was 67%, i.e. two thirds of the individuals without the indicator “concurrent use of three or more psychotropic drugs” did not utilise PIP. Individuals utilising PIP were fourfold more likely to have the indicator “concurrent use of three or more psychotropic drugs” compared to those without PIP (likelihood ratio).

Table 3 Prevalence of the indicator “concurrent use of three or more psychotropic drugs” and Potentially Inappropriate Psychotropics (PIP) among the elderly aged 75 years and older utilising psychotropic drugs in Sweden in 2006.

	“Concurrent use of three or more psychotropic drugs” %	PIP (PICP and/or PIPS) %	PICP %	PIPS %
Total (N=384 904)	14.7	39.1	12.1	36.0
Men (N=120 513)	13.2	39.9	12.2	36.7
Women (N=264 391)	15.4	38.8	12.1	35.7
75-84 years (N=235 006)	13.9	39.3	12.0	36.2
85 years and older (N=149 898)	15.9	38.8	12.4	35.7
Ordinary prescriptions only (N=267 905)	8.9	38.4	9.6	36.2
Multi-dose dispensed drugs only (N=98 960)	27.6	40.3	17.5	35.0

PIP: Potentially Inappropriate Psychotropic drugs, a collective term for PICP and PIPS

PICP: Potentially Inappropriate Combinations of Psychotropics (a subcategory of PIP)

PIPS: Potentially Inappropriate Psychotropic Substances (a subcategory of PIP)

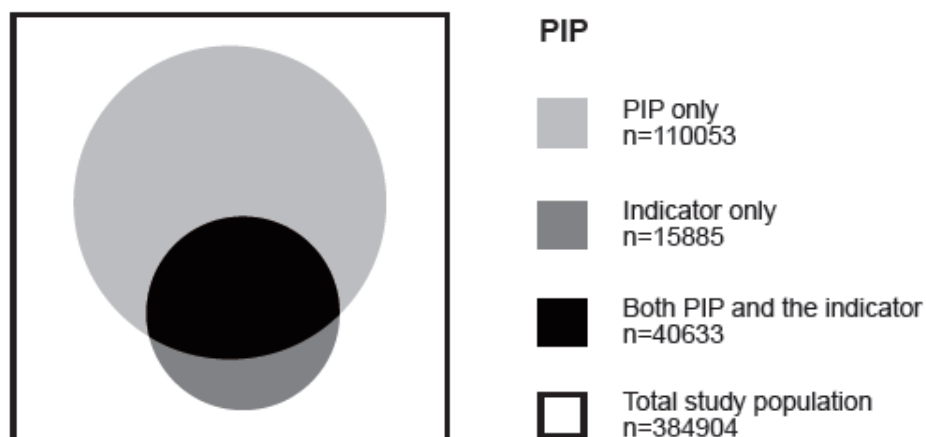


Figure 2 A Venn diagram illustrating the agreement between utilisation of Potentially Inappropriate Psychotropic drugs (PIP) and the *indicator* “concurrent use of three or more psychotropic drugs” among the elderly aged 75 years and older utilising psychotropic drugs in Sweden in 2006.

5.2 Paper II: Trends in the utilisation of psychotropic drugs among the elderly

Among the individuals who were 75 years old over time, utilisation of PIPS decreased 38% from 2000-2008, while utilisation of DTC drugs increased 31% (Figure 3). The largest relative decreases in PIPS were observed for hypnotics (45%) and antipsychotics (45%). For DTC drugs, the largest relative increases were observed among antidepressants (37%) and hypnotics (36%).

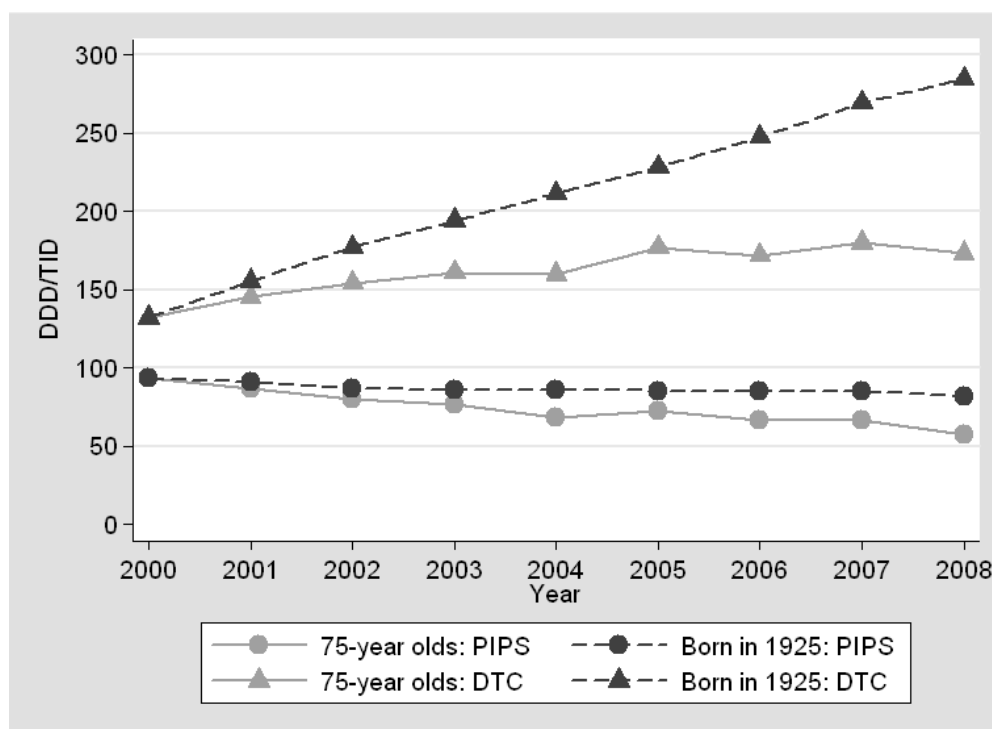


Figure 3 Trends in utilisation of Potentially Inappropriate Psychotropic Substances (PIPS) and drugs recommended by Drug and Therapeutics Committees (DTCs) in Sweden among individuals aged 75 years old and individuals born in 1925. DDD/TID; Defined Daily Doses/Thousand Inhabitants and Day

Among those born in 1925, PIPS utilisation decreased 12% from 2000-2008 and DTC drugs increased 115%. Regarding PIPS, the largest relative decrease was observed among the antipsychotics (62%), followed by antidepressants (21%). The largest relative increases in DTC drugs were observed for antipsychotics (138%), antidepressants (126%) and hypnotics (120%).

The sensitivity analysis, in which trends in utilisation of all drugs recommended by DTCs irrespective of the population size represented by the DTC, showed that utilisation of these drugs increased 30% from 2000-2008 among those aged 75 years and 105% among those born in 1925. There were no inconsistencies on the

psychotropic drug group level among those who were 75 years old over time. Among those born in 1925, the discrepancies concerned less pronounced increases for antipsychotics (49%) and antidepressants (108%).

5.3 Paper III: Psychotropic drug utilisation in relation to mental disorders and institutionalisation among 95-year olds

Among the 338 participants, 60% (CI 55-65%) utilised psychotropic drugs. Hypnotics were most common (44%; CI 38-49%). The conventional antipsychotics were utilised by 96% (CI 92-100%) of the participants with antipsychotic drugs. The majority of participants with anxiolytic drugs utilised oxazepam (72%; CI 60-82%). The long-acting benzodiazepine flunitrazepam was utilised by 31% (CI 23-39%) of the participants with hypnotics, and the short-acting z-hypnotics were utilised by 37% (CI 30-46%). The new generation antidepressants were most common among the antidepressants (89%; CI 77-96%), and TCAs were utilised by 11% (CI 4-23%). PIP were utilised by one third (33%; CI 28-39%) of the participants. Long-acting benzodiazepines were utilised by 21% (CI 17-26%), and psychotropics with anticholinergic effects by 7% (CI 4-10%).

Of the participants with dementia, 67% (CI 59-74%) utilised psychotropic drugs. The prevalence was 53% (CI 45-61%) among the participants without dementia. Except hypnotics, all psychotropic drug groups were more commonly utilised among participants with dementia than among those without dementia. Psychotropics with anticholinergic effects were more common among those with than without dementia; 12% (CI 8-18%) vs. 1% (CI 0-4%); $p < 0.01$.

The nursing home residents had a higher prevalence of psychotropic drug utilisation (68%; CI 61-75%) compared to participants living in community settings (50%; CI 41-58%); $p < 0.01$. Psychotropics with anticholinergic effects were more common in nursing homes than in community settings; 11% (CI 7-16%) vs. 1% (CI 0-5%); $p < 0.01$.

In the adjusted logistic regression analysis, psychotropic drug utilisation was associated with living in a nursing home (OR 1.9; CI 1.1-3.3), but the associations with dementia (OR 1.2; CI 0.7-2.1) or female sex (OR 1.1; CI 0.7-1.9) were not statistically significant.

Among the participants without dementia who were diagnosed with a depressive disorder, less than one out of ten utilised antidepressants (7%; CI 1-24%), while

hypnotics were utilised by more than half (56%; CI 35-75%) and anxiolytics by one third (30%; CI 14-50%). Two of the 14 participants without dementia who were diagnosed with an anxiety disorder utilised antidepressants (14%; CI 2-43%), four utilised anxiolytics (29%; CI 8-58%) and seven utilised hypnotics (50%; CI 23-77%).

5.4 Paper IV: Socioeconomic determinants of psychotropic drug utilisation among the elderly

The study included 384 712 individuals, and their characteristics are presented in Table 4. Among the study participants aged 75-79 years, 23% were categorised in the low income tertile, while the corresponding percentage was 44% among individuals aged 85 years and older. Among the married, 97% had more than one family member, while 1% of the never married, 4% of the divorced and 8% of the widowed had the same.

Table 4 Characteristics of individuals aged 75 years and older utilising psychotropic drugs in Sweden in 2006.

	Men (N=120 426)	Women (N=264 286)	Total (N=384 712)
Age			
75–79 years, %	32.9	28.4	29.8
80–84 years, %	33.0	30.5	31.3
85+ years, %	34.1	41.1	38.9
Missing, %	0.0	0.0	0.0
Income, €*			
High income, median (%)	21 215 (33.0)	17 457 (33.0)	18 743 (33.0)
Middle income, median (%)	14 937 (33.8)	12 620 (33.9)	13 126 (33.9)
Low income, median (%)	11 748 (33.1)	10 281 (33.0)	10 632 (33.1)
Missing, (%)	(0.2)	(0.1)	(0.1)
Marital status			
Married, %	48.5	22.1	30.4
Never married, %	7.0	5.1	5.7
Divorced, %	8.4	9.7	9.3
Widowed, %	22.3	53.9	44.0
Missing, % †	13.9	9.2	10.7

* Family disposable income for year 2005, adjusted for family size. SEK 1 = € 0.10 (January 2006).

† Marital status was missing for all individuals who died or emigrated during 2006 (n=40 957). When these were excluded, marital status was missing for 225 individuals.

Among individuals aged 75 years or older who utilised psychotropic drugs, 22% had purchased three or more psychotropic drugs during 2006. In the adjusted logistic regression analysis, older age, female sex and low income were associated with a higher probability for utilisation of three or more psychotropic drugs (Figure 4). The never married, the divorced, and the widows/widowers were more likely than the married to utilise three or more psychotropic drugs (Figure 5). With regards to income and marital status, their associations with utilisation of three or more psychotropic drugs were more pronounced among the younger elderly (75-79 years) than among those aged 85 years and older.

Utilisation of PIP was observed among 39% of individuals aged 75 years or older with psychotropic drugs. In the adjusted logistic regression analysis, older age and female sex were associated with a lower probability for utilisation of PIP, while low income was associated with a higher probability for PIP utilisation (Figure 4). As presented in Figure 5, the never married and the divorced were more likely to utilise PIP. The probability for PIP utilisation was marginally higher among the widowed. The association between utilisation of PIP and marital status was more pronounced among the younger elderly (75-79 years) than among those aged 85 years and older.

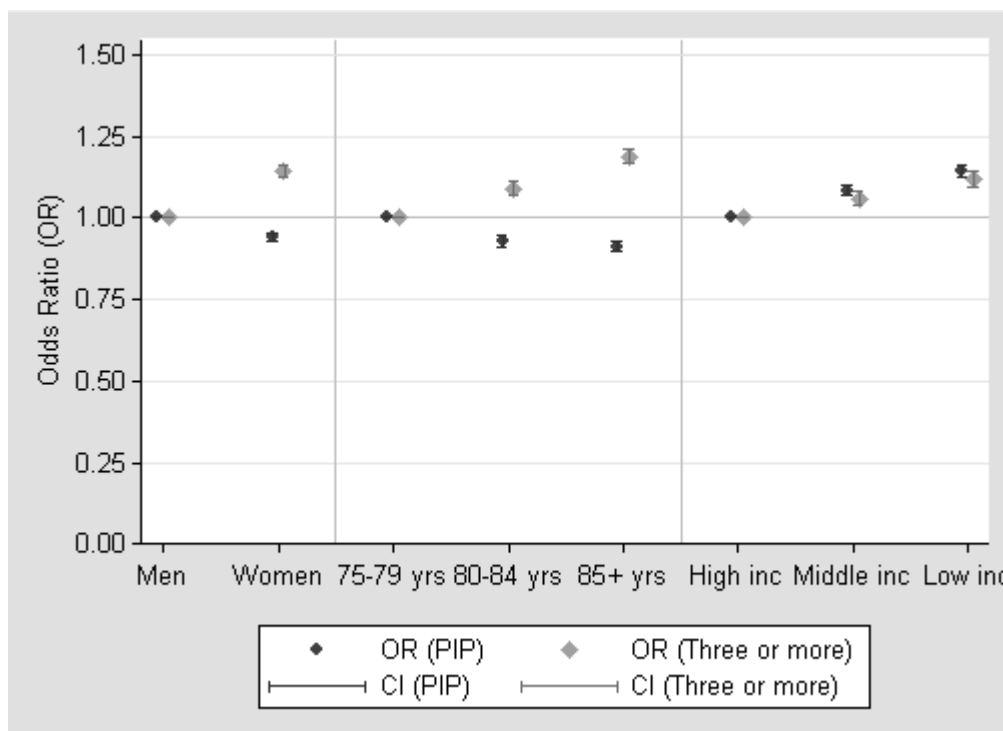


Figure 4 Associations between sex, age, income and utilisation of Potentially Inappropriate Psychotropic drugs (PIP) and three or more psychotropics, respectively, among individuals aged 75 years and older utilising psychotropic drugs in Sweden in 2006. Results are presented with adjusted odds ratios (OR) and 95% confidence intervals (CI).

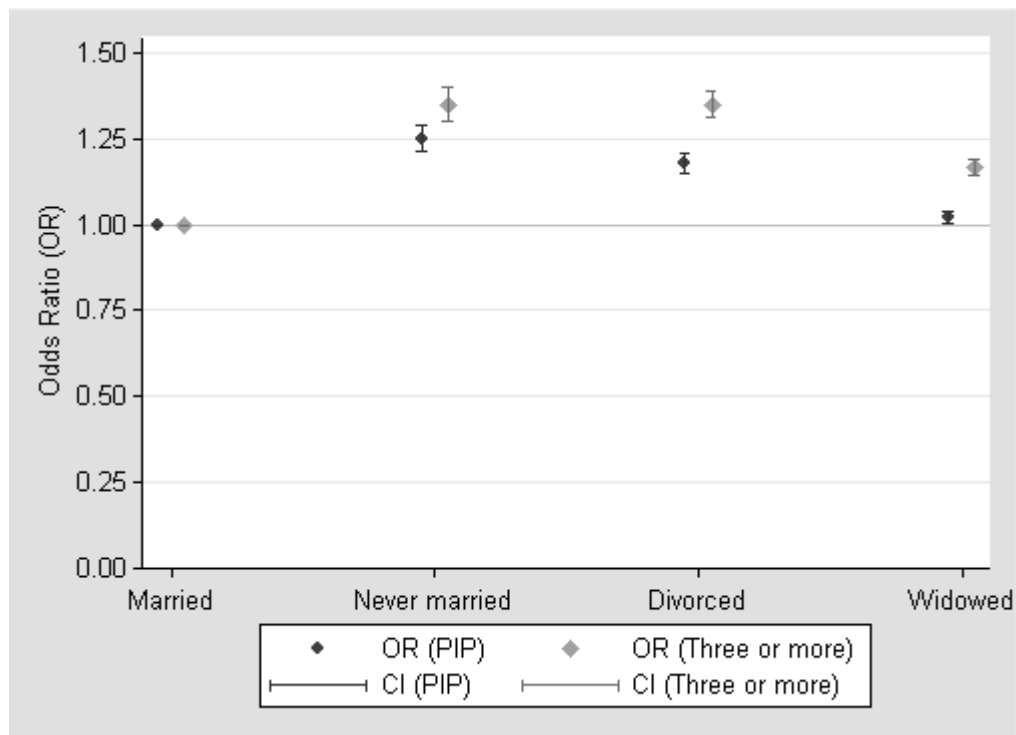


Figure 5 Associations between marital status and utilisation of Potentially Inappropriate Psychotropic drugs (PIP) and three or more psychotropics, respectively, among individuals aged 75 years and older utilising psychotropic drugs in Sweden in 2006. Results are presented with adjusted odds ratios (OR) and 95% confidence intervals (CI).

6 DISCUSSION

6.1 Main findings

This thesis aimed to assess and analyse potentially inappropriate utilisation of psychotropic drugs among the elderly in Sweden. The main findings include that the indicator “concurrent use of three or more psychotropic drugs” identified only one fourth of the elderly who utilised PIP. This poor agreement was expected since the two indicators focus on different aspects of drug utilisation; number of drugs and inappropriate drugs. However, this finding has implications regarding the choice of indicator in future assessments.

About half of the elderly aged 75 years and older utilised psychotropic drugs, and one fifth of all elderly utilised PIP in 2006. Utilisation of PIP was more common among those with low income and the non-married when compared to those with high income and the married, respectively. Although the magnitudes were small, the findings suggest socioeconomic inequities in psychotropic drug utilisation among the elderly.

Sixty per cent of the 95-year olds utilised psychotropic drugs in 1996-1998, and PIP was utilised by one third. Less than one tenth of the 95-year olds with depression utilised antidepressants, while hypnotics and anxiolytics were more common. The findings indicate a need for improvement in the pharmacological treatment of depression among the oldest old. During 2000-2008, utilisation of PIPS decreased and utilisation of recommended drugs increased, both among 75-year olds over time and with ageing. This indicates an improvement regarding the choice of psychotropic drug over time, but also an increase in psychotropic drug utilisation.

6.2 General discussion

6.2.1 Utilisation of psychotropic drugs among the elderly

Half of all individuals aged 75 years and older in Sweden utilised psychotropic drugs in 2006. The prevalence was higher among women than among men, and increased with age. These utilisation patterns are in agreement with previous findings from Sweden and other European countries (56, 70, 71). The high

prevalence of psychotropic drug utilisation confirms the public health importance of analysing and improving psychotropic drug utilisation patterns among the elderly. The findings in this thesis further showed that, among individuals aged 75 years and older who all utilised psychotropic drugs, utilisation of several psychotropic drugs was associated with female sex, older age, low income, and being non-married. These groups also tend to have higher rates of psychiatric morbidity (23, 28, 29, 46, 48-50). However, the differences in psychotropic drug utilisation might not be fully explained by their increased psychiatric morbidity. According to previous research, women have a more positive attitude towards seeking help for mental health problems compared to men, and the higher likelihood for women to express mental health problems may contribute to higher rates of psychotropic drug utilisation (23, 143). Older age and being divorced has also been associated with seeking help for mental health problems (23). Further, among individuals presenting with mental health problems, those with a lower socioeconomic status may be more likely to receive a psychotropic drug prescription compared to individuals with a higher socioeconomic status (23, 24). Individuals in higher socioeconomic groups might have an increased awareness of non-pharmacological treatment options for e.g. sleep problems or depressive symptoms. Such non-pharmacological treatment alternatives, for example therapy, are generally more expensive than antidepressant drugs, and their use may also be related to financial resources.

Knowledge about how psychotropic drugs are utilised among individuals aged 90 years and older is limited, since this group is often underrepresented in pharmacoepidemiological studies on elderly (56, 70, 71). Findings presented in this thesis show that 60% of the 95-year olds in 1996-1998 utilised psychotropic drugs. Hypnotics were common and the utilisation was not associated with institutionalisation, dementia, depression, or anxiety. Although sleep disorders were not diagnosed in this study, previous Swedish research has shown that two thirds of individuals aged 90 years and older who regularly utilised hypnotics did not report sleep disturbances (100). This highly prevalent utilisation of hypnotic drugs may suggest utilisation without a clinical indication, i.e. inappropriate utilisation, although it is possible that sleep disturbances were not reported if they were alleviated by the hypnotic drugs.

Antipsychotic drugs are commonly utilised for behavioural and psychological symptoms of dementia, such as aggression, although they may increase the risk for cerebrovascular events and mortality (144-146). In the Gothenburg 95+ Study, one fourth of the participants with dementia utilised antipsychotic drugs, compared to only one per cent among those without dementia. This is in agreement with previous Swedish findings (100). Research from the Nordic

countries and the United States has shown that a considerable proportion of antipsychotic drugs among the elderly are not utilised according to guidelines, for example without an appropriate indication (89, 147, 148). This indicates a need for improvement regarding the utilisation of antipsychotics among the elderly.

All psychotropic drug groups except hypnotics were more commonly utilised among 95-year olds with dementia than among those without dementia, and among participants living in nursing homes than among those living in community settings. The majority (85%) of the 95-year olds with dementia lived in nursing homes (47). In the adjusted analysis, nursing home residents were more likely than participants in community settings to utilise psychotropic drugs, irrespective of dementia status. Research on psychotropic drug utilisation in relation to institutionalisation in this very old population group is limited, but previous Swedish studies focusing on somewhat younger populations have also found that psychotropic drug utilisation is more common in nursing homes than in community settings (72, 149). This might be related to a higher morbidity among the nursing home residents, or the utilisation of psychotropic drugs to compensate for lack of staff (147).

Previous research has shown that the utilisation of antidepressants among the elderly has increased over time (99, 150-152). The introduction of the new generation antidepressants with a superior benefit-risk profile compared to the TCAs has likely influenced this trend (81). Before the new generation antidepressants were introduced, the prevalence of antidepressant utilisation among an 85-year old sample in Gothenburg was 14% (72). This is similar to the prevalence observed among the 95-year olds in this thesis (14%), despite that the majority (90%) of the 95-year olds utilised the new generation antidepressants. The proportion of new generation antidepressants among 95-year olds in Gothenburg who utilised antidepressants was similar (91%) in 2006, according to the SPDR. It is possible that the increase in the prevalence of antidepressant utilisation attributed to the new generation antidepressants has been less pronounced in this very old population, perhaps due to cautiousness or unwillingness to try newer drugs among very old and vulnerable individuals. The prevalence of antidepressant utilisation might have increased since the 95-year olds were examined, although recent research among individuals aged 90 years and older is scarce.

A lack of drugs that are clinically indicated is an important aspect of inappropriate psychotropic drug utilisation among the elderly. Information on mental disorders on an individual level is necessary to investigate this issue. Less

than one out of ten 95-year olds diagnosed with depression utilised antidepressants, while hypnotics and anxiolytics were considerably more common. This is in agreement with previous research (94, 100, 153, 154). The high utilisation of hypnotics and anxiolytics among those with a depressive disorder could be explained by treatment of sleep disturbances and anxiety, which are common symptoms of depression (49). Treating these symptoms instead of the underlying, and perhaps unrecognised, depression might have contributed to the high utilisation of anxiolytics and hypnotics. This could indicate a need for improvement in the diagnostics and treatment of depressive disorders among the very old. Knowledge about how antidepressants are utilised in relation to depression in this very old population is limited in current practise, since there is a lack of recent population-based studies where the participants are examined for mental disorders and drug utilisation. This emphasises the importance of population-based studies with information on morbidity for analysing these aspects of inappropriate drug utilisation.

6.2.2 Indicators of inappropriate psychotropic drug utilisation among the elderly

The extent and distribution of problems in drug utilisation among the elderly can be measured with relevant indicators of inappropriate drug utilisation. A high validity and reliability of the indicator is required to establish the indicator's relevance. To facilitate an adequate choice of indicator in research and other quality assessments, such as the annual national assessments of quality and efficiency in the Swedish health care ("Öppna jämförelser") (124), it is important to assess and compare the characteristics of different indicators.

The indicator "concurrent use of three or more psychotropic drugs" focuses on the number of psychotropic drugs, but does not consider the types of psychotropic drugs. Research concerning the validity of the indicator "concurrent use of three or more psychotropic drugs" is limited and inconclusive (125, 126). On the contrary, utilisation of potentially inappropriate drugs, such as PIP, has been associated with an increased risk of several adverse health outcomes (67, 103-109). The agreement between PIP and the indicator "concurrent use of three or more psychotropic drugs" was assessed in paper I. Only one fourth of all individuals who utilised PIP were identified by the indicator "concurrent use of three or more psychotropic drugs". Two thirds of all individuals who had the indicator utilised PIP. The poor agreement between the indicators was expected, since the indicators focus on different aspects of drug utilisation. Poor agreement between indicators of number of drugs and indicators of drugs to avoid has also been reported previously (155). Utilisation of several drugs is not synonymous with inappropriate utilisation, nor does utilisation of few drugs automatically

correspond to appropriate utilisation. The focus on number of drugs as a measure of inappropriate drug utilisation among the elderly has been questioned (96). Further, previous research has shown no association between the total number of drugs and physical and cognitive function among the elderly when drugs with anticholinergic and sedative effects were excluded (156). The findings therefore support using indicators that focus on specific inappropriate drugs or combinations of drugs, such as PIP, as a complement or substitute for indicators of number of drugs in assessments of inappropriate drug utilisation among the elderly.

6.2.3 Utilisation of PIP among the elderly

The high prevalence of PIP observed in this thesis, despite that the risks are considered to outweigh the potential benefits, or that safer and equally effective alternatives are available, is in agreement with previous findings on utilisation of inappropriate drugs among the elderly (31, 63, 66, 67, 101). This supports the acknowledgement of inappropriate drug utilisation among the elderly as an important public health issue, and indicates a need for improvement. Possible explanations for the high utilisation of PIP could be a lack of regular and systematic reviews of the patients' drug utilisation, incomplete or unavailable information about the drugs currently utilised by the patient, or poor physician continuity (96). Previous research from Sweden has shown that elderly individuals with several prescribers are more likely to utilise inappropriate drugs compared to those with few prescribers (95). Physicians may be reluctant to withdraw or make changes in drugs that were initiated by another physician (21). Further, a lack of education and training regarding drug utilisation among the elderly may also contribute to inappropriate utilisation (96). In this thesis, the long-acting benzodiazepines and psychotropics with anticholinergic effects were the most common PIP. Alternative drugs with a more beneficial safety profile, such as the short-acting z-hypnotics, the atypical antipsychotics and the new generation antidepressants, were introduced in the early nineties (74). It is possible that some elderly have been utilising the inappropriate drugs for a long time, and are unwilling to change to newer drugs.

In this thesis, the prevalence of PIP increased with age, and was higher among women than among men in the total population aged 75 years and older. The sex differences are in agreement with previous findings (66, 111), but the age trends are not consistent in the literature (31, 63, 66, 95, 157). The inconsistencies may be associated with the use of different criteria for identifying inappropriate drug utilisation. For example, whether the criteria only consider drugs that should always be avoided, or also consider drugs that should be avoided in the presence

of a particular condition. In the latter case, the prevalence of the condition itself may be associated with age or sex differences. The inconsistencies may be partly explained by differences in if and how the associations with age and sex were adjusted for potential confounders, such as health status (63, 111).

As presented in this thesis, the prevalence of psychotropic drug utilisation increases with age among the elderly, and is higher among women than among men. Further, the probability that an individual utilises inappropriate drugs increases with the total number of drugs (63, 66, 158). Therefore, an additional aspect of inappropriate psychotropic drug utilisation may be discovered when utilisation patterns are analysed among individuals who all utilise psychotropic drugs. As previously described, utilisation of PIP was more common among women than among men, and increased with age in the total population aged 75 years and older. However, in the population of elderly who all utilised psychotropic drugs, women were slightly less likely to utilise PIP compared to men, and individuals in the oldest age group had a somewhat lower likelihood for utilisation of PIP compared to those in the youngest age group. Similar sex differences have been reported in a study from the United Kingdom (63). Elderly women in that study were more likely to utilise antidepressants, but among those who all utilised antidepressants, women were less likely than men to utilise a potentially inappropriate antidepressant. According to previous research from Norway, physicians describe women as having more knowledge about health issues, and as being more demanding and involved in decision-making compared to men (159). These characteristics may be associated with higher demands regarding quality of care and the utilisation of appropriate and safe drugs among women. However, it should also be noted that the reversed association regarding antidepressants in the study from the United Kingdom was not observed for anxiolytics or hypnotics, or in relation to age. Thus, to understand the apparently complex associations between age, sex and inappropriate drug utilisation, a more detailed analysis which adequately accounts for potential confounders is required.

To increase the understanding about changes in drug utilisation patterns in relation to ageing and time, trends during 2000-2008 were analysed in this thesis. Utilisation of PIPS versus recommended psychotropic drugs was investigated in two different groups; among 75-year olds over time and among those born in 1925 over time. This design facilitated a distinction between changes in psychotropic drug utilisation with ageing, i.e. trends among those born in 1925 over time, and changes over time among “new” elderly, illustrated by the trends among the 75-year olds over time. The substantial increase in DTC drugs and the small decrease in PIPS among those born in 1925 illustrate that psychotropic

drug utilisation increases with age. The trends among the 75-year olds illustrate changes over time in drug choice, and the findings indicate an increase in the utilisation of recommended drugs and a decline in the utilisation of inappropriate drugs. The decrease in PIPS was more pronounced among the 75-year olds than among those born in 1925, while the opposite was observed for the DTC drugs. This might suggest that the improvements in psychotropic drug utilisation primarily concern changes in drug choice over time among “new” 75-year olds, while with ageing, there is an increase in the overall utilisation of psychotropic drugs. A possible explanation for these differences could be that prescribers and/or patients are unwilling to switch from older drugs they have been utilising for a long time to recommended drugs, and new psychotropic drugs are still added as the patient becomes older, while for “new” elderly and new treatments, recommended drugs are preferred. However, the nature of the data source hinders any distinction between incident or prevalent drug utilisation. Since previous studies from other European countries and the United States have shown similar trends in drug utilisation (63-65), although in larger and aggregated age groups, the findings indicate an improvement over time regarding the type of psychotropic drugs utilised among the elderly. The aggregated data source used in the study of trends is currently the only data source with national coverage where information is available for a long time. Once the individual-based registers on dispensed drugs contain data for a longer time period, more detailed analyses on incident and prevalent utilisation can be performed.

A trend from the utilisation of PIP towards recommended psychotropics is suggested also among the 95-year olds. In the Gothenburg 95+ Study (years 1996-1998), the long-acting benzodiazepine flunitrazepam and the short-acting z-hypnotics were each utilised by one third of the 95-year olds with hypnotics. However, in 2006, 82% of the 95-year olds with hypnotics in Gothenburg utilised z-hypnotics, according to the SPDR. This trend from the utilisation of long-acting towards short-acting hypnotics is in agreement with previous findings among the elderly (84). Further, drugs with anticholinergic effects, such as TCAs and conventional antipsychotics, should be avoided among the elderly, especially among individuals with dementia, due to an increased risk for adverse effects on cognitive function (86, 87). In the Gothenburg 95+ Study, psychotropics with anticholinergic effects were more common among the 95-year olds with dementia than among those without dementia. A considerable utilisation of drugs with anticholinergic effects among individuals with dementia has also been observed in other Swedish studies (95, 132). Alternative drugs with less anticholinergic effects, such as the atypical antipsychotics, have been available since the early nineties (74). The findings in this thesis further suggest a switch in utilisation patterns of antipsychotics drugs among 95-year olds over

time. The conventional antipsychotics were by far the most commonly utilised antipsychotics among the 95-year olds in 1996-1998, while in 2006, the atypical antipsychotics were utilised by 80% of the 95-year olds with antipsychotics in Gothenburg, according to the SPDR. An increase in the utilisation of the atypical antipsychotics has been observed in previous research as well, although their safety advantage over conventional antipsychotics has been questioned (75-77).

Although the findings in this thesis suggest improvements in drug utilisation among the elderly, there appears to be socioeconomic inequities in the utilisation of PIP. This is in conflict with the aims of equity in health care, and the issue is of great public health importance (12). Among the elderly who utilised psychotropic drugs in this thesis, individuals with low income and the non-married were more likely to utilise PIP compared to those with high income and the married, respectively. This pattern is in agreement with previous Swedish (26) and international findings (27, 31, 63, 160, 161). Previous research has also found that individuals with lower socioeconomic status are less likely to utilise newly marketed drugs compared to those with higher socioeconomic status (30), which could indicate inequities in access to new drugs. Although the magnitudes of the socioeconomic differences in PIP utilisation were fairly small in this thesis, the higher utilisation of inappropriate drugs among those with low income and among the non-married is not likely to be fully explained by clinically relevant factors. The findings thus indicate socioeconomic inequities in psychotropic drug utilisation among the elderly.

The origin of the inequities remains unclear, although there are several possible explanations. As described in the Background, the process from the identification of a health problem to drug utilisation is influenced by both medical and non-medical factors, and there is a risk for inequities in drug utilisation in numerous steps of this process (17-25). The decisions regarding drug utilisation and choice of drug may be influenced by the patients' knowledge about health issues and available treatment options, as well as their communication abilities. Patients' requests may influence prescribers' drug choice (162, 163). Research on the relationship between the patients' socioeconomic characteristics and the communication between prescribers and patients is limited, but the available previous findings indicate that patients with a higher socioeconomic status receive more information from prescribers (164, 165). Individuals with higher socioeconomic status tend to have an increased access to health and drug information (166), and might be more likely to request drugs with a favourable risk-benefit profile compared to those with lower socioeconomic status. Structural factors, such as drug reimbursement schemes, may also be important. The Swedish drug reimbursement scheme reduces the patients' costs for drugs,

and the price differences between inappropriate drugs and recommended drugs are now marginal in Sweden (68). Generic alternatives were available in 2006 for many of the recently introduced psychotropic drugs, primarily for the new generation antidepressants and the short-acting z-hypnotics, and to a lesser extent for the atypical antipsychotics (74). However, findings from the United States have shown that drug costs might influence the choice of drug (163). The utilisation of PIP could thus be a conscious and preferred choice for the patient due to costs in some cases, but this would imply structural inequities regarding access to drugs, which would also have important public health implications.

The non-married, especially the divorced and the never married, were more likely to utilise PIP compared to the married in this thesis. This might be associated with the social support gained from marriage, which could aid in decisions about health care seeking and drug utilisation, as well as in the communication with the prescriber about e.g. adverse drug reactions. However, previous research on marital status and inappropriate drug utilisation is scarce and inconclusive. A European study found that elderly in community settings who lived alone were less likely to utilise inappropriate drugs compared to those who were cohabiting (31). A study from the United States found that low social support was associated with a higher likelihood of inappropriate drug utilisation among elderly in community settings (161). Further, the association between PIP and marital status in this thesis was more pronounced among the younger elderly than among the older elderly. The proportion of elderly living in nursing homes increases dramatically with age (43), and the married couple might not be permitted to live together in the same nursing home, or the partner might still live at home. Therefore, the social support received from the partner may decline with increasing age.

6.2.4 Efforts aimed at improving drug utilisation among the elderly

The findings in this thesis together with previous research illustrate that inappropriate drug utilisation among the elderly is a major public health issue. Therefore, efforts to improve drug utilisation among the elderly are of great importance. According to a systematic literature review by the Swedish Council on Health Technology Assessment, several different measures may improve drug utilisation among the elderly (96). Education and information, primarily to physicians, and multidisciplinary collaboration and follow-up regarding drug utilisation may reduce the utilisation of inappropriate drugs among the elderly. Further, enhanced medical assessments and diagnostics among the elderly may direct the focus on any underlying disorder and limit the symptomatic treatment, which may reduce suffering and health care utilisation among the elderly. Active

interventions, e.g. face-to-face education, are generally more likely to succeed in improving drug utilisation compared to those with passive information only, and interventions incorporating several strategies tend to be more successful than single interventions (167). Some examples of effective interventions aimed at reducing inappropriate drug utilisation among the elderly in the Nordic countries have been published recently. A Swedish study found that group-education among general practitioners about the utilisation of benzodiazepines and antipsychotic drugs and the risk of confusion among the elderly was associated with a decrease in the utilisation of benzodiazepines 9 months after the education (168). In a study from Denmark, improvements in drug utilisation were seen when general practitioners attended an educational meeting about polypharmacy and appropriateness in drug utilisation among the elderly and received feedback on their patients' drugs (169). A study from Finland found that drug utilisation improved among elderly who received drug utilisation reviews, particularly concerning reduced dosages of psychotropic drugs, and a large proportion of the drug utilisation changes remained one year after the intervention (170).

Previous research has found that prescribers consider guidelines of recommended drugs as important in the drug selection process (171). In Sweden, the DTCs have made substantial efforts to spread and argue for new recommendations among their local prescribers (172). During 2005-2007, the DTCs directed specific focus on drugs among the elderly, and this may have contributed to an increased awareness and improvement in drug utilisation among the elderly. There have been a number of other initiatives aimed at improving drug utilisation among the elderly in Sweden. One example is the Sälma project ("Safe drug utilisation for an improved quality of life among the elderly") (173). Sälma supported various interventions directed at improving routines and drug utilisation among the elderly, and also aimed to implement the successful interventions into standard practise. The Swedish government has provided financial support to stimulate drug utilisation reviews among the elderly, and to improve the health care professionals' knowledge about drug utilisation among the elderly (174). Regional comparisons of quality and efficiency in the Swedish health care system ("Öppna jämförelser") are annually published by SALAR and the National Board of Health and Welfare (124). The regional comparisons include several indicators of drug utilisation among the elderly, and regional variations may direct attention to possibilities for improvement. These efforts may also have had positive effects on the utilisation of psychotropic drugs for elderly.

6.3 Methodological considerations

6.3.1 Classification of PIP

The PIP criteria were developed by an expert group, and were based on systematic literature reviews, internationally published explicit criteria, Swedish guidelines and recommendations. Using criteria adjusted to the Swedish setting is a strength of this thesis. The criteria were recently updated (112), but no substantial changes concerning psychotropic drugs had been made. There are, however, some limitations associated with using such explicit criteria to assess inappropriate drug utilisation. The criteria do not incorporate patients' preferences or individuality, the indications for drug utilisation, dosage, or the lack of drugs that are clinically indicated. In some cases, drugs or combinations of drugs classified as PIP might have been appropriately utilised. For example the TCAs, which have anticholinergic effects, are sometimes utilised for neuropathic pain where doses generally are lower than when they are utilised for depression. Such utilisation might be appropriate. Previous research has suggested that physicians may utilise TCAs primarily for non-psychiatric symptoms (e.g. neuropathic pain) where the treatment alternatives are few and utilisation may be appropriate, while they prefer the new generation antidepressants mainly for depression (175). Therefore, it should be acknowledged that the so often necessary dichotomisation into appropriate versus inappropriate drug utilisation is a simplification of the clinical situation.

6.3.2 Information on drug utilisation

One of the strengths of this thesis is the use of multiple and complementing data sources to study different aspects of inappropriate utilisation of psychotropic drugs among the elderly. The SPDR has national coverage on all drugs dispensed in Swedish pharmacies, and covers about 84% of the total volume of drugs sold in Sweden (7). However, drugs utilised in hospitals or sold over-the-counter are not included. The rather long study period of one year decreases the risk of excluding the most severe and hospitalised patients, since they are not likely to be hospitalised during an entire year. Furthermore, psychotropic drugs are not available over-the-counter in Sweden. Individuals who do not purchase their prescribed drug at the pharmacy, i.e. the primary non-adherers, are not included in the SPDR. Primary non-adherence has been associated with low income and attributed to drug affordability (176, 177), and it is therefore possible that the association between income and drug utilisation found in this thesis is underestimated.

Aggregated drug sales statistics have been available for several years, and may therefore be used to assess trends over time. Although such data do not reveal drug utilisation patterns on an individual level, e.g. number of individuals who utilised the drug, comparability over time and between countries is facilitated by the DDD unit. However, aggregated drug sales statistics are affected by the prescribed dosage as well as the prevalence of drug utilisation. The time trends can thus be influenced by changes in prescribed dosage in addition to changes in the number of individuals who utilise the drug, however, this is not possible to separate in this data source. This limitation has implications when analysing changes over time in larger drug groups, e.g. antidepressants as a group, where the distribution of different drugs within the drug group, e.g. SSRIs versus TCAs, may change over time. Studying trends in utilisation of more homogeneous drug groups, such as SSRI, is not as sensitive.

The Gothenburg 95+ Study is a unique study including a population-based sample of 95-year olds living in nursing homes or in community settings, who were examined for drug utilisation and mental disorders. Information on drug utilisation was primarily collected from multi-dose dispensing lists. These lists were missing for some individuals, and the information was then instead collected during home/nursing home visits. The differing methods for data collection might have introduced information bias. The examinations were performed 1996-1998, and utilisation patterns may have changed since then. However, the patterns within the psychotropic drug groups were compared with data from the SPDR ten years later, and the findings are still of clinical and public health importance. The prevalence rates of psychotropic drug utilisation were not compared due to the methodological differences between the two data sources. The distribution of drugs within a drug group is likely to change over time, and the relation between the PDD and the DDD differs between drugs among the elderly, e.g. SSRIs versus TCAs (131, 132). Therefore, aggregated drug sales statistics were not considered an appropriate data source to assess changes in prevalence of psychotropic drug utilisation over time. The prevalence of psychotropic drug utilisation in the Gothenburg 95+ Study was higher than among individuals aged 90 years and older in a study conducted in Stockholm (100). This might be explained by the exclusion of drugs utilised as needed in the Stockholm study. Further, previous findings indicate a higher psychotropic drug utilisation in Gothenburg compared to Stockholm (178). This has implications for the external validity of the results. While a response rate of 65% can be considered satisfactory given the high age of the sample, there is a risk for selection bias. If morbidity or drug utilisation was associated with non-response, the prevalence estimates may be underestimated.

6.3.3 Diagnoses of mental disorders among the 95-year olds

An assessment of mental disorders with sufficient quality is necessary to address some issues related to inappropriate psychotropic drug utilisation. The collection of such data requires a substantial effort. As described in the Methods section, the National Patient Register has reported a poor coverage regarding psychiatric care (134), and not all mental health problems are identified in clinical practise (133). In the Gothenburg 95+ Study, all participants were examined by trained psychiatrists. The diagnostic procedure for mental disorders among a 95-year old sample is associated with challenges. As previously described (179), one fifth of the 95-year olds had severely impaired hearing or vision. For some participants, this led to difficulties in performing some of the cognitive tests that were used to diagnose dementia. In some cases, other sources of information, such as the close informant interviews, were used to complement the diagnostics of dementia. A previous validation study of the CPRS among elderly inpatients (mean age 70 years) found that ageing or mild cognitive dysfunction did not influence the reliability of the scale (180). In the Gothenburg 95+ Study, the inter-rater reliability was high for the diagnostic agreement (136). According to the DSM-III-R criteria used in the Gothenburg 95+ Study, a diagnostic hierarchy was applied. This meant that if a participant was diagnosed with dementia, no other mental disorders were diagnosed; i.e. dementia is an exclusion criterion for e.g. depression according to the DSM-III-R. The prevalence of dementia increases with age among the elderly, as previously described (46-48). The use of a diagnostic hierarchy therefore has implications for the prevalence estimates of disorders other than dementia, since this hierarchy decreases the population at risk for being diagnosed with e.g. depression. However, the reliability of these diagnoses would be poor among individuals with dementia due to their cognitive impairments, since the diagnostics are primarily based on self-reported information. Furthermore, since drugs with anticholinergic effects increase the risk of cognitive decline (86), utilisation of these drugs might have influenced the diagnostics of dementia in the Gothenburg 95+ Study.

6.3.4 Socioeconomic determinants

Socioeconomic status can be measured with various indicators, e.g. income, occupation or education. Income is an indicator of current financial resources and standards (181). A large part of the income among the elderly comes from pensions. Current financial standards may also be influenced by savings and possessions, but that information was not available in this thesis. Income generally decreases after retirement, and the distribution of income is thus relatively narrow in the elderly population. However, in Norway, where the pension system is similar to that in Sweden, income level among the elderly has

been associated with differences in health status (182). Previous research from Germany has found income to be a stronger predictor of health status among the elderly compared to education, occupational status, assets, or home ownership (28). In this thesis, only three income groups were formed. This might have contributed to the small magnitudes in the associations with the measures of drug utilisation.

Access to education and employment changes over time (181). Education is generally considered to be an appropriate indicator of socioeconomic status among the elderly (181), at least among the younger elderly (183). However, information on education was not available in this thesis. In general, occupation is not an appropriate indicator of socioeconomic status among the elderly due to retirement and the risk of misclassification, particularly among elderly women (181). Occupation before retirement may not reflect the main occupation since increasing age and declining health status may lead to changes in occupation. Marital status was used as a surrogate indicator of social support. However, marital status only focuses on the spouse, and a limitation is thus the lack of information on social support from other individuals. This was not possible to capture in this thesis.

The cross-sectional design precludes any conclusion regarding causality in the association between socioeconomic determinants and drug utilisation. The possibility of reverse causality should be acknowledged, i.e. that poor health status and psychotropic drug utilisation were responsible for a loss of income and/or a lower probability of marrying. It is likely that the relative income categorisations have remained relatively stable over time. Marital status is more likely to change among the elderly, and there might be a risk of misclassification bias. Information on marital status was collected in the end of the study period, while family size was determined before the study period. As previously described, the correlation between marital status and the number of family members was high; there was more than one family member among 97% of the married, 1% of the never married, 4% of the divorced, and 8% of the widowed. The disagreement between marital status and number of family members might therefore represent those who were misclassified.

7 CONCLUSIONS AND IMPLICATIONS

Potentially inappropriate utilisation of psychotropic drugs affects a considerable proportion of the elderly population, and this issue is of great public health importance. Specific pharmacological treatment for mental disorders was uncommon among 95-year olds; only one tenth of those diagnosed with depression utilised antidepressants. The findings do however indicate a trend towards the utilisation of recommended rather than inappropriate psychotropic drugs among the elderly.

The agreement between the indicators PIP and “concurrent use of three or more psychotropic drugs” was poor. This was expected, since they focus on different aspects of drug utilisation. Still, the findings emphasise the importance of choosing valid indicators to assess inappropriate drug utilisation among the elderly, as well as the need to primarily consider the clinical relevance, as opposed to convenience of use, in the choice of indicator. Indicators focusing on specific inappropriate drugs or combinations of drugs should be used as a complement or substitute for indicators of number of drugs in assessments of inappropriate drug utilisation among the elderly.

The findings in this thesis indicate socioeconomic inequities in psychotropic drug utilisation among the elderly, which may be in conflict with the aims of equity in health care. It is of great public health importance to ensure that appropriate drug utilisation is not biased based on the demographic or socioeconomic characteristics of the patient. The differing levels of health knowledge and health behaviour among the various socioeconomic groups need to be acknowledged in clinical practise, and efforts to increase communication between patients and prescribers should be promoted.

The increasing numbers of elderly and the extensive drug utilisation in this population constitute a major public health issue and poses significant challenges for the health care. The high levels of PIP among the elderly, the lack of clinically indicated drugs, especially for depression, and the socioeconomic inequities in drug utilisation reveal a large potential for improvement in drug utilisation among the elderly. These issues need to be firmly addressed. Regular and systematic reviews of the patients’ drug utilisation and an increased focus on physician continuity and education may reduce the utilisation of inappropriate drugs among the elderly.

8 FUTURE RESEARCH

Based on the findings in this thesis, areas of interest for future research have been identified. It is important to investigate why inappropriate drugs are utilised despite the availability of safer and equally effective alternatives. Such knowledge can direct attention toward critical areas to focus in efforts to improve drug utilisation. Analyses of physician views and patient preferences are crucial to efficiently target future interventions aimed at reducing inappropriate drug utilisation among the elderly.

Extensive international research supports the use of explicit criteria, and in this thesis, criteria that had been adapted to the Swedish setting (i.e. PIP) were used (3). However, these criteria primarily focus on drugs and combinations of drugs to avoid. To complement the findings in this thesis, future studies should address additional dimensions in potentially inappropriate utilisation of drugs among the elderly, such as indications and diagnoses, drug dosage regimens, and patients' preferences.

Research from the United States has found that the patients' costs for drugs can be a barrier for physicians to appropriately utilise drugs for the elderly (19, 163). However, these findings may not apply to Sweden or other Nordic countries due to differences in structural factors, such as insurance coverage and the relative size of patients' costs for drugs. An investigation about the relation between structural factors and the decision-making process among physicians in Sweden or other Nordic countries is warranted. The Nordic health care systems aim to provide health care to the entire population on equal terms; still the findings in this thesis suggest socioeconomic inequities in inappropriate drug utilisation among the elderly. It is therefore of great public health importance to assess the origin of these inequities and develop strategies to reduce them.

Due to the increasing number of elderly in the population and the high prevalence of inappropriate drug utilisation, further knowledge of interventions that effectively improves rational and equitable drug utilisation is essential. Further, once the SPDR encompasses data for a longer period of time, individual-based trends in utilisation of inappropriate drugs and recommended drugs should be analysed to complement the findings in this thesis.

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