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Drug Use and Side Effects in the Elderly

Findings From the Kungsholmen Project

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Der Glaube an die Wahrheit beginnt mit dem Zweifel an allen bis dahin geglaubten Wahrheiten. (Friedrich Nietzsche)

To My Family

ABSTRACT

The aim of this thesis was to find occurrence of drug side effects in the elderly by studying the association between changes in clinical parameters and prevalence of self-reported symptoms and the use of drugs in an elderly population.

The studies were performed in the Kungsholmen project, a longitudinal population based study of aging and dementia in Stockholm. Data from baseline (1987-89), 1st follow-up (1991-93), 2nd follow-up (1994-96), and 3rd follow-up (1997-98) were used. The first two articles describe cross-sectional studies examining the prevalence of low blood pressure (Paper I) and sodium and potassium disturbances (Paper II) with respect to medication (baseline, n=1748 and 1558). The third paper examined the association between drug use and hyperglycemia, as measured by increased HbA1c levels (2nd follow-up, n=578). The fourth article is a longitudinal (6 years follow-up) study of age-related impairment of renal function in connection to drug use (baseline to 3rd follow-up, n=242). The fifth article examines the use of antidepressants and anxiolytics in relation to self reported somatic and psychiatric symptoms (3rd follow-up, n=419). The most important results are summarised below.

Study I: The use of potassium-sparing diuretics, dopaminergic antiparkinsonian drugs and neuroleptics were significantly associated with low systolic blood pressure and dopaminergic antiparkinsonian drugs with low diastolic blood pressure.

Study II: The occurrence of hyponatraemia was associated with the use of carbamazepine, laxatives (enema), diuretics and ACE-inhibitors and hypernatraemia with osmotically active laxatives. Hypokalaemia was associated with thiazide-related and combination diuretics and hyperkalaemia with potassium-sparing diuretics, β-blockers, cytostatic drugs and tricyclic antidepressants.

Study III: Use of loop diuretics was significantly associated with high HbA1c levels in both women and men. Eighteen percent of users had high levels compared with 8% in non-users.

Study IV: The prevalence of renal impairment, defined as estimated creatinine clearance (C_E) <50 ml/min, was 33 % at baseline and 93 % in 3rd follow-up. The use of drugs that should be avoided or be prescribed in reduced doses in mild or moderate renal insufficiency increased over time, with few exceptions. Doses decreased for digoxin, spironolactone and allopurinol, but increased for drugs against peptic ulcer, ACE-inhibitors and citalopram.

Study V: Elderly treated with antidepressants showed a high total score on the Comprehensive Psychopathological Rating Scale (CPRS) (23.6±10.9) and score for depressive symptoms (6.4±7.2). The scores were even higher for users of anxiolytics (26.3±23.2 and 7.6±14.4). The use of antidepressants was significantly associated with several somatic symptoms such as vertigo/dizziness, tendency to fall, involuntary urination, and shortness of breath. The use of anxiolytic drugs was associated with vertigo/dizziness and shortness of breath.

Conclusions: Side effects of drugs occur frequently in an elderly population and with many drugs that are generally not considered in clinical practice.

There is a continuous age-related loss of renal function. However, apparently physicians often do not adjust the treatment according to this very important age-related physiological change, which in turn increases the risk of side effects.

Our results also indicate ineffective and inappropriate treatment of depression as well as side effects of anxiolytic and antidepressant therapy in the elderly.

SAMMANFATTNING

Syftet med denna avhandling var att undersöka förekomsten av läkemedelsbiverkningar hos äldre genom att studera sambandet mellan förändringar av kliniska parametrar samt frekvens av självrapporterade symptom och läkemedelsanvändning i en äldre population.

Studierna genomfördes inom Kungsholmsprojektet, en longitudinell populationsbaserad studie av åldrande och demens i Stockholm. Vi använde oss av data från baslinjen (1987-89), första (1991-93), andra (1994-96) och tredje (1997-98) uppföljningen. I de två första artiklarna beskrivs studier som undersöker förekomsten av lågt blodtryck (artikel 1) och elektrolytrubbningar (artikel 2) med avseende på medicinering (baslinjen, n=1748 resp. 1558). I den tredje artikeln har vi undersökt sambandet mellan läkemedelsanvändning och hyperglykemi, mätt som förhöjda Hb1A1c-värden (andra uppföljningen, n=578). Den fjärde artikeln är en longitudinell studie (6 års uppföljning) av åldersrelaterad försämring av njurfunktionen och dess relation till läkemedelsanvändningen (från baslinjen till tredje uppföljningen, n=242). Den femte artikeln undersöker användningen av antidepressiva och lugnande läkemedel i förhållande till självrapporterade somatiska och psykiska symptom (tredje uppföljningen, n=419). Det viktigaste resultaten sammanfattas nedan.

Studie I: Användning av kaliumsparande läkemedel, dopaminerga läkemedel vid parkinsonism samt neuroleptika var signifikant associerade med lågt systoliskt blodtryck, och dopaminerga läkemedel vid parkinsonism med lågt diastoliskt blodtryck.

Studie II: Förekomst av hyponatremi var associerad med med användning av karbamazepin, laxativa (klysma), diuretika samt ACE-hämmare, och hypernatremi med osmotiskt aktiva laxativa. Hypokalemi var associerad med tiazidrelaterade och kombinationsdiuretika, och hyperkalemi med kaliumsparande diuretika, betablockerare, cytostatika och tricykliska antidepressiva.

Studie III: Användning av loopdiuretika var signifikant associerad med förhöjda HbA1c- värden hos både kvinnor och män. Arton procent av användarna hade förhöjda värden jämfört med 8 % hos icke-användare.

Studie IV: Förekomsten av försämrad njurfunktion, definierad som uppskattat kreatininclearance (C_E) <50 ml/min, var 33% vid baslinjen och 93% vid den tredje uppföljningen. Användningen av läkemedel som bör undvikas eller förskrivas i reducerad dos vid lätt eller medelsvår njursvikt ökade, med få undantag, under denna tid. Doserna minskade för digoxin, spironolakton och allopurinol, men ökade för medel vid magsår, ACE-hämmare samt citalopram.

Studie V: Äldre som behandlades med antidepressiva uppvisade höga poäng i Comprehensive Psychopathological Rating Scale (CPRS) både totalt (23.6±10.9) och för depressiva symptom (6.4±7.2). Poängantalet var ännu högre för användare av ångestdäpande läkemedel (26.3±23.2 resp. 7.6±14.4). Användning av antidepressiva var signikant associerad med ett flertal somatiska symptom såsom yrsel, falltendens, urininkontinens och andnöd. Användning av ångestdämpande läkemedel var associerad med yrsel och andnöd.

Slutsatser: Läkemedelsbiverkningar förekommer frekvent i en äldre population och det med många läkemedel som man i allmänhet inte tar hänsyn till i det kliniska arbetet.

Det föreligger ett kontinuerligt åldersrelaterat bortfall av njurfunktion. Trots detta tycks läkarna ofta underlåta att anpassa behandlingen efter denna mycket viktiga åldersrelaterade fysiologiska förändring, vilket i sin tur ökar risken för biverkningar.

Våra resultat tyder också på ineffektiv och ibland felaktig behandling av depression liksom på biverkningar av lugnande och antidepressiva läkemedel hos äldre.

LIST OF PUBLICATIONS

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

I.   Passare G, Guo Z, Winblad B and Fastbom J. Drug Use and Low Blood Pressure in the Elderly. A study of data from the Kungsholmen Project. *Clin Drug Invest* 1998;15(6):497-506.

II. Passare G, Viitanen M, Törring O, Winblad B and Fastbom J. Sodium and Potassium Disturbances in the Elderly. Prevalence and association with Drug use. *Clin Drug Invest* 2004;24(9):535-544.

III. Passare G, Fastbom J, Törring O and Viitanen M. Drug use and increased HbA1c levels in non-diabetic very elderly persons: the Kungsholmen project. *Eur J Clin Pharmacol* 2004;60(2):121-126.

IV. Passare G, Fastbom J and Viitanen M. Renal function and drug use in an elderly population. The Kungsholmen project. *Manuscript*.

V.   Passare G, Fastbom J, Berger A-K and Viitanen M. The use of antidepressants and anxiloytics in very old persons, association with self-reported somatic and psychiatric symptoms. Data from the Kungsholmen project. *Manuscript*.

CONTENTS

LIST OF ABBREVIATIONS

ACE	Angiotensin converting enzyme
ADH	Antidiuretic hormone
ADL	Activities of daily living
ADR	Adverse drugs reaction
ASA	Acetylsalicylic acid
ATC	Anatomical, therapeutic and chemical classification
BMI	Body mass index
Ca^{2+}	Calcium
CCr	Creatinine clearance
C_E	Estimated creatinine clearance
CI	Confidence interval
CNS	Central nervous system
CPRS	Comprehensive psychopathological rating scale
Cr-EDTA	Chromium-51 ethylenediamine tetra-acetic acid
CYP	Cytochrome P450
CVD	Cerebrovascular disease
DDD	Defined daily dose
DSM-III-R	Diagnostic and statistical manual of mental disordes, 3rd edition revised
EVF	Extracellular volume fraction
GFR	Glomerular filtration rate
Hb	Hemoglobin
HbA1c	Glycosylated hemoglobin
Hg	Mercury
ICD 8,9	International classification of diseases, 8th and 9th Revision
K^+	Potassium
LPK	Leucocyte particle concentration
MAO	Monoamine oxidase inhibitor
MD	Major depression
Mg^{2+}	Magnesium
MMSE	Mini-mental state examination
Na^+	Sodium
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
SD	Standard deviation
SIADH	Syndrome of inappropriate ADH secretion
SCr	Serum creatinine
SR	Sedimentation Rate
TCA	Tricyclic antidepressants
TSH	Thyroid stimulating hormon
SSRI	Selective serotonin reuptake inhibitors
WHO	World Health Organisation

INTRODUCTION

DRUG SIDE EFFECTS AND THE ELDERLY

According to the definition adopted by the WHO, an adverse drug reaction is any negative and undesired effect of a drug that occurs from use in normal dosage.[1, 2, 3] All drugs produce effects besides the intended ones. Sometimes these effects are beneficial but more often of a harmful nature.

Elderly patients are subject to side effects to a substantially larger extent than younger patients. Studies have shown that elderly are 2-4 times more likely to experience an adverse drug reaction.[4, 5] Age alone does not seem to account for an increased risk for negative effects, but aging tends to lower the tolerance to an event. The number of reported side effects increases steeply with higher age. This is partly due to changes in drug pharmacokinetics, for example impaired renal function, but also to increased sensitivity to drug effects. Older patients also have a lowered ability to maintain homeostasis, i.e. physiological equilibrium, when subject to outer changes, which in turn narrows their tolerance to drug effects.[6, 7]

In hospitalised elderly incidence rates of side effects of between 1.5% and 35% have been reported.[5] Adverse reactions also in many cases lead to hospitalisation[8]. Studies have shown that 2-12% of the patients in geriatric and infectious clinics have an adverse drug reaction as the main or a contributing cause for hospitalisation.[9-11] In Sweden this corresponds to 40.000 patients per year. A meta-analysis based on 36 papers published during the period 1966-1989, representing a number of different countries, showed that drug related problems were the cause for on average 5.1 percent of all hospitalisations.[12] In a Swedish study from 1983 the corresponding percentage was 16%[13]. Once a patient has been hospitalised, the risk of contracting new, serious adverse reactions is 6-7%.[14, 15] Cardiovascular problems such as congestive heart failure, angina, and hypotension was reported to account for 53 percent of drug-related hospital admissions. Moreover, central nervous system (CNS) disorders like confusion and dizziness were associated with 35 percent of the admissions, while gastrointestinal and genitourinary abnormalities accounted for 21 percent and 19 percent of the admissions, respectively.[16] Drugs that are commonly involved include diuretics, non-steroidal antinflammatory drugs (NSAID), ACE-inhibitors, blood pressure lowering drugs and psychotropic agents.

For most drugs, however, minor pharmacological side effects are more common. The size and impact of this type of side effects has not yet been satisfactorily investigated but it is probably not negligible and may influence the quality of life for the patients.

Deaths caused by adverse drug reactions are the fourth most frequent cause of death in the USA.[14] The true mortality figures are probably even higher than these, since they are based on hospital material. Patients dying outside of hospitals, of for example drug-provoked malignant arrhythmia, were not included. Norwegian studies have found that 18% of all deaths in a medical clinic were directly or indirectly associated with side effects of drugs.[17]

AGE-RELATED PHYSIOLOGICAL CHANGES

Aging leads to physiological changes that may alter the effect of many drugs. Usually this results in an increased risk of side effects. Two types of changes occur, pharmacokinetic and pharmacodynamic.

Pharmacokinetic changes

Pharmacokinetics is "the mathematics of the absorption, distribution, metabolism and excretion of drugs in the body". Aging leads to several pharmacokinetic changes, resulting in prolonged half-life of drugs and thereby duration of action, and/or accumulation of drug molecules leading to increased effect (Table 1).

Gastrointestinal changes that may lead to changes in the drug absorption include increased gastric pH, decreased intestestinal blood flow secondary to decreased cardiac output, alterations in gastric emptying time and gastrointestinal motility.[18-21] However, overall the effect of aging on drug absorption is fairly small.

In elderly the amount of total body water decreases, leading to an increased proportion of body fat.[22] In men the amount of body fat in relation to lean body mass may be doubled by the age of 70 and in women increased by one third.[23, 24] This is of importance when it comes to the distribution of strongly lipid-soluble drugs, for instance diazepam. The increased volume of distribution results in prolonged half-life and thereby duration of action of lipid-soluble drugs. The distribution volume of water-soluble drugs such as furosemide and digoxin, may instead decrease, potentially leading to an increased concentration, in older patients.

The duration of the drug effect is influenced by the rate of elimination.[25] Many drugs can be eliminated directly through the kidneys. However, non-polar (lipid soluble or lipophilic) drugs first must be transformed transformed into polar (water soluble or hydrophilic) metabolites before they can be excreted through the kidneys. Drug metabolism mainly takes place in the liver[26, 27] and with increasing age changes in liver size, blood flow (decrease of up to 50%), and capacity of some isoenzymes, may cause a reduction of liver metabolism. This can in turn impair the elimination of non-polar (lipid soluble) drugs. The excretion, of the parent drug and/or its metabolites, through

the kidneys can be substantially affected by aging. The renal function is continuously declining at a slow rate from age 30-40. Even in persons who do not suffer from any disease affecting renal function there is a steady 6 to 10 % reduction in glomerular filtration rate and renal plasma flow every ten years.[28-30] At age 80, the renal blood flow may be reduced by 50% in comparison with young adults, and the glomerular filtration show a similar decrease, leading to a much slower renal elimination of drugs and drug metabolites.[31, 32] In contrast, the most common measure of kidney function, serum creatinine, often remains normal, due to a decreased production of creatinine caused by an age related reduction in muscle mass. Measurements of serum creatinine should therefore not be the basis for dosage of drugs with renal elimination.

Table 1. Pharmacokinetic change influencing drug effects in the elderly

Physiologic parameter	Age related change	Significance
Absorption	Decreased salivary flow Increased gastric pH Delayed gastric emptying Decreased absorptive surface Reduced splanchnic blood flow Decreased gastrointestinal motility	Mildly decreased absorption
Distribution	Decreased lean body mass Increased body fat:lean body mass ratio Decreased total body water Decreased serum albumin Increased alpha-1 acid glycoprotein	Increased distribution and half life of lipid soluble drugs Higher concentration of water soluble drugs Decreased free fraction of basic drugs
Metabolism	Decreased hepatic metabolic capacity Decreased hepatic mass Decreased hepatic blood flow	Decreased Phase I bio-transformation (oxidation /reduction, hydrolysis), leading to decreased first-pass metabolism and/or elimination of lipid soluble drugs
Elimination	Decreased renal blood flow Decreased glomerular filtration rate	Decreased elimination of drugs and metabolites

Pharmacodynamic changes

Pharmacodynamics involves various aspects of the interaction between a medical agent and its targets in the body. Increasing age is associated with several alterations in the

pharmacodynamics that may lead to significant modifications in the cardiovascular and central nervous system among others (Table 2).[33] Most often the changes in the drug reactions have a multifactorial cause and depend very much on the specific organ and the drug used. One reason for modified drug sensibility in old age is an increase or reduction in the number of drug receptors. For instance, beta-adrenergic receptors in the heart become less sensitive.[34] Other changes involve receptor affinity or altered translation of a receptor-initiated cellular response.[35] Drug sensitivity may also be due to changes in the capacity of various organs and physiological reflexes or equilibria.[36] It is also known that genetic factors may influence pharmacodynamics, in that the reserve capacity of various organs are affected differently by the ongoing ageing process in different individuals.[37] The changes due to ageing tend to decrease the desirable effects of the drug therapy and increase the adverse effects. Furthermore, the capacity to respond to these adverse effects and to other physiological challenges decreases with higher age.

With increasing age, the brain develops an increased sensitivity to centrally acting drugs, such as sedatives-hypnotics and opioid analgesics. Furthermore, a reduction of the brain's cholinergic system – which is marked in Alzheimer's disease, but to some extent seen also with normal ageing – results in an increased sensitivity to drugs with anticholinergic effects. This can then lead to cognitive disturbances of various degree, delirium or even a dementia-like state.[38-41]

The baroreflex, which regulates the blood pressure for example following changes in body posture, is impaired in elderly individuals. This may cause a drop in blood pressure when raising to an upright position (orthostatic or postural hypotension). The impairment also increases the risk for drug-induced hypotension. This is particularly true of many cardiovascular drugs – including beta-adrenergic receptor antagonists, diuretics and vasodilators such as nitrates, calcium antagonists and ACE-inhibitors – but also psychotropic drugs such as neuroleptics and tricyclic antidepressants (TCA), as well as antiparkinsonian drugs.[42-45]

Another example of pharmacodynamic changes is the increased sensitivity to warfarin, which may result in an increased anticoagulant effect. Moreover, with increasing age several organs, such as the heart, bowel, and bladder, become more sensitive to anticholinergic medications.

One should expect that these increased drug responses will also increase the risk of various side effects of drugs.[40, 46-48] Table 3 lists some common side effects in the elderly and their potential clinical consequences.

Table 2. Examples of important age-related pharmacodynamic changes and their mechanisms.

Pharmacodynamic change	Drugs	Consequences
Increased sensitivity of the brain	Bensodiazepines, opioids	Increased sedation, risk of cognitive impairment, delirium and falls
Reduced capacity of the brain cholinergic system	Anticholinergic drugs	Risk of cognitive impairment and delirium
Impaired baroreflex	Cardiovascular drugs, neuroleptics, tricyclic antidepressants, antiparkinsonian drugs	Postural hypotension, ortostatic reactions
Decrease in the number of beta-receptors	Beta-adrenergic receptor blockers	Reduced effect
Increased sensitivity to warfarin	Warfarin	Increased anticoagulant effect

POLYPHARMACY

The number of drugs has been shown to be the single most important risk factors for adverse drug reactions.[49, 50] The incidence of side effects, as well as drug-drug interactions, increases sharply with increasing number of drugs.[51-54]

Polypharmacy is a reality for many elderly today. Drug use in old people has increased markedly during the last two decades.[55] Two thirds of all people aged 65+ and over 90% of elderly persons 80+ take medication regularly.[55-59] Swedish studies have shown that elderly on average use 4-5 different drugs[55] and for those living in geriatric departments the average number of used drugs is around 10.[60]

Table 3. Common side effects in the elderly and clinical outcomes

Drug/drug group	Adverse reactions	Clinical outcomes
NSAID	Gastric irritation, ulcers, chronic blood loss, nephrotoxicity	Hemorrhage, anemia, sodium retention, renal failure, may decrease effectiveness of antihypertensive drugs
Anticholinergic drugs	Dry mouth, decreased gut motility, bladder hypotonia, decreased cognition, sedation, orthostatic hypotension, blurry vision	Constipation, urinary retention, confusion, instability and falls
Anticoagulants	Bleeding complications	Hemorrhage
Antidepressants (tricyclics)	Anticholinergic effects, heart block	Falls, confusion, urinary retention
Antipsychotics	Sedation, tardive dyskinesia, dystonia, anticholinergic effects, hypotension	Falls, hip fractures, confusion, social disability
Beta-blockers	Decreased myocardial contractility, decreased cardiac conduction, mild sedation, orthostatic hypotension	Bradycardia, heart failure, possible confusion, falls
Digoxin	Decreased cardiac conduction, gastrointestinal disturbances	Arrhythmias, nausea, anorexia
Insulin, sulfonylureas,	Hypoglycemia	Falls, confusion, brain injury
Opioids	Decreased gut motility, sedation	Confusion, constipation
Sedatives-hypnotics	Excessive sedation, cognitive impairment, gait disturbances, impaired psychomotor performance	Falls and fractures, confusion

Modified from Kane RL, Ouslander JG, Abrass IB. Essentials of clinical geriatrics. 4th ed. New York: McGraw-Hill, 1999.

MECHANISMS OF SIDE EFFECTS

The frequency, character and intensity of side effects vary between different drugs and also between chemically related substances (for instance within the groups of ACE-inhibitors and beta-blockers). The sensitivity to the different effects of a medical substance also varies largely among patients.[36] This is partly due to genetic variations in both pharmacokinetics and allergic disposition, partly depending on age and other drug treatment.

A thorough understanding of the physiological mechanisms is of great importance in order to avoid adverse reactions. However, unfortunately, the mechanisms behind many adverse reactions are not fully known. Drug side effects can be divided into two types:[61] Type A consists of reactions that are due to pharmacological effects of a physical or chemical nature. These effects are predictable and dose-dependent, implying that it is often possible to reduce them by simply avoiding high doses of the drug. Examples of type A side effects include nausea from SSRI drugs, and vertigo from antihypertensives. Type B reactions on the other hand are generally due to idiosyncratic or immunological reasons, particular to the individual patient rather than to the mechanism of action of the agent *per se*. One example is allergic reactions from penicillin. In most cases the mechanisms behind the type B effects are not known. These reactions can be very serious and in some cases even fatal.

GENDER DIFFERENCES

Side effects are reported more often in women than in men. There are several explanations of this. A major reason is probably that women more often consult their physician, but other factors that can also be of importance, including physiological (hormones, body constitution etc), as well as cultural and psychosocial differences. Women use more medicines than men. They also tend to be more susceptible to adverse reactions than men.[62]

During the past 10 –15 years biological differences between women and men have been considered as possible reasons for differences in adverse reactions. There is for example a gender difference in the activity of the drug metabolising enzyme CYP3A4 in the cytochrome P450 system[45] in the liver. There are also constitutional (e.g. lower body mass in women), as well as hormonal and metabolic differences.[23] For example total body potassium level declines with age, but more so in women than in men,[63, 64] which may explain why hydrochlortiazide decrease more potassium levels in female patients.[65] The so-called CURE-study[66] has shown that klopigdogrel (Plavix®) had a good effect in men but not in women. According to several studies, drugs against cardiac arrhythmias[67] and neuroleptics[68, 69] may have gender specific effects. For example antidepressants have been reported to be more effective in women.[70, 71] Coughing caused by ACE-inhibitors is more common in women.[72] Thus there is evidence that medication sometimes have different effects in women and men. Yet, most clinical trials have been done in men.

CHANGES IN LABORATORY VALUES IN THE ELDERLY

With advancing age, laboratory reference values increase or decrease, while some remain unchanged.[73] The interpretation of laboratory data in the elderly is further

confounded by the multiple diseases, polypharmacy, and atypical disease presentations commonly found in an old population. Table 4 shows the various alterations of laboratory data that are typical for the elderly.

Table 4. Changes in laboratory reference values in the elderly.

Unaltered	Decreased	Increased
Liver function	S-albumine	S-ALP
S-bilirubin	S-B$_{12}$	S-Urate
S-ASAT	S-Mg	S-Cholesterol
S-ALAT	S-HDL (women)	S-HDL (men)
Coagulations tests	B-LPK	S-Triglycerides
Electrolytes	Creatinine clearance	S-TSH
S-Na		B-glucose (not fasting)
S-K		Glucose intolerance test
S-Ca		
Blood values		
B-Hb		
B-EFV %		
B-Erythrocytes		
Renal function		
S-Creatinine		
Thyroidea		
S-T$_4$		

Modified from Dehlin O. and Rundgren Å. Geriatrik. Studentlitteratur, Lund. 1995.

DIFFICULTIES TO IDENTIFY SIDE EFFECTS IN ELDERLY

It would be easy if we could ask the patients about symptoms and side effects, however it is often more compicated than that. In many cases side effects are interpreted as a normal phenomenon due to the patient's advanced age,[74, 75] or token for a symptom motivating even further drug prescription. For instance insomnia can be caused by diuretics, cardiovascular drugs, laxatives and even hypnotics.[76] and lack of appetite may be due to digoxin.[77] A serious problem exists when both doctors and patients do not realise that practically all symptoms in the elderly can be caused or worsened by drugs. As a result, many adverse reactions are overlooked or not recognised until they have caused significant harm. Moreover, the side effects do not necessarily appear directly in connection with the start of the medication. An important rule for a physician is to always keep drug side effects in mind as a diagnostic alternative when investigating both clear and diffuse disorders in the elderly.

8

WHY IS IT IMPORTANT TO STUDY SIDE EFFECTS IN THE ELDERLY?

Our knowledge about the kinetics and dynamics of drugs and their side effects in the elderly is far from satisfactory. The Swedish drug formulary FASS gives numerous recommendations for caution with dosage to elderly patients but these warnings usually do not appear to be based on controlled studies, but rather on the overall notion that older persons tend to have a reduced functioning of vital organs, such as kidneys and liver, and that they are generally more susceptible to adverse drug reactions than younger patients. Therefore it is important to carry out population-based studies in order for future drug trials to be planned so that the side effects can be accurately differentiated according to age. Descriptions of side effects should clearly indicate frequency in various age groups. There are previous studies showing that drug-related hospitalisation can in many cases be prevented[13, 78-80] but this requires better knowledge about the panorama of drug side-effects in the elderly. This thesis based on data from a population-based study, can hopefully contribute to these topics on drug use in the elderly.

THE RATIONALE FOR THE PRESENT THESIS

Most of the studies focusing on adverse drug reactions in the elderly have been performed on hospitalised people. Few of them deal with outpatients and hardly any are population-based. This thesis tries to explore drug side effects in a normal population of very old elderly. I have focused on side effects that are common, and/or may have serious consequences in the elderly.

Hypotension is probably common but it is often unrecognised as a side effect. In the general population the prevalence has been reported to be about 17%.[81] Drug-induced orthostatic hypotension is a well-known phenomenon,[82] whereas drug-induced chronic hypotension has been less studied in the medical literature. Many drugs have been reported to induce hypotension and these can be divided into two major categories: a) drugs used to treat hypertension for example beta-receptor blocking drugs and diuretics, and b) drugs with hypotension as a side effect, for example organic nitrates, antiparkinsonian drugs and neuroleptics.[82] Ageing may increase the risk of hypotensive effects of these drugs, partly due to the above mentioned pharmacokinetic changes. In addition, impaired baroreceptor reflex function, together with a greater risk of sodium and volume depletion due to hormonal changes and venous insufficiency in the elderly, leads to an increased sensitivity to hypotensive stimuli.[44, 82, 83]

Another common type of side effect in the elderly is electrolyte disturbances . Many of derangements in acid-base and electrolyte balance are probably of minor importance, but some may have serious consequences if left untreated.[84] Hyponatremia may for instance give neurological symptoms and in serious cases irreversible brain

damage.[85] Hypernatremia in elderly is often associated with serious latent diseases. It may cause CNS disturbances and contribute to an increased mortality.[86] Hyperkalemia can be directly cardiotoxic, while hypokalaemia may lead to hypotonia, heart arrhythmia and muscular weakness.[87] Drug use is among the more common causes of electrolytic disorders.[88, 89] Still, only few studies have examined the prevalence of electrolyte disturbances in relation to drug use in the elderly.

Drugs can alter the metabolic status of patients, by enhancing or diminishing the effects of hormones, vitamins, or energy sources such as glucose and lipids. Many drugs can influence glucose homeostasis, causing either hypo- or hyperglycemia. Therefore it is important to review all drugs when a diabetic patient looses metabolic control.[90-92] Hyperglycemic effects have been reported for for example diuretics, beta-receptor blocking agents, histamine H_2-blockers and glucocorticoids. However very little is known about how often these drugs affect blood glucose levels in the elderly.

The renal function is of primary importance for the elimination of drugs that are excreted unmetabolised or as active metabolites.[93] Both in elderly patients and patients with an impaired renal function the dosage of drugs eliminated though kidneys should be regularly adjusted to the current level of renal function.[94] This is particularly important for therapies longer than one week. If this is not done the drug will accumulate in the body, eventually reaching levels causing side effects. This dose adjustment is particularly important in the elderly patients.[94] Although several studies have examined the age-related decline in renal function, very few have included the very old elderly. In addition few have explored the drug use and doses in relation to renal function in elderly.

One of the most common group of drugs in the elderly is the antidepressants. With the advent of the SSRI, the use of these drugs have increased dramatically in all age groups including the elderly. However, in recent years there is a growing number of reports about various side effects of antidepressants,some with serious consequences, including falls,[95, 96] bleedings[97, 98] and micturition problems.[99] Also, doubts have been raised about the efficacy of the SSRI in treating depression in the elderly.[100]

AIMS

The overall aim of the thesis is to find evidence for association between use of drugs and impairment of physiological and biochemical parameters or self-reported symptoms in the elderly, suggesting side effects. The specific aims of the five studies are:

1. To examine the prevalence of low blood pressure in an older population with respect to drugs with potential hypotensive effects.

2. To study the incidence of sodium and potassium disturbances with respect to medication with potential effects on electrolytes levels.

3. To describe the association between the use of drugs with potential hyperglycemic effects and increased HbA1c levels in non-diabetic elderly.

4. To determine the prevalence of age-related renal impairment and to relate it to the use and dosage of medications that should be avoided or used with caution in renal impairment.

5. To study the use of antidepressant and anxiolytic drugs in relation to self-reported somatic and psychiatric symptoms, in order to find evidence for undertreatment and/or side effects of these drugs.

METHODS

THE KUNGSHOLMEN PROJECT

The Kungsholmen project included all the inhabitants registered on October 1987 in the Kungsholmen parish of Stockholm, born in 1912 or earlier. All registered in the administrative office whether living in institutions or at home were included. This project aimed to examine the medical, social and psychological aspects of aging with emphasis on dementia. Out of the total population of 2368 persons 1810 (76%) entered the study. At the start the mean age of the participants was 81.7 years, ranging from 75 to 101 years. Females accounted for 76 % of the population. In 1991 two additional cohorts were included, one with persons 75 years of age and one from the St Göran district of Stockholm. In 1994 one rural cohort (Nordanstig) was added to the project.
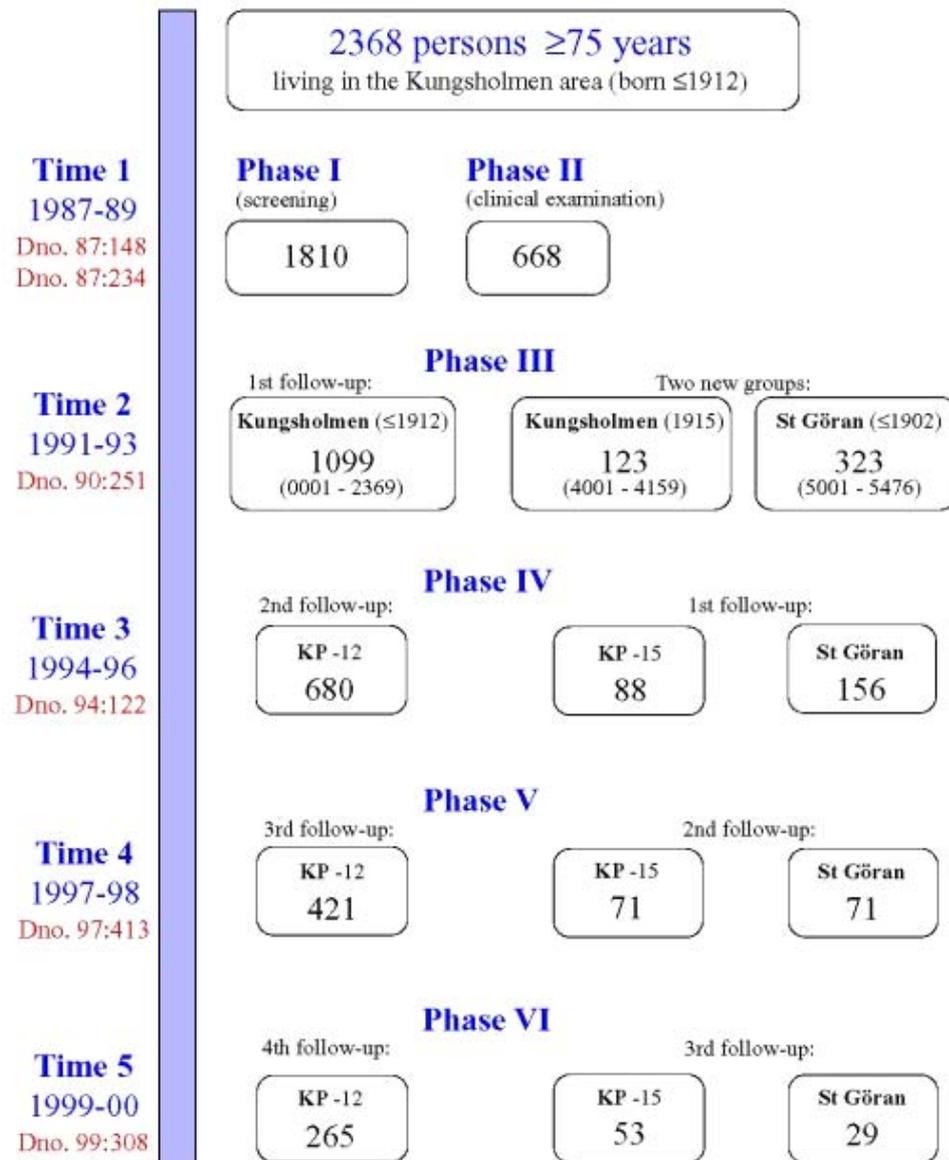
The Kungsholmen Project consists of several phases: The baseline data collection /examination (Phase I) was performed between 1987 and 1989. The elderly were interviewed by one or two nurses who administrated a questionnaire including health and social questions. A clinical examination was done by a physician. The interview also included questions about the current drug use. In this phase the nurses performed a Mini Mental State Examination (MMSE) in order to screen for possible dementia cases. This was followed by a clinical phase (Phase II) where subjects with MMSE score <24 and a matched control group with MMSE ≥24 were more extensively examined for the presence of dementia, using DSM-III-R criteria.

The first follow-up (Phase III) was made 1991-1993, the second (Phase IV) in 1994-1996, the third (Phase V) in 1997-98 and the fourth (Phase VI) in 1999-2000. The subjects were interwiewed and clinically examined using essentially the same procedures as in phase I-II.

For a more detailed description of the design the reader is referred to previous publications from the project.[55, 101, 102]

THE KUNGSHOLMEN PROJECT
Design and participants

2368 persons ≥75 years
living in the Kungsholmen area (born ≤1912)

Time 1
1987-89
Dno. 87:148
Dno. 87:234

Phase I
(screening)
1810

Phase II
(clinical examination)
668

Phase III

Time 2
1991-93
Dno. 90:251

1st follow-up:
Kungsholmen (≤1912)
1099
(0001 - 2369)

Two new groups:
Kungsholmen (1915)
123
(4001 - 4159)

St Göran (≤1902)
323
(5001 - 5476)

Phase IV

Time 3
1994-96
Dno. 94:122

2nd follow-up:
KP -12
680

KP -15
88

St Göran
156

Phase V

Time 4
1997-98
Dno. 97:413

3rd follow-up:
KP -12
421

2nd follow-up:
KP -15
71

St Göran
71

Phase VI

Time 5
1999-00
Dno. 99:308

4th follow-up:
KP -12
265

3rd follow-up:
KP -15
53

St Göran
29

Dno. 99-025 = Permission to order death certificates and medical records for the deceased.
Dno. 01-020 = Permission to receive information from the inpatient register 1969-2000.

(E von Strauss, 2002)

STUDY POPULATION

The studies in this thesis includes persons from the Kungsholmen population, with complete information about drug use and the outcome parameters (see Table 5). Studies I and II were based on data from baseline (1987-89), study III from 2nd follow-up (1994-96), study IV from all waves from baseline to 3rd follow-up (1997-98) and study V from 3rd follow-up. The overall design of the different studies are summarised in Table 5.

DRUG USE

Data on drug use were obtained from personal interviews. To assist with this the participant was also asked to show containers, prescriptions and medications lists. If the participant was unable to give information it was obtained from a relative, caregiver, medical staff or from prescription lists for those residing in institutions. The drug data included prescription as well as non-prescription drugs. Both regularly used drugs and drugs used on an as needed basis were listed. A drug taken regularly was considered to be used if it was used at the time of the interview, a drug taken as needed was recorded if it had been used some time during the two preceding weeks. The name and strength of the medicine, the administration form and the dosage regime was registered. The drug data were classified according to the Anatomical Therapeutic Chemical (ATC) classification system recommended by the WHO.[103] Classification and coding of data was done by an experienced pharmacist. Where there was doubt or ambiguity the original files were re-examined.

To facilitate comparisons, generic drug names are used in the studies and doses are expressed as percent of DDD, the average daily dose of a drug when used for its main indication in an average (70 kg) adult.

PHYSIOLOGICAL MEASURES

Physical examination included, among others, measurements of blood pressure, body weight and height.

The arterial blood pressure (systolic Korotkoff phase I and diastolic phase V) was measured using a mercury sphygmomanometer with the subject in a sitting position after 5 minutes rest.

The BMI was computed according to the standard formula

BMI = weight/height squared (kg/m^2)

With 20 kg/m^2 being the lower reference value.

Table 5. Summary of the design of the studies in the thesis

	Study I	Study II	Study III	Study IV	Study V
Type of study	Cross-sectional	Cross-sectional	Cross-sectional	Longitudinal	Cross-sectional
Study population	Baseline N=1748	Baseline N=1558	2nd follow-up N=578 (non-diabetic)	Baseline - 3rd follow-up N=242	3rd follow-up N=419
Outcome	Blood pressure	Serum levels of sodium and potassium	HbA1c	Creatinine Estimated creatinine clearance Drug use	Self reported psychiatric and somatic symptoms
Determinants	Drug use	Drug use	Drug use	Creatinine, Estimated creatinine clearance	Use of antidepressants and anxiolytics
Covariates	Age, Gender, Housing Dementia Cardiovascular disease BMI Dehydration Other drugs	Age, Gender, Housing Heart disease CVD Dementia Decreased renal function Hypothyroidism Hyperglycemia Leukocytosis BMI Other drugs	Age, Gender, Housing BMI Hypertension Congestive heart failure Hypokalemia Hyperthyroidism Hypercalcemia High erythrocyte sedimentation rate Other drugs	Age, Gender, Housing	Age, Gender, Housing Type of cohabitation Heart disease MMSE
Statistical analyses	Independent samples t-test Bivariate correlation Logistic regression	Logistic regression	Independent samples t-test Logistic regression	Descriptive statistics	Logistic regression

LABORATORY VALUES

In connection to the medical examination, blood samples were collected for routine measurements including serum sodium (S-Na$^+$), serum potassium (S-K$^+$), serum calcium(S-Ca^{2+}), serum albumin, serum creatinine, red and white (LPK) blood cell count, erythrocyte sedimentation rate (SR), thyroid stimulating hormone (TSH) levels, blood glucose. HbA1c (2nd – 4th follow-up) was performed by means of the HPLC-technique with a Mono S Collumn.[104]

CREATININE CLEARANCE

Creatinine Clearance was estimated (C$_E$) using the Cockroft-Gault equation.[105]

$$C_E \text{ (ml/min)} = \frac{(140\text{-age}) \times \text{weight (kg)}}{72 \times S_{Cr} \text{ (mg/100 ml)}}$$

For women the value is multiplied by 0.85

Table 6 summarises the different clinical parameters examined in the present studies and their respective reference values.

Table 6. Clinical parameters examined and their reference values, in the present studies

Study	Measures	Reference value
I	Hypotension	Systolic blood pressure < 125 mmHg Diastolic blood pressure < 65 mmHg (lower 10th percentile of the values of the study population[106])
II	Hyponatremia Hypernatremia Hypokalemia Hyperkalaemia	Na$^+$ < 136 mmol/l Na$^+$ > 146 mmol/l K$^+$ < 3.5 mmol/l K$^+$ > 5.0 mmol/l (The Merck manual of geriatrics[107])
III	Hyperglycemia	HbA1c > 5,3% (Local lab references)
IV	Mild renal insufficincy Moderate renal insufficiency Severe renal insufficiency	C$_E$ 50-80 ml/min C$_E$ 10-50 ml/min C$_E$ <10 ml/min (Aronoff et al 1999[108])

MEDICAL DIAGNOSES

Data on diseases were collected in three ways: through patient interview, from physician's diagnoses obtained at clinical examination and by reviewing hospital discharge diagnoses. The latter were obtained from the computerised inpatient register that covers all hospitals in the area of Stockholm back to 1969. This register includes main diagnoses and up to five secondary diagnoses from all occasions when a person has been admitted to hospitals. The diagnoses are coded according the International Classification of Disease, 9th edition (ICD-9)

DEMENTIA DIAGNOSIS

The DSM III-R criteria were used for the diagnosis of Alzheimer's disease and other types of dementia. The same three-step diagnostic procedure used at the baseline examination was employed in all phases of the project.[109]

SELF-REPORTED SYMPTOMS

In the second follow-up the participants were asked about eight different symptoms, each of which could be answered by "yes", "no", or "do not know/cannot answer". In Study V we have considered five of these self-reported symptoms that may reflect side effects of antidepressant and anxiolytic drugs: vertigo/dizziness, dry mouth, constipation, often tired, shortness of breath, bronchial problems and swollen legs. We also included self-reported symptoms from Katz ADL, about involuntary urination and urine leakage, and information about tendency to fall from patient examination.

PSYCHIATRIC EVALUATION

A psychiatric evaluation was made at physician examination (participant) and nurse interview (informant), using the Comprehensive Psychopathological Rating Scale (CPRS).[110, 111] The CPRS is a structured instrument including both questions and observations, measuring a wide range of psychiatric signs and symptoms on 6-point scale. A score of 2 or more indicates significant pathology. For comparing psychiatric symptoms for patients who were using antidepressants and anxiolytics, the CPRS symptoms were divided according to their characteristics with regard to depression and anxiety.

STATISTICAL ANALYSIS

We used the computer program SPSS for Macintosh (Study I) and SPSS for Windows (study II-V) for the analyses. The χ^2 test with Pearson analysis was used for analysing differences in frequencies, for example drug use. Independent samples t-test was used for univariate analysis of differences in blood pressure (Study I) and HbA1c (Study III).

For multivariate analysis we used logistic regression. Age, sex, housing were adjusted for in all these analyses. Age was treated as a continuous variable. Housing was classified into three levels: 1-own home, either owned or rented; 2-sheltered accommodation (individual apartments with access to communal facilities with a professional but not medically-skilled caregiver); and 3-institution, consisting of nursing homes and geriatric wards.

Study I

For comparison of blood pressure in men and women independent samples t-test was used. The statistical relation between age and blood pressure was assessed by means of bivariate correlation, using the Pearson correlation coefficient. Logistic regression was used for comparing blood pressure between users and non-users, taking other variables into account. In this analysis, which requires that the dependent variable be dichotomous, we examined the prevalence of blood pressure above and below a cut-off point at the lower 10th percentile of the values in the study population, which was 125 mm Hg for systolic pressure and 65 mm Hg for diastolic pressure. In the first step, age, gender and housing were adjusted for (model 1). In the following analyses we added, respectively: dementia status (model 2), cardiovascular diseases [coronary heart disease, cardiac arrhythmia, heart failure, or stroke] (model 3), low BMI (model 4) and dehydration (model 5). In model 4, housing was not included, because there was a very strong correlation between BMI and different types of housing.

Study II

Logistic regression was used for analysing differences in sodium and potassium levels with respect to age, sex and housing, as well as for comparisons between users and non-users of the drugs. In the latter analyses we adjusted for several possible confounders. In the first step we controlled for age, sex, housing. In the second step we added one of the following confounders: heart disease, cerebrovascular disease (CVD), hypothyreoidism (TSH>4.0 μU/L), leukocytosis (LPK>9.8x10^9/L), hyperglycaemia (glucose>6.1 mmol/l), hypoalbuminemia (albumin<40g/L), decreased renal function (C_E<75 ml/min), low BMI (<20 kg/m^2, malnutrition) and dementia. In the analysis of the association between drug use and hyponatremia we adjusted for heart disease, impaired renal function, hypothyreoidism, hyperglycaemia and hypoalbuminemia. The analysis of hypernatremia was adjusted for cerebrovascular disease, dementia, impaired

renal function and hyperglycaemia. For hypokalaemia we controlled for heart disease, anaemia and low BMI. For hyperkalemia hyperglycaemia, leukocytosis and impaired renal function was accounted for. In all these analysis we also adjusted for concurrent use of other medications showing significant association in first analysis.

Study III

Independent samples t-test was carried out in order to compare the HbA1c levels between men and women and between users and non-users of the studied drugs. Logistic regression was used for analysing the association between hyperglycemia and drug use. The results were adjusted for age, housing level, hypokalemia (K^+<3,5 mmol/l) high BMI (BMI >20 kg/m^2), hyperthyroidism (TSH <0.4 mU/L), increased SR (inflammatory processes, SR>20), hypercalcemia (Ca^{2+}>2.6 mmol/l) and for other drugs with potential hyperglycemic effects. In the final analysis hypertension and congestive heart failure were included in the model.

Study IV

Descriptive statistics were carried out. Data were presented as means and standard deviation (SD), numbers or proportions.

Study V

Frequencies of drug use and mean number of drugs by demographic factors with 95% confidence intervals (CI) were calculated. Logistic regression was used to analyse the associations between symptoms and use of drugs or drug groups. Age, sex, type of housing, civil status and concurrent antidepressant or anxiolytic drug use were controlled for in all models. Some analyses were also adjusted for cognitive status (MMSE) and diagnosis of heart disease.

ETHICAL CONSIDERATIONS

The five studies included in this thesis covered the data collected from baseline to 3rd follow-up of the Kungsholmen project. For each phase of the project approval from the Ethical Committee of the Karolinska Institutet was obtained.

Study I	Dnr: 87:148; Dnr.87:234
Study II	Dnr: 87:148; Dnr.87:234
Study III	Dnr: 94:122
Study IV	Dnr: 87:148; Dnr.87:234; 90:251; 94:122; 97:413
Study V	Dnr: 97:413

Informed consent was obtained from all participants or next-of-kin for demented subjects, after details of the procedure were fully explained.

In addition all researchers working with the Kungsholmen project database have followed the guidelines of the Swedish Council for research in the Humanities and Social Sciences (HSFR)[112] the principles of autonomy and integrity, the rule of consent and the demand for research.

RESULTS

STUDY I

We defined low blood pressure as a pressure below the 10th percentile of the values of the study population – 125 mm Hg for systolic and 65 mm Hg for diastiolic blood pressure.[106] There were 157 persons with low systolic blood pressure. Within this group 103 (66%) individuals were using drugs with potential hypotensive effects. Low diastolic blood pressure was found in 124 subjects and among these 77 individuals (62%) were taking medicines with potential hypotensive effects. There were no gender differences, but a negative correlation between age and blood pressure, systolic as well as diastolic, in both men and women.

The association between drug use and low blood pressure was examined for drugs with known potential hypotensive effects. Of these six were significantly associated with low blood pressure in a logistic regression model controlling for age, sex and housing. In the following models adjusting for dementia status, cardiovascular disease, low BMI and dehydration, a significant association remained between low systolic blood pressure and potassium-sparing agents, dopaminergic antiparkinsonian drugs, and butyrophenone neuroleptics and between between low diastolic blood pressure and dopaminergic antiparkinsonian drugs (Table 7).

Table 7. Drugs showing significant association with low systolic or diastolic blood pressure in a logistic regression model adjusted for age, sex and housing.

Drug group	ATC	n	Effects on blood pressure		Comment
			Systolic	Diastolic	
Loop diuretics	C03C	299	→	↓	Not significant adjusting for cardiovascular disease, low BMI and dehydration
Potassium-sparing diuretics	C03D	108	↓	→	Significant in all models
Calcium antagonists	C08	153	→	↓	Not significant adjusting for cardiovascular disease
ACE-inhibitors	C09A	8	→	↓	Not significant adjusting for cardiovascular disease
Dopaminergic antiparkinsonian drugs	N04B	22	↓	↓	Significant in all models
Butyrophenone derivatives	N05AD	43	↓	↓	No significant association with diastolic blood pressure adjusting for dementia, low BMI and dehydration

STUDY II

In the study population of 1558 subjects the mean sodium level was 139±2.6 mmol/l, and the mean potassium level 4.2±0.4 mmol/l. There were 154 persons (9.3%) with hyponatremia and 5 persons (0.3%) with hypernatremia. Hypokalaemia was found in 42 (2.5%) and hyperkalaemia was found in 45 subjects (2.7%). Hyponatremia was found more often in women than in men. Hyponatremia, hypokalaemia and hyperkalaemia was more common with increasing age. Hypernatremia was more common in sheltered accommodation and institutions. The prevalence of electrolyte disturbances was generally lower among the 259 individuals who did not use any drugs.

The association with medication was studied for drugs/drug groups with previously documented effects on electrolyte levels (Table 8).

Table 8. Drugs with potential effects on the electrolyte balance, examined in study II.

Antacids	**ACE inhibitors**	Levodopa
Laxatives	Clofibrate	Neuroleptics
Antidiabetics	Corticosteroides	Lithium
Vitamine B$_{12}$	Antibacterials	Anxiolytics
Cardiac glycosides	**Cytostatic drugs**	Hypnotics-sedatives
Diuretics	NSAID	**Antidepressants**
Beta-receptor blockers	Analgesics	Antiasthmatics
Calcium antagonists	**Antiepileptics**	

Drugs for which we found a significant association with disturbed sodium or potassium levels are shown in boldface.

In a logistic regression model adjusting for age, sex, housing and various factors with potential influence on electrolyte balance (see Table 5), including drugs, a number of significant associations were seen. Hyponatremia was found to be associated with the use of carbamazepine, laxatives (enema), diuretics (thiazides, high ceiling diuretics, potassium-sparing diuretics and combination diuretics), and ACE-inhibitors. Among diuretic users 15% had hyponatremia. Hypernatremia was associated with the use of osmotically active laxatives. Hypokalaemia was significantly associated with the use of thiazide related diuretics and combination diuretics, and hyperkalaemia with the use of potassium sparing diuretics, beta-receptor blockers, cytostatic drugs and TCA.

STUDY III

High HbA1c levels (>5.3%) indicating hyperglycemia were seen in 11% of the women and 12% of the men without known diabetes mellitus.

We studied the possible association between high HbA1c-levels and the use of drugs with known potential hyperglycaemic effects, including H_2-receptor antagonists, diuretics, calcium antagonists, glucocorticoids, morphine, phenytoin and β_2-adrenergic receptor agonists. In a logistic regression model adjusting for age, housing and measures of other causes of hyperglycemia, including hypokalaemia, high BMI, hyperthyroidism, inflammation, hypercalcemia and other drugs with potential hyperglycemic effects, the use of loop diuretics was significantly associated with high levels of HbA1c in both women and men. The significance remained even after adjusting for hypertension and congestive heart failure. Eighteen percent of users of loop diuretics had high levels compared with 8% among non-users.

STUDY IV

The estimated creatinine clearance (C_E) declined by an average of 2.2 ml/min/year, from 57 to 35 ml/min, during the ten years between the baseline of the Kungsholmen project (1987-89) and the 3rd follow-up (1997-98). The increase in serum creatinine was much less prominent (Fig. 1).

In relation to this decrease in C_E we investigated the use of drugs that should be avoided or used with caution in patients with renal impairment. For the majority of the examined drugs, including oral antidiabetics, amilorid, NSAID, acetylsalicylic acid, drugs against peptic ulcer, digoxin, ACE-inhibitors, atenolol, allopurinol and citalopram, we observed a successively increasing use during the study period. For some of the medicines, such as digoxin, the daily doses were reduced but in most cases there were no signs of dose reduction. For certain drugs, including NSAID, acetylsalicylic acid, drugs against peptic ulcer, ACE-inhibitors and citalopram, the daily doses even increased.
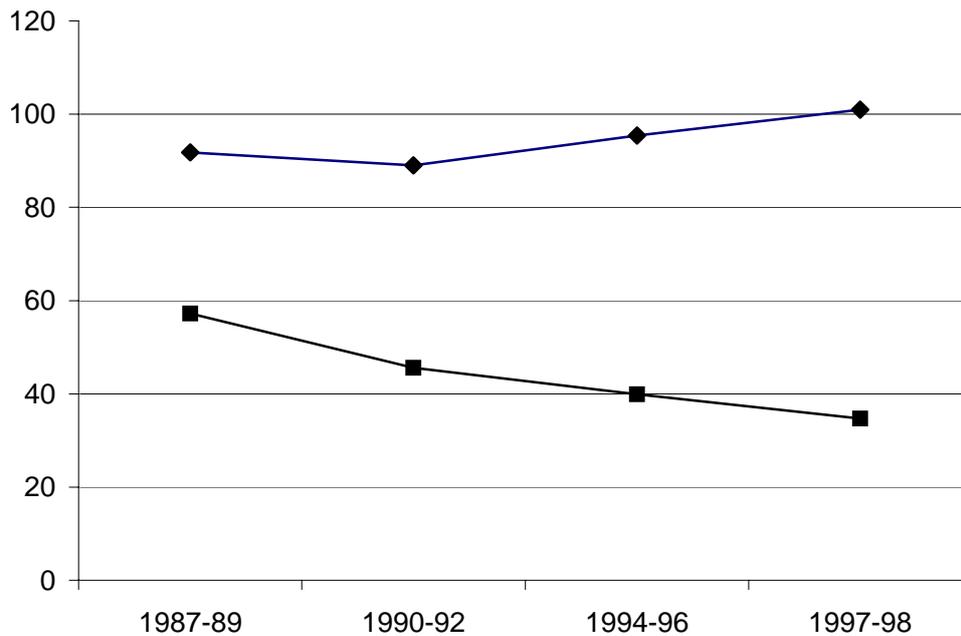
Fig. 1. Changes in serum creatinine (◆) and C_E (■) by age in persons participating in all phases from baseline to 3rd follow-up of the Kungsholmen project.

STUDY V

Elderly persons who used antidepressants and anxiolytics had higher CPRS scores (23.6 and 26.3 respecively) compared to those not using these drugs (17.5). As for the total CPRS score, the score for depressive symptoms was even higher for anxiolytic (7.6) than for antidepressant (6.4) users. We could also establish a significant association between the use of these drugs and some self-reported somatic symptoms. The use of antidepressants was associated with vertigo/dizziness, tendency to fall, involuntary urination, urine leakage, shortness of breath and bronchial problems. The use of anxiolytics was significantly associated with vertigo/dizziness and shortness of breath.

DISCUSSION

This thesis focuses on side effects of drug treatment in a population of very old elderly. We have closely studied the prevalence of low blood pressure, sodium and potassium disturbances and increased levels of HbA1c in relation to regular intake of various medications, drug use in relation to impaired renal function in the elderly and finally, the prevalence of symptoms indicative of undertreatment as well as side effects, in patients using anxiolytic and antidepressant drugs. In this section we shall discuss our main findings and certain methodological issues connected with our research.

METHODOLOGICAL CONSIDERATIONS

We are quite aware that the present studies suffers from some inherent weaknesses. Firstly, the cross-sectional design of study I-III and V does not allow us to prove a causal relationship between drug use and the observed potential side effects, although several conceivable factors were adjusted for in order to minimise for example confounding by indication. Another problem of this design is that the data were gathered only at one time point. As regards drug use this means that we do not know the duration of treatment. The same is true of all other important parameters measured. For example we do not know of variations in blood pressure over time.

Another possible problem is that even though the information on drug use was carefully collected, we cannot rule out the possibility that some subjects forgot to inform us about their exact medication, which would lead to an underestimate of the actual use.

Finally it is important to consider the consequences of studying a selection of the study population. In most cases this would, however, lead to an under estimation of our results. Subjects excluded because of missing data about blood pressure, and various blood parameters, were probably more ill and therefore more sensitive to drug side effects. Likewise, in study IV, the population consisted of all subjects participating in all waves from baseline to 3rd follow-up, thus most likely a more healthy sample.

DRUG USE AND LOW BLOOD PRESSURE IN THE ELDERLY

There are still relatively few studies describing the presence of chronic low blood pressure in elderly persons.[81] Nonetheless, it is known that a low diastolic arterial blood pressure in elderly individuals is associated with an increased risk for cardiovascular diseases due to atherosclerosical processes.[113]

Moreover, a low diastolic blood pressure (below 70 mm Hg) is associated with a higher risk for deveoping dementia in subjects aged over 75 years. The danger of

dementia is mostly pronounced for patients with a chronically low blood pressure.[114] In addition, Patients with dementia often show neurocardiovascular instability, which is a common cause of falls and syncope. Repeated hypotensive episodes aggravated by drug-induced hypotonia may also worsen the cognitive decline in these patients.[115, 116] Hypotension can also produce less serius symptoms such as weakness, dizziness, exthaustion, headache, and drowsiness, thereby affecting the patient's general quality of life. In view of all these effects of hypotension, and since chronic low pressure may even be related with an increased mortality,[117-119] it is an important object of investigation.

Numerous drugs can have hypotensive side effects, but the mechanisms of these effects are difficult to categorise because of their diversity and complicated interactions. Nevertheless, we have tried to summarise them in Table 9. The consequence is often orhostatic reactions but chronic hypotension is probably not uncommon. It has been reported that one sixth of patients with chronic low blood pressure have a drug-induced hypotension.[81]

Our principal finding was the statistical association between the use of potassium-sparing diuretics, dopaminergic antiparkinsonian drugs, and anti-psychotic agents of the butyrophenone type, with low systolic and/or diastolic blood pressure in persons 75 years and older. The association with butyrophenones is of particular interest, since neuroleptics are very commonly used in demented elderly,[55] often without an appropriate indication. At the time of the study the butyrophenone haloperidol was the dominating neuroleptic. Now the use has shifted towards the newer "atypical" neuroleptics, mainly risperidone. However, all neuroleptics have multiple side effects, including hypotension. The dangers with the use of antipsychotic drugs have been discussed in recent studies.[42, 120]

One limitation of this study is that we base our analyses only on single measurements of resting blood pressure. No tests of orthostatic reactions were done. However this has most likely led to an underestimation of the effects of the examined drugs. It is also worth pointing out that our definition of low blood pressure was arbitrary, based on the lower 10th percentile of the blood pressures in the population, since there exists no exact and universal definition of hypotension.

Table 9. Mechanisms of drug induced hypotension.

Mechanism	Drug
Fall in cardiac output, due to direct myocardial depression or to reduced venous return (venodilatation or hypovolemia)	β-blocking agents
Reduction in peripheral vascular resistance	Organic nitrates Sympatholytic drugs Diuretics Calcium antagonists ACE-inhibitors Antiparkinsonian drugs Neuroleptics Tricyclic antidepressants
Miscellanous	Atropine Bromocriptine Disulfiram Metoclopramide Propranolol Salbutamol Simvastatin Terbutaline Vitamin K Antidepressants

ELECTROLYTE DISTURBANCES AND THE USE OF DRUGS

The fluid and electrolyte balance is essential to human life and disturbances in this balance, caused for instance by drug use, may lead to serious consequences.[87, 121, 122] The aim of this study was to investigate to what extent drugs known to influence the electrolyte balance have an impact on the electrolyte levels in very old elderly.

The most common type of electrolyte derangement in our study was hyponatremia, observed in 9.4% of the subjects. Hyponatremia is one of the major problems in geriatric hospitalised patients. In elderly outpatients the preponderance of hyponatremia and the importance of the effect of drug intake on serum sodium concentration are not well known.[123] It is estimated that about 7% of healthy elderly exhibit some degree of hyponatremia. Cross-sectional studies suggest that hyponatremia may be present in 15-18 % of patients in chronic care institutions.[124] Patients who have serum sodium levels above 129 mEq/l are usually asymptomatic.[125]

Hypernatremia, on the other hand, is an uncommon electrolyte disturbance. In our study the incidence was as low as 0.3 %, and similar figures has been reported in other studies.[126] The use of osmotically active laxantives was significantly associated with hypernatremia in our study, but according to other scholars it is difficult to assess this

significance. The hypernatremia should maybe rather be regarded as a component of the dehydration syndrome and an effect of lactulose intake than as an adverse drug reaction.[127]

The second most common electrolyte disturbance in our study was hyperkalaemia, with a frequency of 2.8%. The incidence of hyperkalaemia in the general population has been reported to be less than 5%. Hyperkalaemia in a hospitalised patient is an independent risk factor for death. In one study it was found that 1.4 % of the patients who were hospitalised (406 out of 29,063 patients) developed hyperkalaemia.[128] Our finding that hyperkalaemia was more common than hypokalaemia (2.5%), is confirmed by other studies[84, 88, 129] and may be explained by age-related decrease in GFR, renal acidification defects, and hyporeninemic hypoaldosteronism, in combination with an increased use of drugs that alter the potassium metabolism.

Several studies have shown that electrolyte disturbances are more frequent in women than in men: 21.7 % versus 13 %.[130] In our study this was true of hyponatremia, but otherwise not seen. In general there was a relatively low prevalence of electrolyte disturbances in our study, which can be explained by the fact that the majority of the population were subjects living in their own homes, thus being relatively healthy.

Our main finding was that that even in this population of mostly relatively healthy persons there was a significant correlation between disturbances in the sodium/potassium balance and the use of several types of drugs, including laxatives, diuretics, beta-blockers, ACE inhibitors, cytostatics, carbamazepine and TCA. The prevalence of electrolyte disturbances in nonhospitalised elderly and the importance of the effect of drug intake on serum sodium and potassium concentrations have been little known. However, a number of studies have been published in later years. The most recent have shown that digoxin and lactulose use is associated with lower serum sodium concentrations in the elderly[123], and that carbamazepin may cause hyponatremia [131] in the elderly. In addition, numerous other electrolyte disturbances have been reported in other studies.[130, 132, 88, 89, 133]

A complicating factor commonly encountered in the elderly population is polypharmacy. This may increase the risk of drug-induced changes in electrolytes. It is therefore important to prescribe only indispensable medication, and not to forget to measure sodium and potassium levels regularly.

Table 10. summarises the effects of different drugs on sodium and potassium balance.

Table 10. Mechanisms of some common drug induced electrolyte disturbances.

Drug-induced hyperkalaemia

Transcellular shift	Arginine, β-blockers, cardiac glycosides, chemotherapeutic agents, drug-induced acidosis, suxamethonium
Increased potatissium intake	Potassium penicillin, potassim supplements, salt substitutes
Decreased renal excretion: decreased delivery of sodium to distal tubules – any drug that causes volum depletion, drug-induced renal failure, hypoaldosteronism	ACE-inhibitors, cyclosporin, heparin, NSAID
Decreased tubular secretion of potassium	Potassium-sparing diuretics

Drug-induced hypokalaemia

Increased entry into cells (redistribution)	β-adrenergic agonists, drug-induced metabolic alkalosis, insulin
Increased gastrointestinal losses	Laxative/purgative abuse, vomiting
Increased renal loss	Amphotericin, carbenoxoline, diuretics, drug-induced renal tubular acidosis, gossypol, hypomagnesia, increased mineralocorticoid activitity, steroids, levodopa, licorice, penicillin
Miscellaneus	Flucanozole, haloperidol, ifosfamide/mesna, mitramycin, zimelidine

Drug-induced hyponatremia

Volume depletion, gastointestinal loss, renal salt loss	Carboplatin, cisplatin, diuretics, ketoconazole
Increased production of ADH	Carbamazepine, cyclophosphamide, tricyclic antidepressants, amitryptiline, imipramine, monoamine oxidase inhibitors, haloperidol, phenothiazines, thioridazine, thiothixene, trifluoperazine, bromocriptine, clofibrate, lorcainide, vincristine or vinblastine
Drugs potentiating the action of ADH	Carbamazepine and oxycarbazine, chlorpropamide, tolbutamide, cyclophosphamide,somatostatin, sulphonylureas, ibuprofen, indomethacin, naproxen, propafenone
Exogenous ADH	Oxytocin, vasopressin desmopressin
Shift of water out of the cell	Glycerol, mannitol
Miscellaneus	Captopril, enalapril, irrigation fluids

DRUG USE AND INCREASED HbA1c LEVELS

To our knowledge this is the first study of the association between blood glucose levels and drug use in an elderly population. The main result is a significant association between high levels of HbA1c and use of loop diuretics, suggesting a hyperglycemic effect of these drugs in very elderly persons. The loop diuretics furosemide has been associated with decreased glucose tolerance in several studies.[134-137]

As loop diuretics are among the most common drugs used in the elderly this finding may be clinically important. There are for instance studies that describe higher incidence of coronary artery disease with asymptomatic glucose intolerance,[138-140] and higher coronary heart disease mortality in patients with glucose intolerance than in normal controls.[141] Use of loop diuretics has also been found to aggravate diabetes in patients with known glucose intolerance.[142]

The mechanisms behind the effects of diuretics for developing glucose intolerance consist of hypokalaemia-induced insulin resistance, inhibited release of insulin and decreased glucose uptake.[143-147] These mechanisms are summarised schematically in Fig. 2
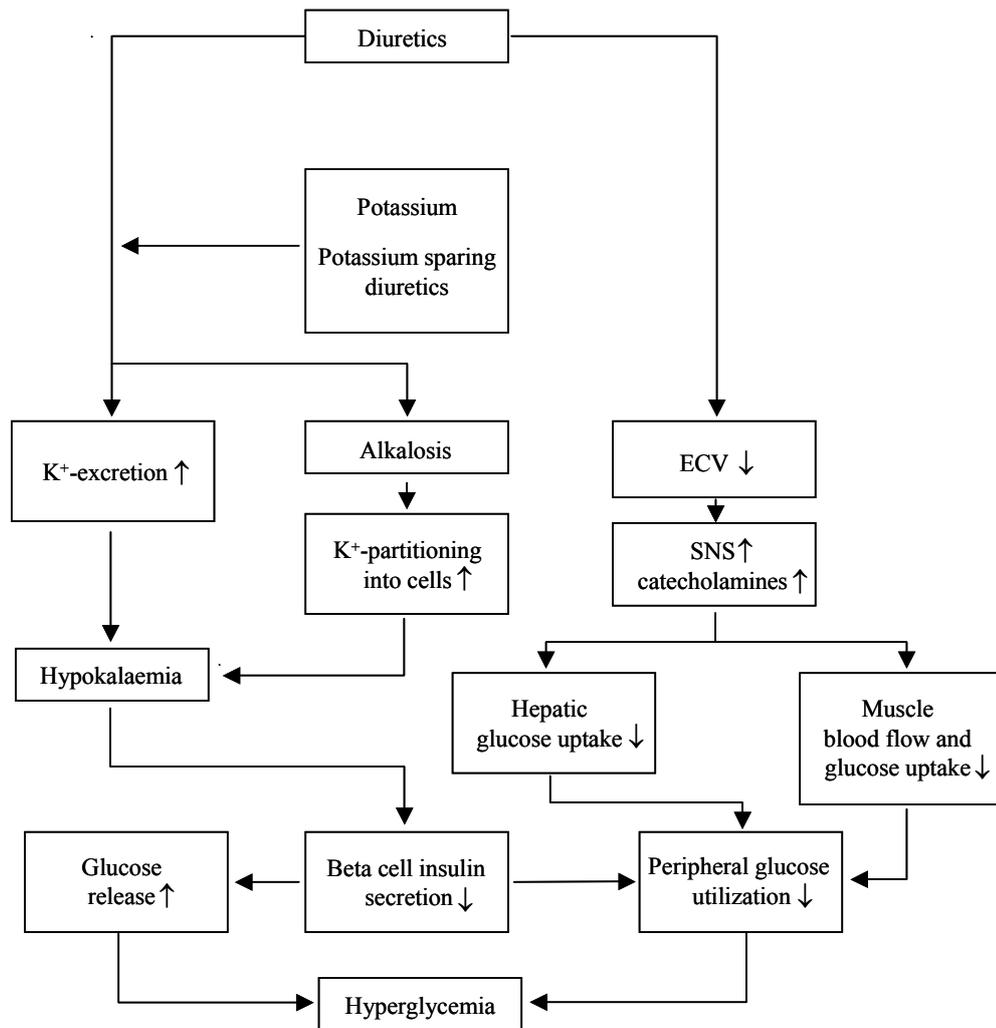
Fig 2. Schematic presentation of some factors contributing to diuretic-induced hyperglycemia (ECV=Extracellular volume, SNS=Sympathetic nervous system).

The main weakness of this study was the low prevalence of diabetes, suggesting that there might be persons with unknown diabetes included in the study population. However, in that case the question is why would there be an overrepresentation of diabetes in users of loop diuretics? We did not find evidence for a selective prescribing of these drugs in elderly with diabetes. Neither could the association between loop diuretic use and high HbA1c levels be explained by hypertension or heart failure in the users.

RENAL FUNCTION AND DRUG USE IN THE ELDERLY

In this longitudinal study we have investigated the decline in renal function with age and the drug use and dosage in connection with this. To our knowledge there are no previous large-scale epidemiological studies on the use of drugs in relation to kidney

function in an elderly population. We found that the GFR decreased on average 2.2 ml/min/year during the 10 year observation period from baseline to third follow-up of the Kungsholmen project. The creatinine levels were increasing, but were still moderate at the latest follow-up (mean value 92 in 1987-89 and 101 in 1997-98). In contrast, we demonstrate that the estimated creatinine clearance (C_E), assessed using the Cockcroft-Gault equation, was well below the reference interval employed for creatinine clearance (Ccr) in adults (90-139 ml/min per 1.73 m^2 in men and 80-125 ml/min per 1.73 m^2 in women[148]) The prevalence of renal impairment (<50 ml/min) in this study using C_E as the criterion was 33 % at baseline and 93% at third follow up.

The most interesting finding of our study is that there was a continuous increase in the use of many drugs that should be avoided or used with caution in patients with renal impairment, with increasing age of the population and decreasing C_E. The fact that drug consumption grows with increasing age is in itself not remarkable.[58, 59] However, here we are dealing with drugs that may cause serious side-effects if the elimination is decreased due to impaired renal excretion. In addition, we observed that for many of these drugs the average daily dose was unchanged or even increased with increasing age of the study population. Table 11 lists recommended dosage guidelines for some common drugs based on creatinine clearance.

We chose to estimate the renal function by means of glomerular filtration rates (GFR) measured by creatinine clearance estimated using the Cockcroft-Gault equation.[105] There has lately appeared a number of articles indicating that S-cystatine are among the best instruments for determining the GFR level.[149] We would like to point out that when the data for this study were collected this analysis was not yet available. In addition, some findings[150] suggest that S-cystatine may not be more sensitive than creatinine clearance computed by means of the Cockcroft-Gault equation. Moreover, even though S-cystatin is increasingly being used for estimations of renal function, its large intraindividual variability makes its practical value rather limited[151]

Some recent studies[152] conclude that it is indeed motivated to control the renal function extra carefully in elderly patients. For instance, one of the most recent studies[153] investigating patients 70 years and over, found that only 2% of the participants had normal renal function (GFR >90 ml/min), 13% had light (GFR 60-89 ml/min), 68% moderate (GFR 30-59 ml/min), and 17% severe (GFR 15-29 ml/min) impairment in GFR. Moderate or severely decreased GFR was observed in 75% of the outpatients, 78% of the patients from the geriatric ward, and 91% of the nursing home patients.

Our results regarding inappropriate drug use in renal impairment have also been confirmed by other studies. For instance, Cantu et al,[154] describe that out of 60 patients

with renal dysfunction for whom a renally eliminated drug was prescribed as many as 27 (45%) were receiving dosages in excess of the manufacturer's recommendations.

There are also several studies indicating that even a low dose of acetylsalicylic acid may produce an impairment of the renal function in elderly.[155, 156] Our study clearly shows that there is a notable increase in the number of users of low dose acetylsalicylic acid medications.

Table 11. Recommended dosage guidelines based on creatinine clearance (ml/min) (Modified from Papaioannou et al 2000[157])

Drug	Creatinine clearance	Dose/interval
Allopurinol	>80	50 mg q24h
	60-79	200 mg q24h
	40-59	150 mg q24h
	20-39	100 mg q24h
	10-19	100 mg q48h
	0-9	100 mg q72h
Atenolol	15-35	50 mg q24h
	<15	50 mg q48h
Captopril	10-50	18,75 mg q12h
	<10	12,5 mg q24h
Enalapril	<50	40 mg q24h
Famotidine	<10	20 mg q 24h
Hydrochlorothiazide	<30	Avoid
Lisinopril	<50	40 mg q24h
Metformin	10-50	425 mg q24h
	<10	Avoid
Nitrofurantoin	<10	Avoid
Perindopril	10-50	1,5 mg q24h
	<10	1 mg q24h
Quinapril	<50	40 mg q24h
Ramipril	10-50	15 mg q24h
	<10	10 mg q24h
Ranitidine	<50	150 mg q24h
Spironolactone	10-50	25 mg q24h
	<10	Avoid

THE USE OF ANTIDEPRESSANTS AND ANXIOLYTICS AND SELF-REPORTED SYMPTOMS

The findings of this study both show evidence of undertreatment of depression and side effects of its pharmacological treatment. Firstly, patients treated with antidepressants still showed a rather high total CPRS score as well as score for depression symptoms, suggesting an unsatisfactory effect of these drugs. This is in line with other studies.[158-161] However, other explanations, for example non-compliance cannot be ruled out. In addition, the CPRS scores were higher for persons using anxiolytics than for those using antidepressants, indicating that depression was sometimes treated with anxiolytic instead of antidepressant drugs. Similar results regarding depression were obtained in other studies.[76, 162]

Secondly, the use of antidepressants (SSRI) was significantly correlated with certain symptoms such as vertigo/dizziness, tendency to fall and involuntary urination. The use of anxiety drugs was significantly correlated with vertigo/dizziness and shortness of breath. There are several recent studies describing serious side-effects from the use of SSRI drugs. For example, one study[95] found TCAs and SSRIs to be comparable in increasing elderly patients' risk for falling. The elderly patients receiving SSRIs had 80% more falls than matched patients not receiving antidepressants. Whatever its cause, urinary incontinence is a medical condition that seriously affects the quality of life. In our study have we have found that effects of SSRIs are associated with an increased risk for developing urinary incontinence, which can be explained pharmacologically. Other studies have arrived at similar results.[96, 133]

Table 12. Overview of studies showing evidence of overtreatment and undertreatment with antidepressant drugs

Undertreatment	Overtreatment
Fisher et al., 2003[158]	Fastbom & Schmidt 2003[163]
al-Hihi E et al., 2003[159]	Ulfvarson et al., 2003[164]
Goldstein 2002[160]	
Brown et al., 2002[161]	
Mecocci et al., 2004[162]	

CONCLUSIONS

- Potassium-sparing diuretics, dopaminergic antiparkinsonian drugs and butyrophenone neuroleptics can cause low blood pressure in the elderly.

- Loop diuretics may have hyperglycemic effects in the elderly.

- Disturbances in the sodium/potassium balance are fairly common. Several types of drugs are associated with these disturbances, including laxatives, ACE inhibitors, diuretics, β-blockers, cytostatics, carbamazepine and tricyclic antidepressants.

- The use of drugs that should be prescribed with caution or even avoided with reduced renal functions, is in fact very widespread. In general the renal function in not taken into account when these drugs are being prescribed to elderly patients.

- Elderly using antidepressants may have an inefficient antidepressant effect of these drugs. Depression in the elderly may be inappropriately treated with anxiolytics. There are also signs of side effects from SSRI, of which for example falling tendency and micturition dysfunction have been recently pointed out in the literature.

ACKNOWLEDGEMENTS

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APPENDIX

DISSERTATIONS FROM THE DIVISION OF GERIATRIC EPIDEMIOLOGY AND MEDICINE, DEPARTMENT OF NEUROTEC, KAROLINSKA INSTITUTET, 1998–2005

1998

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

Alyaa Mohammed Ali Mousa. In vitro studies on human first trimester forebrain cells: Differentiation and interactions with immunoregulating molecules.

Bogdanovic Nenad. Towards a multifaceted approach in neuropathological diagnosis.

Fagerberg Ingegerd. Nursing students' narrated, lived experiences of caring, education and the transition into nursing, focusing on care of the elderly.

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

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

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

Palo-Bengtsson Liisa. Dancing as a nursing intervention in the care of persons with dementia. (Licentiate thesis).

Pei Jin-Jing. Protein phosphatases and kinases implicated in Alzheimer's disease abnormal tau phosphorylation.

Tham Kerstin. Unilateral neglect: Aspects of rehabilitation from an occupational therapy perspective.

Torasdotter Marita. A Role of neurotrophins in brain plasticity. (Licentiate thesis).

1999

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

Axelman Karin. Clinical, genetic and genealogical investigations of familial Alzheimer's disease. (Licentiate thesis).

Bonkale Willy Lokwa. Cyclic nucleotide signalling in Alzheimer's disease postmortem brain.

Elffors Lars. Hip fractures – A European perspective.

Jelic Vesna. Focus on quantitative EEG in relation to genetic, biochemical and neuroimaging markers.

Jensen Malene. Amyloid β-peptide and tau the diagnosis and pathogenesis of Alzheimer's disease.

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

Sonde Lars. Low-TENS treatment on post-stroke paretic arm. (Licentiate thesis).

von Euler Mia. Experimental spinal cord injuries – a histopathological, neurogical, and pharmacological study in the rat.

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

Zou Li-Ping. Immunoregulation and immunotherapy in experimental autoimmune neuritis.

2000

Andreasen Niels. Search for reliable diagnostic markers for Alzheimer's Disease.

Ebbeskog Britt. Elderly people's daily living with chronic leg ulcer: Evidence and suffering experience. (Licentiate thesis, in collaboration with the Department of Science and Health, University of Karlskrona/Ronneby, Sweden).

Emami Azita. "We are deaf, though we hear; we are dumb, though we talk; we are blind, though we see". Understanding Iranian late-in-life immigrants. Perceptions and experiences of health, illness and culturally appropriate care.

Eriksson Charlotta. Region-specific expression of the interleukin-1 system in rat brain following endotoxin challenge and excitotoxic neurodegeneration.

Hansebo Görel. Assessment of patients' needs and resources as a basis in supervision for individualised nursing care in nursing home wards.

Herzberg Annika. Relatives' and nursing home staff's experiences of and views on each others. (Licentiate thesis).

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

Jonsson Hans. Anticipating, experiencing and valuing the process from worker to retiree. A longitudinal study of retirement as an occupational transition.

Kumlien Suzanne. "Nursing care after stroke". (Licentiate thesis).

Lilja Margareta. Elderly disabled persons in the home setting. Aspects of activities in daily life.

Nilsson Margareta. Understanding the meaning of past, present and future in advanced age. Very old persons' experiences of ageing.

Palo-Bengtsson Liisa. Social dancing as a caregiver intervention in the care of persons with dementia.

Pham Therese. Effects of neonatal handling and enriched environment of neurotrophins and cognitive function.

Robinson Petra. Younger persons with suspected and early stage dementia: Their experiences, concerns and need for support. (Licentiate thesis).

Skog Margareta. Teaching for learning and learning for teaching in care of elderly with dementia at Silviahemmet.

Sunvisson Helena. Att beskriva och utvärdera betydelsen av interventionsprogram riktade till personer med Parkinson sjukdom för skapande av nya möjligheter att hantera vardagen. (Licentiate thesis).

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

2001

Abbas Ahmed Gadeh El Dum Nagat. Pharmacological and immunological modulation/ manipulation of cytokine and chemokine production in experimental autoimmune neuritis (EAN), a model of inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome). (Licentiate thesis).

Froelich Fabre Susanne. Genetic studies of frontotemporal dementia.

Ingelson Martin. Molecular aspects of tau proteins in Alzheimer's disease and frontotemporal dementia.

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

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

Sennvik Kristina. A study of the β-secretase cleavage of Alzheimer amyloid precursor protein. (Licentiate thesis).

Sonde Lars. Rehabilitation after stroke. Effects of length of stay and treatments to facilitate motor recovery after stroke.

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

Vestling Monika. Alzheimer's disease mutations and cellular signalling.

2002

Andersen N Christian. On characterisation and diagnosis of frontotemporal lobar degeneration syndromes. With special reference to the progressive aphasias.

Cedazo-Minguez Angel. Apolipoprotein E and Alzheimer's disease: Signals and effects.

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

Flood Fiona. Expression studies on the Alzheimer's disease related presenilin and APP genes during development and ageing. (Licentiate thesis).

Garcia-Jiménez Angela. G-proteins and adenylyl cyclase in Alzheimer's disease postmortem brain.

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

Hemmingsson Helena. Student-environment fit for students with physical disabilities.

Herzberg Annika. We, not them and us – a utopia? Relatives' and nursing home staffs' views on and experiences with each other.

Lindau Maria. Clinical differentiation between frontotemporal dementia and Alzheimer's disease.

Nilsberth Camilla. Distribution and pathophysiological role of amyloid precursor protein and presenilin 1.

Randers Ingrid. Upholding older adults' innate and inherent dignity within a caring context.

Sennvik Kristina. A study of β-secretase cleaved Alzheimer amyloid precursor protein.

2003

Abbas Ahmed N. Immunomodulation of cytokine and chemokine production in animal models of neuroinflammatory and neurodegenerative disorders.

Bao Lei. Immunmodulation and immunopathogenesis in the autoimmune disease with emphasis on autoimmune neuritis and arthritis.

Ebbeskog Britt. Elderly patients with slow-healing-leg ulcers.

Götell Eva. Singing, background music and music-events in the communications between persons with dementia and their caregivers.

Huang Chaorui. Mild cognitive impairment: Neuroimaging markers for early diagnosis of dementia.

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

Lundberg Catarina. Older drivers with cognitive impairments: Issues of detection and assessment.

Mulugeta E. Muscarinic M1 and M4 receptor subtypes in normal and pathological conditions in the central nervous system: Studies on human and animal tissues using subtype selective ligands.

Saletti Anja. Nutritional status in elderly receiving municipal services and care. (Licentiate thesis)

Sunvisson Helena. The embodied experience of living with Parkinson's disease.

Zhu Yu. Immunoregulation of experimental autoimmune neuritis focuses on cell immunity.

2004

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

Chen Zhiguo. Excitotoxic neurodegeneration in mouse brain. Roles of immune cells and cytokines

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

Kostyszyn Beata. Studies of presenilin function in neurodegeneration and in human embryonic CNS during development

Popescu Bogdan O. Cell death and signal transduction pathways in Alzheimer's disease: The role of presenilin 1

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

Palmer Katie. Early detection of Alzheimer's disease and dementia in the general population**.**

Ödlund Olin Ann. Nutritional and functional effects of energy-dense food in the frail elderly.

Flood Fiona. Alzheimer's disease-related amyloid precursor protein and presenilin genes: Normal function and pathophysiology.

Laudon Hanna. Functional domains in the Alzheimer's disease-associated presenilin 1 protein.

El-Bakri Nahid Karrar. Estrogen effects on different neurotransmitters in rat hippocampus: Implications for cognitive function.

2005

Adikari Sanjaya. Cytokine-modulated dendritic cell immunotherapy in autoimmune diseases.

Larsson Mauleon Annika. Care for the elderly – a challenge in the anaesthesia context.

Häggström Elisabeth. Municipal care for older people – experiences narrated by caregivers and relatives.

Kihlgren Annica. Older patients in transition – from home care towards emergency care.

PAPERS I-V