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Pasi Lampela

Improving Pharmacotherapy in Older People

a Clinical Approach

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PASI LAMPELA

Improving Pharmacotherapy in Older People – a Clinical Approach

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ABSTRACT

The share of older persons is increasing, as people live longer. However, although age correlates with comorbidity and disability, there is a marked heterogeneity among older age groups in the level of clinical, functional, and social impairment, with individuals on a spectrum from fit to frail. In addition, the response to medication can vary among older persons due to age-associated changes the body and comorbid diseases. However, there is rather limited information about effects of different medicines in this age group, as medicines are generally evaluated in younger age groups. Therefore, an individualized assessment of an older person's health status including assessment of his/her medication is essential.

This thesis aimed to analyze the effect of comprehensive geriatric assessment (CGA), and especially the impact of a medication assessment in individuals aged ≥75 years focusing especially on (I) the disparity on recognizion of adverse drug reactions (ADRs) by patients and their physician, (II) the anticholinergic adverse effects, and the effect of CGA on (III) drug use and (IV) orthostatic hypotension.

The data used in this study is derived from the Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) study. GeMS was a prospective population-based, randomized comparative study that took place in 2004-2007 in Kuopio, Finland. The participants of the study (n=1000) were randomized to intervention (n=500) and control (n=500) groups. All participants were interviewed annually by trained nurses and subjected to blood pressure measurements and blood tests. In addition, those in the intervention group underwent an annual CGA including physician's examination with medication assessment, physiotherapist's counselling and a nutritionist's appointment if needed.

At baseline, there was a great disparity between the patients and their physician in the recognition of ADRs. The physicians identified ADRs in 24 % of the patients, while only 11 % of the patients reported ADRs. When potential anticholinergic ADRs were studied, there was no association between the serum anticholinergic activity (SAA) and potential ADRs (vision, saliva secretion, cognition, mood, physical function). Furthermore, when the SAA was compared with scores from three ranked anticholinergic lists (Carnahan's, Chew's and Rudolph's), only the list of Chew's was associated with SAA. However, there was an association with potential ADRs and the ranked anticholinergic lists. The CGA did not decrease the number of drugs in use over a one-year period, although the numbers of inappropriate drugs decreased, and in addition drug therapy became more rational. The prevalence of orthostatic hypotension decreased as result of repeated interventions.

In conclusion, a CGA with medication assessment has the potential to improve the health of older persons. It should be tailored individually for each person.

National Library of Medine Classification: WT 30, WT 166, QV 56, WG 340
Medical Subject Headings: Geriatric Assessment; Drug Therapy; Pharmaceutical Preparations/adverse effects; Hypotension, Orthostatic; Cholinergic Antagonists; Aged

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TIIVISTELMÄ

Eliniän pidentyessä ikääntyneiden osuus väestöstä kasvaa. Vaikka ikääntyminen onkin yhteydessä lisääntyneeseen sairastavuuteen ja toimintakyvyn rajoituksiin, iäkkäiden terveydentila vaihtelee terveistä monisairaisiin. Lääkkeiden käyttö ikääntyneillä on yleistä, ja lääkkeiden vaikutukset voivat vaihdella suuresti ikääntymiseen liittyvien fyysisten muutosten ja monien sairauksien vuoksi. Lääketutkimukset tehdään kuitenkin useimmiten nuoremmissa ikäryhmissä, joten tietoa lääkkeiden vaikutuksista ikääntyneillä on vain rajoitetusti. Tämän vuoksi iäkkään voinnin yksilöllinen yleisarvio, johon kuuluu kriittinen lääkityksen kokonaisarvio, on oleellinen.

Tässä väitöstutkimuksessa tutkittiin ikääntyneiden terveyden ja toimintakyvyn laaja-alaisen arvioinnin (CGA) ja erityisesti siihen kuuluvan lääkityksen kokonaisarvion vaikutuksia yli 75-vuotiaiden terveydentilaan. Tutkimuksessa keskityttiin erityisesti (I) eroavaisuuksiin lääkkeiden haittavaikutusten (ADR) tunnistamisessa potilaan ja lääkärin välillä, (II) lääkkeiden antikolinergisiin haittavaikutuksiin sekä CGA:n vaikutukseen (III) lääkkeiden käytössä sekä (IV) ortostaattisen hypotension esiintyvyyteen.

Väitöskirjassa analysoitiin HHS (Hyvän Hoidon Strategia) -tutkimuksen tuloksia. HHS-tutkimus toteutettiin Kuopiossa vuosina 2004-2007. Siihen kuuluneet 1000 yli 75-vuotiasta henkilöä satunaistettiin interventio- ja kontrolliryhmiin (molempien ryhmien n=500). Kaikki tutkimukseen osallistuneet kävivät vuosittain hoitajien vastaanotolla, jossa heidät haastateltiin strukturoidun kysymyslomakkeen avulla. Heiltä mitattiin lisäksi verenpaine ja otettiin verikokeita. Interventioryhmän jäsenet osallistuivat lisäksi CGA:an, johon kuuluivat lääkärin tutkimus sekä lääkehoidon arviointi, fysioterapeutin ohjaus sekä ravitsemusterapeutin antama ohjaus tarvittaessa.

Lähtötilanteessa potilaiden ja lääkärin näkemykset potilailla ilmenevistä ADR:sta poikkesivat suuresti toisistaan. Lääkärit havaitsivat ADR:a 24 %:lla potilaista, kun taas ainoastaan 11 % potilaista kertoi haitoista. Mahdollisilla antikolinergisillä haittavaikutuksilla (näöntarkkuus, syljeneritys, kognitio, mieliala, fyysinen toimintakyky) ei ollut yhteyttä potilaiden seerumista mitattuun antikolinergiseen aktiivisuuteen (SAA). Verrattaessa SAA-tuloksia kolmeen lääkeaineita antikolinergisyyden mukaan luokittelevaan listaan (Carnahanin, Chew'n ja Rudolphin) ainoastaan Chew'n lista korreloi SAA-tulosten kanssa. Nämä listat korreloivat kuitenkin mahdollisten antikolinergisten haittavaikutusten kanssa. CGA ei vähentänyt käytössä olevien lääkkeiden määrää vuoden seuranta-aikana, mutta lääkehoito muuttui rationaalisemmaksi sopimattomien lääkkeiden määrän vähentyessä. Vuosittaiset CGA:t laskivat ortostaattisen hypotension prevalenssia.

Yhteenvetona voidaan todeta, että CGA, johon kuuluu lääkityksen arviointi, voi parantaa iäkkäiden terveydentilaa. CGA pitäisi aina toteuttaa yksilöllisesti.

Luokitus: WT 30, WT 166, QV 56, WG 340
Yleinen suomalainen asiasanasto: terveys; terveydentila; toimintakyky; lääkkeet; lääkehoito; haitat; sivuvaikutukset; ortostaattinen hypotensio; antikolinergit; ikääntyneet

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Kuopio, May 2013

Pasi Lampela

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List of the original publications

This dissertation is based on the following original publications, referred to in the text by Roman numerals I-IV.

I Lampela P, Hartikainen S, Sulkava R, Huupponen R. Adverse drug effects in elderly people – a disparity between clinical examination and adverse effects self-reported by the patient. *European Journal of Clinical Pharmacology 63: 509-515, 2007.*

II Lampela P, Lavikainen P, Garcia-Horsman JA, Bell JS, Huupponen R, Hartikainen S. Anticholinergic drug use, serum anticholinergic activity, and adverse drug events among older people: a population-based study. *Drugs & Aging 30: 321-330, 2013.*

III Lampela P, Hartikainen S, Lavikainen P, Sulkava R, Huupponen R. Effects of medication assessment as part of a comprehensive geriatric assessment on drug use over a 1-year period: a population-based intervention study. *Drugs & Aging 27: 507-521, 2010.*

IV Lampela P, Lavikainen P, Huupponen R, Leskinen E, Hartikainen S. Comprehensive geriatric assessment decreases prevalence of orthostatic hypotension in older persons. *Scandinavian Journal of Public Health 41: 351-358, 2013*.

The publications were adapted with the permission of the copyright owners. In addition, some unpublished data are presented.

Contents

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Abbreviations

ACBS	anticholinergic cognitive burden scale
ACE	angiotensin converting enzyme
AD	Alzheimer's disease
ADE	adverse drug event/effect
ADL	activities of daily living
ADR	adverse drug reaction
ADS	anticholinergic drug scale
ANOVA	analysis of variance
ARS	anticholinergic risk scale
ATC	anatomic therapeutic chemical classification system
BP	blood pressure
CGA	comprehensive geriatric assessment
ChEI	cholinesterase inhibitor
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CYP	cytochrome P450
DBI	drug burden index
GABA	gamma-aminobutyric acid
GDS	geriatric depression scale
GeMS	geriatric multidisciplinary strategy for the good care of the elderly
GEM	geriatric evaluation and management
GFR	glomerular filtration rate
IADL	instrumental activities of daily living
LMM	latent Markov model
MAI	medication appropriateness index
MCI	mild cognitive impairment
MDRD	modification of diet in renal disease
MMSE	mini mental state examination
MNA	mini nutritional assessment
OH	orthostatic hypotension
OR	odds ratio
QNB	^{3}H-quinuclidinyl benzylate
RR	risk ratio
SAA	serum anticholinergic activity
START	screening tool of alert doctors to the right treatment
STOPP	screening tool of older person's potentially inappropriate prescriptions
TUG	timed up and go
WAIS	Wechsler adult intelligence scale

1 Introduction

The share of aged people increases in the world. In 2010 approximately 7.6 % of the world population was aged ≥65 years (in the developed countries their share of the total population was 14.9 %, but in the developing countries only 5.8 %), and their share is estimated to increase to 16 % in 2050 (Stegemann et al. 2010). In Finland, their share is even higher, as 17.5 % of the total population of Finland was over 65 years at the end of 2010 (Eurostat 2012), and the number of persons aged 80 years or more was 255 912. It is predicted that in the year 2060 the share of people living in Finland aged ≥65 years will have increased up to 29 % (1.79 million), and there will be a population of 463 000 persons aged ≥85 years (Official Statistics of Finland 2009).

The age segment defined as older persons generally refers to people aged 65 years and over. Aging is however a heterogenous and individual process (Cho et al. 2011). There is a extensive heterogeneity among the age groups in the level of clinical, functional and social impairment. However, it has been noted that comorbidity and disability correlate with age (the likelihood of being frail increases with age), and it is therefore sometimes helpful to consider three different patient groups: the young-old (65-74 years), the old-old (75-84 years) and the oldest-old (≥85 years) (Bernabei et al. 2000).

There are a number of medical conditions that are more prevalent among the older persons, e.g. cardiovascular diseases (hypertension, heart failure, coronary heart disease, myocardial infarction, stroke, peripheral arterial disease, atrial fibrillation), dementia, Parkinson's disease, depression, arthritis, diabetes, gastroesophageal reflux disease, anemia, and thyroid disease (Yazdanyar and Newman 2009, Khangura and Goodlin 2011, Logan 2011, Riley and Manning 2011, Moore et al. 2012). In addition, comorbidities are common, and these factors are often followed by chronic drug therapy and polypharmacy imposing the challenges to their rational treatment.

Older persons are vulnerable to adverse drug reactions, which are considered a potential cause of falls and the resulting hip fractures, as well as confusion and cognitive impairments, urticaria, dementia, excitation, dehydration and hypotension (Stegemann et al. 2010). However, older people, especially those who are frail, are underrepresented in clinical drug trials (McLachlan et al. 2009), and therefore there is a paucity of reliable information about the pros and cons of many drugs in older persons. In addition, older persons are more susceptible to adverse effects and drug interactions and these are more likely to occur in patients who would not be suitable for inclusion in regulatory trials (Brodie 2001). The heterogeneity in outcomes in older persons with differing comorbidity profiles emphasizes the need to provide them with individualized information about the benefits and harms of different diagnostic and treatment strategies (Fraenkel and Fried 2010).

2 Review of the Literature

2.1 CHANGES IN AGING BODY

Aging is associated with a high degree of both intrapatient and interpatient variability in drug response as a result of age-associated changes in organ function and body composition, impairing homeostatic reserve and the risk of comorbid diseases. However, chronological age as such is a poor predictor of variability in responses to medicines (McLachlan et al. 2009). These variations are a result of age-related changes in homeostasis, pharmacokinetics and pharmacodynamics.

2.1.1 Homeostasis

Homeostasis is the ability of a living organism to control its internal environment despite fluctuations in the external environment (O'Neill 1997), and this includes e.g. temperature homeostasis, water and electrolyte homeostasis (e.g. potassium, sodium), and circadian function as well as sleep homeostasis (O'Neill 1997, Cajochen et al. 2006, Gibson et al. 2009). One of the fundamental characteristics of aging is the progressive reduction in homeostatic mechanisms (Turnheim 2004). With aging, body responses to the external environment fluctuations may become exaggerated, delayed in initiation or abnormal in phase (O'Neill 1997). Therefore, following some kind of pharmacological perturbation of a physiological function, more time is required to regain the original steady-state as counter-regulatory measures are reduced (Turnheim 2004). This can be seen in e.g. orthostatic hypotension and increased sensitivity to hypoglycemia in older patients with sulphonylureas.

2.1.2 Pharmacokinetics

Passive absorption in the intestine shows the least change with aging (Boparai and Korc-Grodzicki 2011), but compounds permeating through the intestinal epithelium by carrier-mediated transport-mechanisms (iron, calcium, vitamins, possibly nucleoside drugs) may be absorbed at a lower rate in older persons (Turnheim 2004). The rate of transdermal, subcutaneous and intramuscular drug absorption may also decrease due to reduced blood perfusion.

The most significant pharmacokinetic change in older persons is the reduction in renal drug elimination, as glomerular filtration rate, tubular secretion, and renal blood flow are all reduced (Turnheim 2004). In fact, renal function begins to decline when people reach their mid-30s and continues to decline an average of 6-12 ml/min/1.73m^2 per decade. This results in a decreased clearance of many drugs (e.g. digoxin, water-soluble antibiotics and β-adrenoceptor blockers, lithium, diuretics and non-steroidal anti-inflammatory drugs) and the active metabolites of some other medications (e.g. morphine) (Mangoni and Jackson 2004, Boparai and Korc-

Grodzicki 2011). However, according to Stegemann et al. (2010), one third of population displays a stable renal clearance, measured as GFR, between 30 and 80 years suggesting that diseases common in people over 65 years such as hypertension, vascular diseases and diabetes may be more important than aging itself (Stegemann et al. 2010). Renbase, a Finnish database about the use of drugs in situations of renal failure, lists 487 drugs that should be avoided or for which dosage should be modified in patients with renal failure. Renal function (as assessed by the glomerular filtration rate, GFR) determination has traditionally been based on serum creatinine levels using Cockroft-Gault or Modification of Diet in Renal Disease (MDRD) equations which also incorporate age, sex and height and/or weight data. However both equations, but especially MDRD, may overestimate GFR in older persons (Spruill et al. 2008, Spruill et al. 2009, Van Pottelbergh et al. 2011). As the muscular mass decreases in older persons, the use of creatinine is not optimal among this age group. Therefore, also cystatin C has been used for estimating GFR. Although cystatin C is not independent of body composition, it is not affected by the muscle volume and seems to be a useful marker in the GFR estimation in older persons (Fehrman-Ekholm et al. 2009, Modig et al. 2011). The optimal method for GFR estimation especially in older patients is a topic of ongoing debate (Van Pottelbergh et al. 2011).

The distribution of drugs is altered due to changes in body composition. Lean body mass and total body water become reduced with age, resulting as a lower volume of distribution of hydrophilic drugs (e.g. digoxin and ethanol). Therefore, lower doses may result in a higher drug concentration. On the other hand, the body fat/water ratio increases during age and therefore lipid-soluble drugs (e.g. benzodiazepines, amiodarone, verapamil) have a higher volume of distribution and they will take a longer time to reach a steady-state and take longer to be eliminated, potentially prolonging their duration of action. The relative change in the volume of distribution for lipophilic drugs is more marked in men (body fat increase from 18 to 36 %) than in women (body fat increase from 33 to 45 %) (Turnheim 2004). Serum albumin is an important carrier for many different, especially acidic drugs, but its levels may significantly decrease with malnutrition or chronic diseases. Among those drugs that are highly protein-bound (e.g. diazepam, phenytoin, warfarin, salicylates) this results as an increase in the pharmacologically active unbound drug concentration. On the other hand, basic drugs (e.g. propranolol and lidocain) are bound to α-1-glycoprotein and its concentration may increase during acute illnesses. However, the clinical relevance is probably limited since the transient effect of protein binding on free plasma concentration is rapidly counterbalanced by its effects on clearance (Mangoni and Jackson 2004).

Metabolism occurs mostly in liver, and aging is associated with a reduction in the first-pass metabolism due to decreased liver blood flow, size and mass (Boparai and Korc-Grodzicki 2011). Therefore the bioavailability of those drugs that are metabolized via phase I reactions (oxidation, reduction) by cytochrome P450 (CYP) enzymes may be significantly increased. On the other hand, prodrugs (e.g. some

angiotensin converting enzyme (ACE) -inhibitors, such as enalapril and perindopril) need to be activated by liver enzymes, which may be slowed or reduced (Mangoni and Jackson 2004). However, the interindividual variation in metabolic drug clearance by CYP enzymes or phase I reactions exceeds the decline caused by aging (Turnheim 2004). Unlike phase I reactions, the activities of the phase II reactions (conjugation, acetylation) do not change with aging.

These pharmacokinetic changes may be predictable, but the differences between the age group (from fit to frail, with multiorgan dysfunctions) results in relatively large variability in drug pharmacokinetics among older persons (Cho et al. 2011).

2.1.3 Pharmacodynamics

Pharmacodynamics describes how drugs exert their effect at the site of action and the time course and intensity of pharmacological effect (Boparai and Korc-Grodzicki 2011). It is determined not only by the concentration of the drug at the receptor, but also by the drug-receptor interactions (which can involve variations in receptor number and receptor affinity, second messenger responses and the ultimate cellular response), variations in physiological or homeostatic mechanisms, and changes in functional reserves. Age-related changes are more complex than pharmacokinetic changes, and they tend to be drug class specific (Cho et al. 2011).

The responsiveness of α-adrenoceptors is preserved with advancing age (Mangoni and Jackson 2004), but reduction in response of β-adrenoceptor agonists results apparently due to downregulation of β-adrenoceptors in response to the elevated serum noradrenaline levels (Turnheim 2004). However, Mangoni and Jackson hypothesized that the reduced responses to β-agonists and antagonists were secondary to impaired β-receptor function due to reduced synthesis of cyclic AMP following receptor stimulation. The total number of receptors seems to be maintained but the postreceptor events are changed because of alterations of the intracellular environment (Mangoni and Jackson 2004). In addition, responsiveness of adenosine A_1-receptors and heart muscarinic receptor activity are reduced (Turnheim 2004). However, for the most part, the mechanisms of pharmacodynamic changes have not been well defined, e.g. the risk for major bleeding of those on warfarin is significantly increased although there is little difference in its pharmacokinetics in older patients (Cho et al. 2011).

The baroreflex sensitivity to changes in blood pressure decreases with age (Gupta and Lipsitz 2007). This makes older persons more vulnerable to orthostatic hypotension and blood pressure fall caused by e.g. dihydropyridines and organic nitrates (Kelly and O'Malley 1992, Corsonello et al. 2010).

Brain weight becomes reduced by 20 % between the age of 20 and 80 years, and neuronal loss occurs in several brain regions (Turnheim 2004). The numbers of dopamine D_2 and cholinergic receptors become decreased in the central nervous system (CNS). The reduction of dopamine content and receptor abundance predisposes to extrapyramidal symptoms in response of dopaminergic blockade by neuroleptics. On the other hand, the reduction in acetylcholine content renders older

persons more susceptible to cognitive impairment and other anticholinergic effects e.g. of antipsychotics and tricyclic antidepressants. Advancing age is also associated with increased sensitivity to the CNS effects of benzodiazepines, probably due to $GABA_A$-benzodiazepine receptor complex changes (Mangoni and Jackson 2003, Turnheim 2004, Cho et al. 2011).

These changes have been summarized in Table 1.

Table 1. Changes in aging body resulting as increased susceptibility to adverse drug reactions.

Pharmacokinetic changes	**Examples**
Absorption speed by active mechanisms may be decreased	Iron, calcium, vitamins
Decrease of transdermal, subcutaneous and intramuscular drug absorption rate	
Reduction in renal drug elimination	Digoxin, lithium
Increase of body fat/water ratio	Benzodiazepines, verapamil
Changes in serum protein levels (albumin, α-1-glycoprotein)	Warfarin, propranolol
Reduction of first-pass metabolism in liver	Enalapril
Pharmacodynamic changes	**Examples**
Reduction in β-, A_1- and heart muscarinic receptor activity	
Decreased baroreflex sensitivity	Organic nitrates, dihydropyridines
Reduction in the number of D_2- and cholinergic receptors in the CNS	Haloperidol, metoclopramide
Neuronal loss in several brain regions	
Decreased acetylcholine content	Amitriptyline
Changes in $GABA_A$-benzodiazepine complex	Benzodiazepines

2.2 COMPREHENSIVE GERIATRIC ASSESSMENT

2.2.1 Definition and description

Comprehensive geriatric assessment (CGA) is characterized as a technique for multidimensional diagnosis of vulnerable older persons with the purpose of planning and/or delivering medical, psychosocial, and rehabilitative care (Rubenstein et al. 1991). Its major purposes are to improve diagnostic accuracy, optimize medical treatment, improve medical outcomes (including functional status and quality of life), optimize living location, minimize unnecessary service use, and arrange long-term case management. CGA is usually grouped into the four domains of physical health, functional status, psychological health and socioenvironmental parameters (Rubenstein 2004), and it is one of the cornerstones of modern geriatric care (Ellis et al. 2011). CGA has been shown to be effective in comprehensive meta-analyses (Beswick et al. 2008, Ellis et al. 2011). The main aspects of CGA are shown in Table 2.

Table 2. Main aspects of comprehensive geriatric assessment (CGA) (Wieland and Hirth 2003, Ellis and Langhorne 2005).

CLINICAL GOALS OF CGA	**MAJOR COMPONENTS OF CGA**
-To improve process of care	**Medical assessment**
-To improve outcomes of care	-Problem list
-To contain costs of care	-Comorbid conditions and disease severity
	-Medication review
	-Nutritional status
DIFFERENT SPECIALISTS THAT MAY TAKE PART IN A CGA TEAM	**Assessment of functioning**
	-Basic activities of daily living
-Physician	-Instrumental activities of daily living
-Nurse	-Activity/excercise status
-Physiotherapist	-Gait/balance
-Psychologist	**Psychological assessment**
-Social worker	-Mental status (cognitive) testing
-Nutritionist	-Mood/depression testing
-Occupational therapist	**Social assessment**
-Dentist	-Informal support needs and assets
-Audiologist	-Care resource eligibility/financial assessment
-Pastoral carer	**Environmental assessment**
	-Home safety
	-Transportation and telehealth

It has been postulated in early days of CGA, that geriatric evaluation should be linked with strong long-term management if it were to be effective (Stuck et al. 1993). Subsequent studies and meta-analyses have later shown the beneficial effect of in-hospital CGA wards to changes of being alive and in their own home up to a year after hospital admission. These individuals were also less likely to become institutionalized and to suffer death or deterioration, but more likely to experience improved cognition (Baztán et al. 2009, Van Craen et al. 2010, Ellis et al. 2011). However, inpatient CGA does not seem to reduce long-term mortality (Ellis and Langhorne 2005). Outpatient CGA doesn't seem to confer any survival benefit (Kuo et al. 2004), but it can help older persons to live safely and independently (Beswick et al. 2008). However, CGA has shown a favourable outcome in frail and pre-frail community-dwelling older persons based on the frailty status and activities of daily living by Barthel, although the results were not statistically significant (Li et al. 2010).

An important issue in successful CGA is the adherence of both physician and patient. However, compliance with CGA recommendations may be poor, with adherence rates among both physicians and patients of only around 50 % (Gold and Bergman 2000, Banning 2008). The adherence of physician may be enhanced with effective geriatrician-physician communication, prioritizing and limiting the number of recommendations and incorporating physician education and patient empowerment strategies. On the other hand, patient adherence may be increased if the physician has an understanding of the patient beliefs and resources, he/she uses a combination of methods, simplifying the plan and taking early steps to facilitate implementation. There should also be a continuum of formal and informal support

for the patient to help him/her carry out the plan (Aminzadeh 2000). However, based on their own clinical experience, Greveson and Robinson (2001) commented that many patients referred to a community CGA service have difficult family relationships, resulting in a high level of stress for informal carers and high demands on primary- and community-care professionals. They often have poor psychological adaptation to their physical frailty and are less likely to adhere to recommendations.

2.2.2 Medication assessment

Use of medicines by older people is high and increasing and the share of those without any medication is small, 2-3 % (Barat et al. 2000, Jyrkkä et al. 2006). In fact, almost 90 % of older persons are taking prescribed drugs. In addition, the use of over-the-counter drugs is also common (72 %, Barat et al. 2000). Older persons also take several different medicines, with the mean number of drugs in use varying between 4.2 and 7.6 (Barat et al. 2000, Bregnhoj et al. 2007). There is no clear definition for polypharmacy, and several different alternatives have been used (Veehof et al. 2000, Cannon et al. 2006, Fialová and Onder 2009), although five or more different drugs has often been used as the cut-off value (Muir et al. 2001, Jyrkkä et al. 2006, Viktil et al. 2006). However, setting a strict cut-off to identify polypharmacy is of limited value in a clinical setting, because the number of drug-related problems increase in an approximately linear manner with the increase of drugs used (Viktil et al. 2006).

Polypharmacy has been associated with advanced age and co-morbidity, evidence-based clinical practice guideline recommendations, and hospitalization (Sergi et al. 2011). Risk factors for polypharmacy include older age, poorer health and number of healthcare visits (Hanlon et al. 2001), cardiovascular diseases, diabetes or stomach symptoms, those who often take drugs (especially sedatives/hypnotics) without clear indication and those who develop hypertension or atrial fibrillation over time (Veehof et al. 2000). Furthermore, older people living in institutional care use more medicines than their community-dwelling counterparts (Jyrkkä et al. 2006). Polypharmacy can be defined as appropriate when many medicines may be used to achieve better clinical outcomes for patients. However, inappropriate polypharmacy is associated with negative health outcomes, and it occurs when older persons are prescribed more medicines than are clinically indicated (Patterson et al. 2012).

Although older persons use a high number of medications, they are often excluded from clinical drug trials. This causes a problem since extrapolation of results from younger patients or relatively healthy older individuals to older patients with multiple concurrent illnesses does not provide sufficient data to allow a reliable risk-benefit estimation (McLachlan et al. 2009, Cho et al. 2011).

Adequacy of medication is an important factor when minimizing adverse drug effects among all patients, but especially among frail older persons. Appropriate prescribing has to be based on an understanding of the pathophysiology of the problem and the pharmacology of the drugs available to treat it (Aronson 2004). Spinewine et al. (2007) defined that three of the most important sets of values in

judging appropriateness of prescribing are 1) what the patient needs and prefers, 2) scientific, technical rationalism (including clinical pharmacology) and 3) the general good (mixture of issues, including societal and family-related consequences of prescribing). Suboptimal prescribing has been defined as overuse or polypharmacy, inappropriate use, and underuse, and is associated with significant morbidity and mortality. In particular, inappropriate prescribing is common in older in- and outpatients (Hanlon et al. 2001).

Therefore, an important part of the CGA is the medication assessment, where the drugs in use by the patient are critically reviewed and modified if necessary. Prescribing may be regarded as inappropriate when there exists an alternative therapy that is either more effective or associated with a lower risk (Kaur et al. 2009). The medication assessment is performed by a physician, who (assisted by other health care personnel if needed) evaluates the patient's current medication along with its indications and appropriateness as part of the clinical examination and treatment planning (Ministry of Social Affairs and Health 2011). Finnish authorities have stated that the adequacy of medication treatment should be regularly (at least once a year) evaluated especially for individuals who use several medicines simultaneously, older persons and other special groups (Ministry of Social Affairs and Health 2007, 2011).

The general factors associated with the use of inappropriate medication include older age, female gender, lower educational level, lower household income, poor self-related health, depressive symptoms, lower mini mental state examination (MMSE) score, higher number of visits to the general practitioner per year and higher number of drugs for the last month (Lechevallier-Michel et al. 2005a), and higher price of newer medicines (Pitkälä et al. 2002). In addition, older people often have multiple medical conditions and the appropriate treatment to one condition may be contraindicated in the treatment of the second condition. Cholinesterase inhibitors, for example, are recommended in treatment of Alzheimer's disease (Popp and Arlt 2011), but anticholinergics are an important medicine group in treatment of chronic obstructive pulmonary disease (COPD) (Flynn et al. 2009). If the same patient has both conditions, the recommended treatment would counteract against each other and the treatment has to take this reality into consideration. In addition, older persons with diabetes are at higher risk of hypoglycemia, and their treatment should be individually tailored and treatment goals (in terms of HbA_{1c} levels) might therefore be higher than would be the case in younger adults (Schütt et al. 2012).

2.3 INAPPROPRIATE MEDICATION FOR OLDER PERSONS

Several criteria for identifying potentially inappropriate medications have been published. They can be divided to explicit (criterion-based, e.g. Beers criteria) and implicit (judgment-based, e.g. Medication Appropriateness Index (MAI)) criteria (Hamilton et al. 2009). The oldest of those, Beers criteria (Beers et al. 1991) has been

one of the most commonly used criteria (Marcum and Hanlon 2012). It was originally developed to be used among older persons (aged 65 years or more) residing in nursing homes and included 30 therapeutic classes/medications. The first update in 1997 (Beers et al. 1997) widened the criteria to include all older persons regardless of residence. The second update (Fick et al. 2003) further widened the criteria, which now included 48 medications/classes of 'drugs-to-avoid' and 20 drug-disease interactions. The last update published at the beginning of 2012 includes 53 medications or medication classes and now include a new category; medications to be used with caution in older adults (The American Geriatrics Society 2012 Beers Criteria Update Expert Panel 2012). Canadian researchers have also developed their own criteria (McLeod et al. 1997, Rancourt et al. 2004).

Beers criteria have been developed in the USA, and therefore their usefulness in other countries is limited, due to differences in drug availability, clinical practice, socioeconomic levels and health system regulations (Laroche et al. 2007a). Therefore, some European countries have also developed their own criteria. The first European list of inappropriate medicines for older persons was published in Sweden in 2003 and updated in 2010 (Socialstyrelsen 2003, Socialstyrelsen 2010). The Swedish criteria determined older persons as aged 75 years or more. Other European lists include the French Laroche's criteria (for persons aged 75 years or more) (Laroche et al. 2007a), Screening Tool of Older Person's potentially inappropriate Prescriptions (STOPP) criteria from Ireland for persons aged at least 65 years (Gallagher et al. 2008) and the recently developed Norwegian General Practice criteria (which is partly based on the Beers criteria adapted for Norway (Nyborg et al. 2012). The Finnish database of medication for the elderly was completed in 2010, and it classifies the 350 medicines or combination medicines most commonly used in the treatment of older adult patients. This database classifies not only inappropriate medicines, but also describes medicines suitable for older persons using four classification steps: suitable, limited evidence from clinical trials and/or clinical use and limited efficacy for patients 75 years and over, appropriate under certain conditions, and inappropriate (Bell et al. 2013).

MAI was originally developed by Hanlon et al. 1992. It is based on 10 questions about: 1) indication 2) effectiveness 3) dosage 4) direction 5) practicality 6) drug-drug interactions 7) drug-disease interactions 8) duplication 9) duration and 10) expense. A 3-point scale is used to rank each criterion, which enhances the usefulness of the instrument (Kassam et al. 2003). There is a report that MAI is better at predicting the risk of adverse drug events (ADE) than the Beers criteria (Lund et al. 2010). However, there has also been criticism of the weighting of the scale; since if the drug is ineffective for the medical condition (the second question), then the prescription is inappropriate and none of the other questions matters (Aronson 2004).

The differences in the different criteria mainly reflect differences in medication availability and prescription patterns in the different countries (Chang and Chan 2011). STOPP criteria have been claimed to identify a higher proportion of patients suffering adverse events related to inappropriate medication than Beers' criteria

(2003 update) (Gallagher and O'Mahony 2008, Hamilton et al. 2011). In addition, in a comparison of the different criteria, the STOPP, Rancourt and Laroche came closest to fully meeting the optimal explicit criteria (Chang and Chan 2011).

2.3.1 Home-dwelling persons

There are several studies which have investigated the quality of drug treatment in the home-dwelling aged population. Use of inappropriate medication depends on the criteria used, and the prescribing culture as well as the population of the country. Beers criteria has been the most commonly used system to determine inappropriate medications. In general, the use of at least one inappropriate medicine is found to be common especially in older persons.

The share of older persons with inappropriate medication according to Beers criteria has ranged from 12.5 % to 49 % (Pitkälä et al. 2002, De Wilde et al. 2007, Lund et al. 2010, Leikola et al. 2011). On the other hand, using the MAI criteria, up to 84 – 99 % of patients had one or more inappropriate ratings on their medication even after exclusion of the ratings concerning the expense of medication (Bregnhoj et al. 2007, Lund et al. 2010).

Factors associated with inappropriate medication include $\geq$3 drugs in use and depressive symptoms (Stuck et al. 1994). On the other hand, Steinman et al. (2006) claimed that patients using fewer than eight medicines were more likely to be missing a potentially beneficial drug than to be taking a medication considered inappropriate.

2.3.2 Hospitalized patients

Among hospitalized patients, Beers criteria have been widely used but also the use of the Irish STOPP/START (Screening Tool of Alert doctors to the Right Treatment) criteria have been common. When using Beers criteria, inappropriate medication was considered to being used by 25 – 66 % of patients (Page II et al. 2006, Laroche et al. 2007b, Gallagher and O'Mahony 2008), whereas with STOPP/START criteria their share has been 35 – 77 % (Gallagher and O'Mahony 2008, Lang et al. 2010).

Although up to 66 % of the patients in hospital may receive inappropriate medication based on the Beers criteria, there does not seem to be any significant connection between inappropriate medication and adverse drug reactions (ADR), mortality, length of stay or discharge to higher levels of care (Onder et al. 2005, Laroche et al. 2007b, Page II et al. 2006). For example, in the study of Page II et al. (2006) 27.5 % of older patients in the internal medicine services were prescribed medications listed by Beers. While 31.9 % of the patients experienced ADEs, only 9.2 % of the ADEs were attributed to the medications listed in the Beers criteria. Similar results were found in a French study, in which the prevalence of ADRs was 16.4 and 20.4 % with patients without or with any inappropriate medicines based on modified Beers criteria, respectively. Prior to admission, 66 % of patients were given at least one inappropriate drug, but in only 5.9 % of all those receiving inappropriate medications were the ADRs directly attributable to these drugs (Laroche et al.

2007b). It seems that interventions that are more comprehensive than Beers are necessary to reduce the risk of ADEs and the associated morbidity and mortality in the acute care of the elderly (Page II et al. 2006). When Beers and STOPP criteria were used to identify hospital admissions caused by potentially inappropriate medication, the STOPP criteria identified higher a proportion of patients than Beers criteria (11.5 % and 6 %, respectively) (Gallagher and O'Mahony 2008). Budnitz et al. (2011) estimated that 6.6 % of hospitalizations for ADEs could be attributed to potentially inappropriate medications according to Beers criteria, and half of these involved digoxin.

There are few reports which have evaluated the impact of specialized units in decreasing inappropriate medications. In the study of Saltvedt et al. (2005), patients aged at least 75 years, admitted as emergencies to hospital were subjected to either a general medical ward or to an interdisciplinary geriatric evaluation and management (GEM) unit which consisted of geriatrician, residents, nurses, enrolled nurses, occupational therapists, and a physiotherapist. Potentially inappropriate medication (by Beers) at inclusion was noted in 10 %/9 % of patients in GEM unit/medical ward, respectively. At discharge their share had decreased (4 %/6 % GEM unit/medical ward), but the difference was not statistically significant. There were more initiations of antidepressants, and more terminations of digitalis glycosides, β-receptor antagonists as well as antipsychotics in the GEM unit than in general medical ward. On the other hand, a beneficial effect has been observed also in the general medicine inpatient service at the Veterans Affairs medical center. Muir et al. (2001) used visual intervention (medication grid) delivered to physicians resulting a decrease in the number of medications in the intervention group by 0.92 per patient while it increased by 1.65 per patient in the control group.

In a study conducted in internal medicine units in a Brazilian university hospital, the medications most commonly involved in suspected ADRs were identified as anti-infectious agents, drugs acting on the CNS, gastrointestinal tract and metabolism (Camargo et al. 2006). On the other hand, in a study at the acute medical geriatric unit of the university hospital in France, the most common inappropriate medications in patients experiencing ADRs were anticholinergic antidepressants, cerebral vasodilators, long-acting benzodiazepines and concomitant use of two or more psychotropic drugs from the same therapeutic class (Laroche et al. 2007b).

In a U.S. study examining hospitalizations due to recognized adverse drug events in older persons, four medications or medication classes (warfarin, insulins, oral antiplatelet agents, and oral hypoglycemic agents) were implicated in 67 % of hospitalizations caused by ADEs (Budnitz et al. 2011).

2.3.3 Nursing-home residents

Older persons living in nursing homes are generally frail and at increased risk of polypharmacy, side effects and drug-drug interactions; furthermore it has been reported that drug use (drugs for the nervous system and sensory organs) tends to increase after admission into a nursing home (Koopmans et al. 2003). The share of

persons using inappropriate medication according to the Beers criteria has been in the range of 13 – 43 % (Nygaard et al. 2003, Lapane et al. 2007). Cognitively intact residents have been found to use more scheduled drugs than cognitively impaired individuals (Koopmans et al. 2003, Nygaard et al. 2003). When Nygaard et al. (2003) reviewed drug use, 13 % were found to be using inappropriate medication according to Beers criteria, but when the authors used their own criteria (which, in addition to drugs listed by Beers, included 11 drugs that were not included in Beers criteria), the prevalence of subjects on inappropriate drugs increased to 25.3 % (21.6 % vs. 44.2 %, mentally impaired vs. intact). There was a weak association between the number of drugs in use and the numbers of inappropriate drugs. However, an increase in drug use does not necessarily translate into poor prescribing practices, but continuous drug review is needed in this population (Koopmans et al. 2003).

One important topic is the use of antipsychotics, which is common in nursing homes, with a prevalence between 28 % to 80 % (Briesacher et al. 2005, Hosia-Randell and Pitkälä 2005, Alanen et al. 2006a) as compared to a prevalence of less than 10 % in home-dwelling persons aged 75 years or more (Desplenter et al. 2011). It has been claimed that there may not be adequate indications in all cases and a critical evaluation of treatment may be lacking (Alanen et al. 2006a, 2006b); in the study of Briesacher et al. (2005), only 42 % of those on antipsychotics were receiving therapy in accordance with the nursing home prescribing guidelines.

Frail persons living in nursing homes may often be admitted to hospitals for a period of time. In a study by Boockvar et al. (2004), medication changes were common during patient transfer between a hospital and a nursing home. The changes were mostly discontinuations, followed by class changes and substitutions (Boockvar et al. 2004), however hospitalization may also increase drug prescription at discharge (Corsonello et al. 2007). Boockvar et al. (2004) reported that ADEs attributable to medication changes occurred during 20 % of bidirectional transfers. The overall risk of ADE/drug alteration was 4.4 %. Most ADEs occurred in the nursing home after readmission, and intervention at the time of nursing home readmission holds the potential to prevent most ADEs.

Schmader et al (2004) compared inpatient/outpatient GEM with usual care. Outpatient GEM resulted in 35 % reduction in the risk of serious ADR after discharge compared with usual care, but the inpatient geriatric unit had no effect. Inpatient geriatric unit care reduced unnecessary and inappropriate drug use and underuse, while outpatient GEM care reduced the number of conditions for which there were omitted drugs significantly during the outpatient period. When compared with usual care, it seems that outpatient GEM reduces serious ADRs, whereas inpatient and outpatient GEM reduces suboptimal prescribing in vulnerable older patients.

2.4 IDENTIFICATION OF ADVERSE DRUG REACTIONS BY PHYSICIAN AND PATIENT

Adverse drug reaction (ADR) has been defined by the European Parliament as "a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function" (Directive 2001/83/EC, Article 1). This definition is practically unchanged from the 40-year-old definition issued by the World Health Organization (Edwards and Aronson 2000). On the other hand, adverse drug event (ADE) is an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to the drug (Edwards and Aronson 2000). However, there is a wide variety in terms in use to depicit patient safety related to medication, and unfortunately the different terms (e.g. adverse drug reactions/events), are not used uniformly in the literature making it difficult to compare the results of the studies (Pintor-Mármol et al. 2012).

ADRs are common among hospitalized older patients, although more than 80 % of ADRs leading to admission or occurring in hospital are type A (dose-related) in nature, i.e. predictable from the known pharmacology of the drug and therefore potentially avoidable (Routledge et al. 2003). In the meta-analysis of 39 prospective studies among U.S. hospitalized patients in U.S., serious ADRs occurred in 6.7 % and fatal ADRs in 0.3 % of all patients (Lazarou et al. 1998). An even higher prevalence of ADRs was reported in the study of Camargo et al. (2006), where 43 % of patients in internal medicine units had at least one suspected ADR. Among them, 20 % had manifested before the patient was admitted and 80 % during hospitalization. Risk factors for the development of ADRs include follow-up length and number of medications but not age, gender or number of diagnoses (Camargo et al. 2006). On the other hand, Laroche et al. (2007b) concluded that a high number of drugs is the main ADR facilitating factor, with the inappropriateness of drugs being a subordinate factor.

ADRs may have a major impact on the quality of life of older patients. ADRs may arise from medication errors, but also the appropriate medication may provoke ADRs (Ferner and Aronson 2006). It has been claimed that only a small amount of ADRs are ever detected (Hannan 1999). Furthermore, only a small amount of ADRs are reported to the pharmacovigilance centre by general practitioners (Moride et al. 1997). The low detection rate of ADRs may be a result of the fact that only in some cases are adverse events immediate or well known, while other events may be delayed, unfamiliar or patients may not realize that the problem has anything to do with the medication they are taking (Britten 2009, Lorimer et al. 2012). In addition, sensitivity to physical symptoms varies between individuals (Britten 2009). Furthermore, in the actual clinical setting physicians may not discuss about risks of medicines with patients (Britten et al. 2004), although patients may want to be given more information than they receive about adverse effects (Britten 2009). Although

information about ADRs is available in leaflets, few people read them. Instead, they prefer that their physician should inform them about ADRs (Lorimer et al. 2012).

Furthermore, the method of data collection may dramatically influence the results (Sheftell et al. 2004). Sheftell et al. demonstrated, that those subjects who did not self-report adverse events after receiving triptan therapy are much more likely to report positively if presented with a list of side effects. However, in randomized, placebo-controlled trials of statin drugs, a significant number (4-26 %) of patients in the control groups actually discontinued placebo use because of perceived adverse effects. In fact, symptom rate in placebo groups have varied substantially across trials and were often markedly lower than those found in the general population (Rief et al. 2006).

On the other hand, physicians may not detect ADRs at the same rate than patients or nurses. Patients with rheumatoid arthritis (Gäwert et al. 2011) and depressed outpatients (Zimmerman et al. 2010) report more ADRs/ADEs than are recognized by their physicians. Furthermore, among patients undergoing chemotherapy, nurses were more able to detect symptoms being self-reported by patients than identified by the physicians (Cirillo et al. 2009). In fact, there is a report describing the dichotomy in considering what is an ADR between physician and patient, agreement being best in the easily observable and well-known ADRs e.g. alopecia and stomatitis (Gäwert et al. 2011).

ADR studies are often performed in younger populations or in patients with a specific illness, and thus information from older people is limited. Oladimeji et al. (2008) studied risk factors for self-reported ADEs using an internet survey from persons aged $\geq$65 years; a significant percentage (18 %) reported an ADE (visit to physician to report an unwanted reaction or medical problem in the past year). The risk of self-reporting an ADE was related to being female, number of pharmacies used by patients, symptoms experienced, concern beliefs about medicines and having a graduate academic degree.

2.5 ANTICHOLINERGIC-LIKE ADVERSE DRUG REACTIONS

2.5.1 Physiology

Cholinergic neurotransmission occurs through the binding of the neurotransmitter acetylcholine to either muscarinic or nicotinic receptors. However, the term anticholinergic traditionally refers only to the effects of muscarinic receptor antagonism (Gerretsen and Pollock 2011). G-protein-type muscarinic receptors are widely distributed throughout the human body and mediate distinct physiological functions according to location and receptor subtype (Abrams et al. 2006). In the CNS, acetylcholine mediates many cognitive processes, e.g. attention, memory and learning functions (Jakubik et al. 2008). Five different subtypes (M_1-M_5) of muscarinic receptors are known (Alexander et al. 2011), and their distribution is shown in Table 3. All subtypes have been found in brain, and especially subtype M_1, but also M_2 and

M_4 have been linked to cognitive processes (Kay and Ebinger 2008). Cholinergic transmission is particularly important in the processing of recent memories, visuospatial and perceptual functions, and psychomotor speed but does not seem to be involved in either language or executive functioning (Kay et al. 2005).

In periphery, muscarinic receptors mediate many physiological functions, e.g. dilatation of blood vessels and decrease in blood pressure, miosis, increase of secretion of endocrine glands and bronchoconstriction.

Table 3. Muscarinic receptors in the CNS and other tissues (Kay et al. 2005).

	General distribution in the CNS	**Non-CNS locations**
M_1	Abundant in cerebral cortex, hippocampus and neostriatum; constitute 40-50 % of total acetylcholine receptors	Salivary glands, symphatetic ganglia
M_2	Located throughout brain	Smooth muscle, cardiac muscle
M_3	Low levels throughout brain	Smooth muscle, salivary glands, eyes
M_4	Abundant in neostriatum, cortex, and hippocampus	Salivary glands
M_5	Projection neurons of substantia nigra pars compacta and ventral tegmental area, and hippocampus	Eyes (ciliary muscle)

2.5.2 Anticholinergic adverse effects

Due to the wide distribution of muscarinic receptors, anticholinergic drugs may evoke a variety of ADRs (Table 4). Anticholinergic drugs can be either lipid-soluble tertiary ammonium compounds (e.g. atropine and dicyclomine) or lipid-insoluble quaternary ammonium compounds (e.g. tiotropium bromide). Lipid-soluble anticholinergics have more systemic side-effects than lipid-insoluble anticholinergics (Flynn et al. 2009). Anticholinergic ADRs can be divided into peripheral (e.g. blurred vision, dry mouth, urinary retention, constipation, tachycardia and atrial fibrillation) and central ADRs (Wawruch et al. 2012). Central anticholinergic ADRs occur, when anticholinergic drug penetrates through the blood-brain barrier into the CNS. In general, they may include drowsiness, confusion, delirium and cognitive decline.

Table 4. Adverse effects of anticholinergic medication (Lieberman 2004, Penttilä et al. 2005a).

Peripheral anticholinergic side-effects	**Central anticholinergic side-effects**
Decreased salivation	Impaired concentration
Decreased bronchial secretions	Confusion
Decreased sweating	Attention deficit
Increased pupil size	Memory impairment
Inhibition of accommodation	
Increased heart rate	
Difficulty urinating (detrusor muscle relaxation, trigone and sphincter contraction)	
Decreased gastrointestinal motility	

2.5.3 Measurement of anticholinergicity

Determination of an anticholinergic drug effects and their concentrations in serum has been challenging (Mangoni et al. 2012). In addition to 'pure' anticholinergics (e.g. atropine, scopolamine, tropicamide, oxybutynin, darifenacin, tiotropium), many drugs possess anticholinergic properties, thus increasing the risk of anticholinergic ADRs. In addition, there may be several drugs whose anticholinergic properties are not known. Therefore, there is a wide variety on different studies about drugs classified as anticholinergics (e.g. Carnahan et al. 2006, Chew et al. 2008, Rudolph et al. 2008).

Several different *in vivo* methods (e.g. saliva or sweat secretion, papillary reflex or heart rate variability) have been applied to measure anticholinergic effects. However, none of these methods is specific for changes in cholinergic neurotransmission, and it has been recommended that they should be used together with subjective assessments of anticholinergic effects (Penttilä et al. 2005a, 2005b). Two different approaches are discussed below.

2.5.3.1 The Serum Anticholinergic Activity (SAA) assay

Binding of different drugs to muscarinic receptors has long been studied *in vitro* e.g. by using carbachol-induced contractions in guinea-pig ileum (Shein and Smith 1978) and in isolated fundus of rat stomach (Atkinson and Ladinsky 1972). In addition, radioactive ligands, such as [^{3}H]-N-methyl-4-piperidyl benzilate (Rehavi et al. 1977), ^{3}H-propyl benzilyl choline mustard (Fjalland et al. 1977) and ^{3}H-atropine (Golds et al. 1980) have been used to determine binding to muscarinic receptors obtained from mouse or rat brain. However, especially ^{3}H-quinuclidinyl benzylate (QNB) has been widely used in rat brain homogenate (Yamamura and Snyder 1974, Snyder and Yamamura 1977, Hyslop and Taylor 1980). Tune and Coyle (1980) developed the serum anticholinergic activity (SAA) assay that is based on the use of QNB. This compound has affinity for all muscarinic receptors, and therefore binds to muscarinic receptors in rat brain homogenate. When serum containing potent muscarinic antagonists is added to the QNB-homogenate, the specific binding of QNB is reduced in proportion to the concentration of the displacing agents. A decrease in the radioactivity can be used to determine the potency of antimuscarinic agent by comparing results to a standard curve of displacement obtained with known amounts of atropine. This has remained as the most widely utilized assay for quantifying anticholinergic load (e.g. Tune and Coyle 1981, Mondimore et al. 1983, Flacker et al. 1998, Pollock et al. 1998, Chengappa et al. 2000, Mulsant et al. 2003, Carnahan et al. 2006, Chew et al. 2006).

There is extensive variance in the published SAA results, and several studies have expressed the units of SAA in different ways making the synthesizing of these studies more difficult (Carnahan et al. 2002a). In addition, the measured SAA don't necessarily reflect the medication that has been used by patients. E.g., in the study of Mulsant et al. (2003) 10 % of the home-dwelling population had no detectable SAA

activity, although 38 % of these persons were taking anticholinergic drugs. On the other hand, when SAA was tested from acutely ill older patients not taking any recognized anticholinergic medication, 80 % of them had detectable SAA activity (Flacker and Wei 2001). Previously published results are presented in Table 5.

SAA levels have been associated with anticholinergic adverse effects, e.g. decrease in MMSE score among community-dwelling aged persons (Mulsant et al. 2003) and depressed patients after electroconvulsive therapy (Mondimore et al. 1983). In addition, an association with higher SAA levels and delirium has been reported in surgical patients (Tune et al. 1981, Golinger et al. 1987) and in acutely ill older inpatients (Flacker et al. 1998). Higher SAA levels are also associated with greater impairment in self-care capacity among nursing-home residents with dementia (Rovner 1988). However, the levels of SAA vary substantially between the studies (Table 5).

An increase of SAA has been associated with dry mouth, tachycardia, constipation and urinary disturbances, but not with MMSE or auditive working memory as measured with digit span performance, although visuomotor performance has declined (Pollock et al. 1998, Chengappa et al. 2000, Mulsant et al. 2004). In the recent study by Mangoni et al. (2012), SAA was positively associated with the Katz activities of daily index (ADL) score, but not with morbidity as measured by the Charlson comorbidity index.

Among older persons (mean age 86±7 years), there was a significant association between the score of drugs classified with Anticholinergic Drug Scale and the SAA results (Carnahan et al. 2006). The SAA method has also been used to determine anticholinergic effects of drugs *in vitro*. Tune et al. (1992) analysed 25 drugs using a standard concentration (10^{-8} mol/l). The highest activity was found with cimetidine (3 pmol/ml of atropine equivalents). However, this single concentration may not be clinically relevant for many of the drugs studied. Chew et al. determined six clinically relevant concentrations for 107 medications and used these concentrations to estimate the anticholinergic activity of these drugs (Chew et al. 2006, 2008).

In general, the results about SAA levels and anticholinergic adverse effects are mixed. This may result from several factors. Oral daily dosages generally do not correlate with plasma concentrations, which are the result of individual pharmacokinetic variations (Schor et al. 1992). Although SAA has been shown to correlate with anticholinergic activity measured in the cerebrospinal fluid (Plaschke et al. 2007), different drugs may have different abilities to penetrate into the CNS and thus provoke CNS-related symptoms and the relevance of their measurement from peripheral blood sample (which SAA uses) is questionable. SAA measures the displacement of QNB from muscarinic samples, but one must bear in mind, that QNB is displaced not only by cholinergic antagonists but also by agonists (Carnahan et al. 2002a). In addition, the biological membranes used in the SAA assay are obtained from rat cortex and striatum. In these areas, two thirds of muscarinic receptors belong to M_1 and M_4 subtypes (Levey 1993). Therefore, SAA may not necessarily predict responses to peripheral effects, such as M_3-mediated salivation

Table 5. Serum SAA levels reported in previous studies.

Age (y)	Population/ Disease	n	SAA level (atropine equivalents)	Special	Reference
17.5	Retarded man	1	17.5 pmol/ml	Haloperidol-induced akathisia treated with benztropine 2mg x2.	Harris et al. 1981
m 36	Scizophrenic and manic depressive	109		Higher SAA levels (optimal 10 pmol/ml) associated with lower incidence of extrapyramidal adverse effects of antipsychotics.	Tune and Coyle 1981
m 37-40	Scizophrenic and manic depressive	24	olanzapine: 0.96±0.55 pmol clozapine: 5.47±3.33 pmol	SAA measurement after stable levels of target doses.	Chengappa et al. 2000
m 49	Depressed	20		SAA >15 ng/ml (51.8 pmol/ml) was associated with cognitive decline 1 hour after electroconvulsive therapy.	Mondimore et al. 1983
m 55	Cardiac surgery patients	29		SAA >1.5 pmol/sample in 7/8 delirious patients vs. 4/17 in non-delirious patients.	Tune et al. 1981
> 55	Probable dementia	86	2 -> 7 pmol/ml (olanzapine) 4 pmol/ml (stable) (risperidone)	Change of SAA level with increasing drug plasma concentration. No correlation with SAA and risperidone plasma level.	Mulsant et al. 2004
m 58	Surgical intensive care unit patients	25	2.8±3.5 vs. 16.1±11.4 pmol/ml	No delirium vs. delirium.	Golinger et al. 1987
≥ 65	Community-dwelling	201	range 0.50-5.70 pmol/ml	SAA was detectable in 89.6 % of participants. Those with SAA >=2.80 pmol/ml were 13 times more likely to have a MMSE score ≤24 compared to those with undetectable SAA.	Mulsant et al. 2003
≥ 65	Hip fracture	71	median 2.8 pmol/ml (range 1.1-4.9)	Median in those with/without delirium 4.0/ 2.1 pmol/ml, respectively.	Mangoni et al. 2012
m 67	Surgical	36	scopolamine i.m. 121.1±85.5 vs. placebo 11.6±18.2 pmol/ml	Higher SAA levels were associated with cognitive impairment.	Miller et al. 1988
≥ 70	Inpatients	10	0.23-1.72 pmol/ml	Patients without a recent anticholinergic medication history. SAA was present in 8/10 subjects.	Flacker and Wei 2001
m 73	Depressed	61	nortriptyline: 0.6 pmol paroxetine: 0.1 pmol	SAA response after 1-6 weeks of treatment.	Pollock et al. 1998
≥ 75	Acute inpatients	67	0.6±0.8 vs. 1.8±1.6 nM/200ul	No delirium vs. delirium.	Flacker et al. 1998
m 81	Nursing home patients with dementia	22	0.0-9.95 pmol/ml, median 0.83 pmol/ml	Patients with Ach levels above the median had greater impairment in self-care capacity.	Rovner et al. 1988

and eye contractibility. In addition, it is possible that patients receiving the highest number of anticholinergic drugs may also be best able to tolerate those compounds (Teramura-Grönblad et al. 2011). Furthermore, SAA activity has also been demonstrated in patients who are not taking any recognized anticholinergic medications (Flacker and Wei 2001). It is possible that at least some of the detected SAA activity results from clinically important endogenous anticholinergic substances, such as dynorphin A, myelin basic protein, protamine and cortisol (which is known to increase during stress) that have been shown to have muscarinic activity *in vitro* (Flacker and Wei 2001, Carnahan et al. 2002a). Therefore, anticholinergic medications are apparently not the only determinant of SAA, and it is important to make a careful consideration in the interpretation of findings using the SAA assay (Carnahan et al. 2002a).

2.5.3.2 Lists of anticholinergic drugs

Tune et al. (1992) took the first step in the listing of anticholinergic properties of different drugs measured with the SAA assay, as they estimated the anticholinergic effects of 25 drugs. Since then, several ranked lists of anticholinergic drugs have been developed; those published in the 2000s are presented in Table 6.

Han et al (2001) studied medical inpatients with delirium using the Class of Drug developed by Summers (1978) and a clinician-rated anticholinergic score, where they established a list of 340 medications including those used in their population and those reported to have an anticholinergic effect from the literature. Then, three geriatric psychiatrists independently rated the anticholinergic effect of drugs on a scale from 0 to 3. They used the same anticholinergic score with community-dwelling men with hypertension (Han et al. 2008). Medications that were used in the study population but were not included in the score, were reviewed and rated by three geriatricians. Anticholinergic exposure was associated to delirium symptom severity and verbal memory as well as executive function.

Based on the work of Han et al. (2001), Carnahan and his colleagues developed the Anticholinergic Drug Scale (ADS); the scores of this scale have been found to associate with the SAA results (Carnahan et al. 2002b, Carnahan et al. 2006). The ADS classifies drugs between 0-3 based on their anticholinergic activity. The ADS includes 536 drugs, of which 117 exhibited anticholinergic activity.

Minzenberg et al. (2004) ranked 28 psychiatric drugs in use by schizophrenia patients. For these drugs, they established a pharmacological index (calculated from published studies reporting *in vitro* brain muscarinic receptor antagonism) and a clinical index (based on a panel of 10 practicing psychiatrists with extensive experience in clinical psychopharmacology). They rated the drugs' anticholinergic potencies relative to 1 mg benztropine mesylate. Both indexes highly correlated with each other and also with decreased neuropsychological measures.

In the study by Ancelin et al. (2006), the anticholinergic burden of the home-dwelling study population was quantified by a literature review including known

Table 6. Ranked lists of anticholinergic drugs published after the year 2000.

Age (y)	Population	n	Anticholinergic drugs listed	Classification	Additional information	Reference
≥ 65	Inpatients with delirium	278	47		DRN+clinician-rated score (drugs in study population and those reported to have anticholinergic effect in the literature)	Han et al. 2001
86±7	LT patients	201	N/A	0 - 3	Modified version of Han's Clinician's rated anticholinergic scale	Carnahan et al. 2002b
86±7	LT patients	297	117	0 – 3	SAA measurement associated with ADS, dose adjustment	Carnahan et al. 2006
m 40	Schizophrenic patients	106+50	28	bnz eqv	Psychiatric drugs, pharmacological and clinical index	Mintzenberg et al. 2004
> 60	CD	372	27	0 - 3	Literature review (known anticholinergic drugs) +expert opinion	Ancelin et al. 2006
70-79	CD	3075	?		Drugs with anticholinergic and sedative properties	Hilmer et al. 2007
≥ 65	Older adults attending primary care clinics	3013	88	1 – 3	Studies between 1966-2007 about anticholinergic activities of a drug and its association with cognitive function in older adults+expert opinion	Boustani et al. 2008
	Laboratory assay		39	0 - +++	Drugs commonly used by older adults	Chew et al. 2008
≥ 65	CD men with hypertension	544	60		Literature review+expert opinion, drugs used by the study group	Han et al. 2008
≥ 65	GEM clinic patients	132+117	49	1 - 3	500 most used drugs by veterans, excluding topical, otologic and inhaled drug preparations	Rudolph et al. 2008

DRN = Summers' Drug Risk Number, SAA = serum anticholinergic activity assay, ADS = anticholinergic drug scale,
GEM = geriatric evaluation and management, bnz eqv = benztropine equivalents, LT = long-term care, CD = community-dwelling

anticholinergic drugs with their serum anticholinergic activity where available. Then each participant's records were examined by a pharmacologist, physician and biologist resulting a classification of the anticholinergic burden between 0-3. The study participants had 27 different anticholinergic drugs in use. These workers reported that those subjects continuously using anticholinergic drugs displayed significant deficits in cognitive functioning.

The Anticholinergic Risk Scale (ARS), developed by Rudolph et al. (2008), includes 49 anticholinergic drugs. For the list, the 500 most prescribed medications within the Veterans Affairs Boston Healthcare System were reviewed by a geriatrician and 2 geropharmacists to identify drugs with known potential for evoking anticholinergic adverse effects (excluding topical, ophthalmic, otologic, and inhaled drugs). These drugs were then subjected to a literature and database search, after which they were rated 0-3 according to their anticholinergic potential. They reported a dose-response relationship with higher ARS scores and anticholinergic ADEs, both central (falls, dizziness and confusion) and peripheral (dry mouth, dry eyes, constipation) in patients aged 65 years and more. Recently, Lowry et al. (2011a) reported that institutionalization, the Charlson comorbidity index and non-antimuscarinic polypharmacy were associated with the ARS in older hospitalized patients, but increasing age and dementia were negatively associated with ARS score. Higher ARS scores have been found to associate in poorer physiological well-being (Teramura-Grönblad et al. 2011) and they have been negatively associated with several components of the Barthel Index. They also predict in-hospital mortality in the presence of hyponatremia (Lowry et al. 2011b), and 3-month mortality among older hip fracture patients (Mangoni et al. 2012). However, higher ARS scores did not seem to be associated with mortality in older persons living in long-term care (Kumpula et al. 2011).

The Anticholinergic Cognitive Burden Scale (ACBS) devised by Boustani et al. (2008) is a tool developed explicitly for categorizing drugs according to the severity of their cognitive effects. ACBS is based on a systematic literature review supplemented by input from an expert panel of clinicians, and it focuses on central rather than peripheral anticholinergic effects. In the study of Kolanowski et al. (2009), no association was found between ACBS and engagement in activity of nursing-home residents with dementia. In addition, use of anticholinergic medications determined by ACBS did not increase the risk of incident delirium in hospitalized older adults with cognitive impairment (Campbell et al. 2011), but it did increase the cumulative risk of cognitive impairment (as measured by a decline in the MMSE score) and mortality (Fox et al. 2011).

The Drug Burden Index (DBI) has been developed to measure anticholinergic and sedative medication burden among persons aged 70-79 years (Hilmer et al. 2007). It subdivides medicines into 3 groups with respect to risk: 1) drugs with anticholinergic and 2) sedative effects, and 3) total number of medications. Drugs were identified from a literature search. They demonstrated that exposure to anticholinergic and sedative drugs was associated with poorer physical and

cognitive function in community-dwelling older people. It was also associated with falls, incontinence and geriatric depression scale (GDS) but not with MMSE (Wilson et al. 2011), slower walking speed, poorer performance on chair stands and TUG as well as lower scores in instrumental activities of daily living (IADL) and Barthel index (Gnjidic et al. 2011). DBI has also been able to predict length of stay in hospital but not in-hospital mortality (Lowry et al. 2012).

Chew et al. (2008) measured *in vitro* the anticholinergic activity of 107 medications commonly used by older persons. They used pharmacokinetic data to translate the relationship between concentration and anticholinergic activity into an estimated relationship between the dose and anticholinergic activity.

However, despite the advantages of the antimuscarinic drug scoring systems (limited training required, effortless use by healthcare professionals in various healthcare settings, and the capacity to predict outcomes over and above crude measures of antimuscarinic drug exposure), several issues limit their widespread application in clinical practice. These systems have been tested only in limited healthcare settings, follow-up measurements are rare, and the calculation of anticholinergic exposure is time-consuming since there is no software that automatically calculates the score. In addition, some drugs (e.g. olanzapine) have affinity also to other receptors than muscarinic receptors, so it is difficult to ascertain whether the effects of these drugs are primarily due to their affinity to the muscarinic receptors (Mangoni 2011).

2.5.4 Use of anticholinergics

Anticholinergic drugs block muscarinic receptors. They are clinically used in the treatment of overactive bladder (Abrams et al. 2006) and chronic airway diseases like asthma and COPD (Barnes 2004, Flynn et al. 2009). Other indications include topical use in ophthalmology, treatment of motion sickness and in hospitals to treat bradycardia, and in treatment of organophosphate poisoning. There are also drugs (e.g. amitriptyline and quetiapine) in which anticholinergic properties are unwanted adverse effects.

The use of anticholinergic drugs varies based on the setting. Among community-dwelling older persons, 9 – 37 % use at least one anticholinergic medication (Lechevallier-Michel et al. 2005b, Ancelin et al. 2006, Ness et al. 2006, Hilmer et al. 2007, Sittironnarit et al. 2011). Among those living in institutionalized care, the numbers of subjects taking anticholinergics has been reported as being between 35 – 82 %, with the highest amounts being reported among those with dementia (Seifert et al. 1983, Kolanowski et al. 2009, Kumpula et al. 2011).

Hospitalization has been found to lead to a significant increase in the prevalence of anticholinergic medicine users (10.5 % -> 14.2 %, admission -> discharge) among older persons (Wawruch et al. 2012). It was stated that the most important risk factors of using anticholinertic drugs were immobilization, urinary incontinence and retention, constipation, gastroduodenal ulcer disease as well as neurologic and psychiatric comorbidities (depression, Parkinson's disease, epilepsy). Tramadol was

the most frequently prescribed drug with anticholinergic activity. Most anticholinergic drugs recorded were CNS drugs, H_2-antihistamines and antispasmodics.

Patients with dementia are more likely to use anticholinergics than matched controls (Roe et al. 2002). Dementia patients are often treated with cholinesterase inhibitors (ChEI) such as donepezil, galantamine and rivastigmine (Popp and Arlt 2011). However, compared with individuals not having ChEIs, those on ChEIs have an increased risk of subsequently receiving anticholinergic drugs (4.5 % vs. 3.1 % for those with or without ChEIs, respectively) (Gill et al. 2005). Johnell and Fastbom (2008) performed a register-based survey including 700 000 older persons and came to similar conclusions (9 % of those in ChEIs were using anticholinergic drugs vs. 5 % not on ChEIs). Furthermore, a recent report by Teramura-Grönblad et al. (2011) reported concomitant use of anticholinergic drugs and ChEIs in 10.7 % of older persons living in residential care. The use of ChEIs is associated with an increased risk of receiving an anticholinergic drug to manage urinary incontinence, and urinary antispasmodics have been the most extensively used anticholinergic drug among those receiving ChEIs (Gill et al. 2005, Johnell and Fastbom 2008), the other common anticholinergics being non-selective monoamine reuptake inhibitors and hydroxyzine (Johnell and Fastbom 2008). Although incontinence is a known adverse effect of ChEIs, concurrent use of anticholinergic drugs and ChEIs should be kept to an absolute minimum since anticholinergic drugs are likely to reduce the already small effect of ChEIs on cognition (Johnell and Fastbom 2008).

2.5.5 Effects of anticholinergics on measured outcomes

Older people are thought to be particularly vulnerable to the central ADEs of anticholinergic drugs. In general, conditions for which anticholinergic medications tend to be prescribed, such as urinary incontinence or chronic obstructive pulmonary disease, typically occur in later life (Gerretsen and Pollock 2011). However, there may also be some age-specific changes in the CNS. Aging reduces the number of muscarinic receptors in the brain, and regions rich in muscarinic receptor density, the corpus striatum and the cortical mantle show a greater rate of decline (up to 50 %) than those areas that have a relatively low number of muscarinic receptors (thalamic, hippocampal and cerebellar regions) (Dewey et al. 1990). In addition, many conditions that are common among older persons (diabetes, Alzheimer's disease, Parkinson's disease, cerebral stroke and head injuries) may increase the permeability of blood-brain barrier and in that way the brain penetration of anticholinergics may increase (Kay et al. 2008, Farrall and Wardlaw 2009, Stolp and Dziegielewska 2009, Weiss et al. 2009). Furthermore, individuals with apolipoprotein E4 allele, which is a major risk factor for Alzheimer's disease, have lower cognitive function as a group, and therefore may be more vulnerable to anticholinergic adverse effects (Uusvaara et al. 2009).

Anticholinergic drugs have been associated with decreased functional abilities as measured with ADL (Kumpula et al. 2011, Teramura-Grönblad et al. 2011, Lowry et

al. 2011b, Lowry et al. 2012, Koshoedo et al. 2012) and IADL (Han et al. 2008). The use of anticholinergic drugs is associated with poor psychological well-being (Kumpula et al. 2011). However, among dementia patients, use of anticholinergics has been associated with decreased self-care capacity (Rovner et al. 1988) but not with engagement in activity, which is an important indicator of the quality of life in patients with dementia (Kolanowski et al. 2009).

There are mixed results with anticholinergics and cognitive functions. Some studies have reported a decrease in MMSE score (Mulsant et al. 2003, Uusvaara et al. 2009). In addition, the risk of cognitive decline after electroconvulsive therapy (measured as an MMSE score decrease of at least 2 points) increased with elevated serum anticholinergic activity levels (Mondimore et al. 1983). In the study of Lu and Tune (2003) with Alzheimer disease patients, chronic exposure to anticholinergics decreased MMSE score at 2 years. There are also studies where anticholinergic drugs have had no effect on MMSE score (Miller et al. 1988, Sittironnarit et al. 2011). In addition, Lechevallier-Michel et al. (2005b) reported an only barely statistically significant decrease in MMSE on persons with anticholinergics. MMSE is a measurement tool of global cognitive function, but it appears to be less useful in detecting mild or transient impairment of the sort that often becomes clinically important in the early phases of drug toxicity (Miller et al. 1988). Minzenberg et al. (2004) used WAIS-R to determine global cognition, and anticholinergic medication had no effect on this parameter. In addition, in some studies anticholinergic drugs have had no effect on working memory. The results concerning anticholinergics and visuomotor functions are mixed, ranging from no effect to a decrease. In addition, tests about executive functions have produced mixed results. Verbal memory and learning, as well as verbal fluency are often unaffected by anticholinergics although some decrease has also been found. Visuospatial functions may be impaired or be unaffected by anticholinergics. Visual memory is mainly reduced by the anticholinergics. Language functions are either unaffected or decreased (For these results, see Table 7).

The use of anticholinergics has been associated with delirium in presurgical and postoperative patients (Tune et al. 1981, Miller et al. 1988) and patients with acute stroke (Caeiro et al. 2004), although no association was found in older patients at nursing home or in acute care ward (Schor et al. 1992, Luukkanen et al. 2011). In the older patients already diagnosed with delirium, exposure to anticholinergic medications has been independently and specifically associated with a subsequent increase in the severity of delirium symptoms (Han et al. 2001). However, in the study of Seifert et al. (1983), anticholinergics were not associated with confusion among older nursing-home residents (Table 8). On the other hand, the use of anticholinergics has been found as a strong predictor of mild cognitive impairment, but it did not increase the risk of dementia in the 8-year follow-up (Ancelin et al. 2006).

The use of anticholinergics has not been associated with increased mortality in older persons in long-term residential care (Kumpula et al. 2011, Luukkanen et al.

Table 7. Effects of anticholinergics on cognitive functions.

Age (y)	Residence	Global cognition	Working memory	Visuomotor functions	Executive functions	Verbal memory and learning	Verbal fluency	Visuospatial functions	Visual memory	Language functions	Reference
m 27	Healthy		(↓)/0	↓		↓	0				Curran et al. 1991
m 40	Schizophr. outpatients	0	0	0	↓/0	↓	0	↓	↓/(0)	↓	Minzenberg et al. 2004
> 60	Outpatients				↓/0		↓	↓		↓	Ancelin et al. 2006
≥ 70	Community	(↓)					↓		↓		Lechevallier-Michel et al. 2005b
≥ 65	Community	↓									Mulsant et al. 2003
> 65	Community					↓					Han et al. 2008
> 65	Community	↓									Fox et al. 2011
75-90	Community	0			↓	0	↓	0		0	Uusvaara et al. 2013
70-79	Community			↓							Hilmer et al. 2007
> 60	Healthy	0	0	0		0	0	0		↓/0	Sittironnarit
> 60	AD/MCI	0	0	0		0	0	0		0	et al. 2011
63-96	Dementia		0	↓							Mulsant et al. 2004
m 76,77	AD patients	↓									Lu and Tune 2003
m 67	Presurgical	0		0		↓					Miller et al. 1988

m = mean, ↓= decrease, ↑ = increase, 0 = no change, AD = Alzheimer's disease, MCI = mild cognitive impairment

Tests used:

Global cognition	MMSE; WAIS-R (Wechsler Adult Intelligence Scale)
Working memory	Digit and visual span forward; Digit span performance; Digit-span WAIS3; Digit and visual span backward; CogState; Baddeley reasoning task; Mental rotation
Visuomotor functions	Trails A; Trail making A; Digit cancellation; Symbol copying; Digit Symbol Substitution Test (WAIS); Digit symbol coding; Symbol digit modalities test; Pursuit rotor; Tapping
Executive functions	Trails B; Stroop color and word test; Wisconsin card sorting test; Ruff figural fluency test
Verbal memory and learning	California verbal learning test, trial 1 and sum of trials 1-5; Rey auditory-verbal learning test; Logical memory I and II (story A); Hopkins verbal recall test; Prose recall
Verbal fluency	Isaacs' set test; Delis-Kaplan executive function system; Verbal category fluency test; Word fluency
Visuospatial functions	Rey-Osterrieth complex figure design (copy accuracy)
Visual memory	Benton visual retention test; Serial visuospatial learning test, trial 1 and sum of trials 1-5; Rey-Osterrieth Complex figure design (delayed recall); Facial learning and recall
Language functions	Stroop color and word test, trial 1; Boston naming test

Table 8. Effects of anticholinergics on clinical conditions.

Age (y)	Residence	ADL	IADL	Self-care capacity	Delirium/ confusion	Engagement	Mortality	Reference
≥ 65	Community		↓					Han et al. 2008
≥ 65	Community						↑	Fox et al. 2011
≥ 65	Inpatients				↑			Han et al. 2001
≥ 65	Inpatients				0			Schor et al. 1992
m 79	Orthopaedic rehabilitation patients	↓						Koshoedo et al. 2012
55	Cardiac surgery postoperative patients				↑			Tune et al. 1981
> 70	Geriatric ward, nursing home				0			Luukkanen et al. 2011
> 65	Hip-fracture surgery patients						↑	Panula et al. 2009
m 78-83	Long-term care						0	Kumpula et al. 2011
m 80	Community						0	Uusvaara et al. 2011
m 82-83	Residential care	↓						Teramura-Grönblad et al. 2011
m 83	Nursing home				0			Seifert et al. 1983
m 84	Inpatients	↓						Lowry et al. 2011b, c
m 85	Nursing-home patients with dementia					0		Kolanowski et al. 2009
≥ 65	Inpatients, cognitive impairment				0			Campbell et al. 2011
m 80	Nursing home patients with dementia			↓				Rovner et al. 1988

ADL = activities of daily living, IADL = instrumental activities of daily living, ↓ = decrease, ↑ = increase, 0 = no effect, m = mean

2011) or in older patients with stable cardiovascular disease (Uusvaara et al. 2011), but among older male hip-fracture surgery patients, their use increased mortality (Panula et al. 2009).

However, one must bear in mind that anticholinergic-type effects may be commonly experienced also in individuals without anticholinergics in use. The study of Ness et al. (2006) compared anticholinergic symptoms between those subjects on anticholinergics and without anticholinergics, and the mean number of anticholinergic symptoms was 3.1 and 2.5 (those with and without anticholinergics, respectively). Only two symptoms, dry mouth and constipation, were more prevalent in the anticholinergic group. The frequencies of drowsiness, dry eyes and dry mouth were common in both groups.

2.6 ORTHOSTATIC HYPOTENSION

Orthostatic hypotension (OH) is a common manifestation of blood pressure dysregulation (Robertson 2008). It has been defined as a decrease of systolic/diastolic BP $\geq$ 20/10 mmHg measured 1 or 3 minutes after standing up from a supine position (Consensus statement 1996). OH can be divided into acute OH (which is usually secondary to medication, fluid or blood loss, or adrenal insufficiency) and chronic OH (frequently due to altered blood pressure regulatory mechanisms and autonomic dysfunction) (Gupta and Lipsitz 2007). However, there is also a faster form of OH which is called initial OH. This occurs immediately upon standing and typically passes within a few seconds but it may be associated with syncope in susceptible individuals. The slower form of OH, called delayed OH develops between 5 min and 45 min after taking an upright posture (Robertson 2008). Among older persons, there is considerable variation in OH over time, being most prevalent in the morning when the individual first arises (Ooi et al. 1997). OH is associated with significant morbidity and mortality (Masaki et al. 1998, Gupta and Lipsitz 2007, Verwoert et al. 2008) and it is an independent risk marker for cardiovascular disease (Benvenuto and Krakoff 2011) and atrial fibrillation (Fedorowski et al. 2010a). In addition, it is associated with the risk of coronary heart disease (Verwoert et al. 2008) and stroke (Eigenbrodt et al. 2000). Furthermore, in older nursing home residents, OH is also an independent risk factor for recurrent falls (Ooi et al. 2000).

Postprandial hypotension is often found in patients with orthostatic hypotension (Senard et al. 2001). This is also common in geriatric patients and an important but under-regocnized cause of syncope. Postprandial hypotension occurs within 2 hours after a meal (Luciano et al. 2010).

2.6.1 Pathophysiology

In healthy people, approximately 500-1000 ml of blood is transferred below the diaphragm upon assuming an erect posture, leading to decreased venous return to the heart, reduced ventricular filling, and a transient decrease in cardiac output and blood pressure. This triggers the activation of both high-pressure baroreceptors in the carotid sinus and aortic arch, and low-pressure receptors in the heart and lungs, resulting in increased sympathetic outflow and decreased parasympathetic outflow from the CNS, restoring cardiac output and blood pressure by increasing heart rate and vascular resistance (Gupta and Lipsitz

2007, Medow et al. 2008). In addition, there is an activation of the renin-angiotensin system, and consequent aldosterone release (Robertson 2008). Heart rate, stroke volume and vascular resistance influence to the blood pressure, and therefore impairments in the response of any of these parameters during postural change may result in OH (Gupta and Lipsitz 2007).

Aging is associated with a decrease in baroreflex sensitivity, resulting as a diminished heart rate response and an impaired α_1-adrenergic vasoconstrictor response to sympathetic activation. In addition, age-related reduction in parasympathetic tone results in less cardioacceleration during the vagal withdrawal that normally occurs with standing. Furthermore, the aged heart becomes stiff and non-compliant which results in an impaired diastolic filling. Aging is associated with a reduction in renin, angiotensin, and aldosterone, and an elevation in natriuretic peptides. This decreases the ability of the kidneys to conserve salt and water during periods of fluid restriction or volume loss, leading to rapid dehydration. They all greatly increase the risk of hypotension. Furthermore, systolic blood pressure tends to increase with age, and this further impairs adaptive responses to hypotensive stresses (Gupta and Lipsitz 2007).

In addition to these physiological changes, there are also pathologic causes for OH. These are secondary to central or peripheral nervous system diseases that result in autonomic insufficiency (Gupta and Lipsitz 2007) (Figure 1).

2.6.2 Prevalence and risk factors of OH

Orthostatic hypotension (OH) has a major effect on the quality of life of older individuals in whom it is a common condition with a prevalence ranging from 5 % to 30 % (Low 2008), although some conditions may increase the prevalence even further. In the older population, OH-related hospitalization rates are higher in men than in women, probably due to the better cerebral autoregulation in females (Deegan et al. 2011). In the study of Ooi et al. (1997), OH occurred in more than half of frail, elderly nursing home residents. Aging increases prevalence of OH (Rutan et al. 1992, Tilvis et al. 1996, Masaki et al. 1998, Wu et al. 2009). Among community-dwelling, non-instutionalized persons living in the USA, its prevalence increased from 15 % in the age group 65-69 up to 26 % in those aged 85+ (Rutan et al. 1992). Masaki et al. (1998) had lower prevalences (5.1 % - 10.9 % between age groups of 71-74 to 85+) in men living in Hawaii. Diabetes increases the prevalence of OH. In the study of Wu et al. (2009), the prevalence of OH increased from 13.8 % (normal glucose tolerance) to 17.7 % (pre-diabetes) and 25.5 % (diabetes). This study was conducted with younger participants (mean age 39.4-57.7 years depending on the group). The OH is more common in dementia with Lewy body, Alzheimer's disease and Parkinson's disease compared to normal controls (Andersson et al. 2008, Sonnesyn et al. 2009). The prevalence of OH/low blood pressure has claimed to be as high as 52 % in persons with dementia (Passant et al. 1997), and it is common even in mild dementia (41 % and 14 % in dementia and controls, respectively) (Sonnesyn et al. 2009).

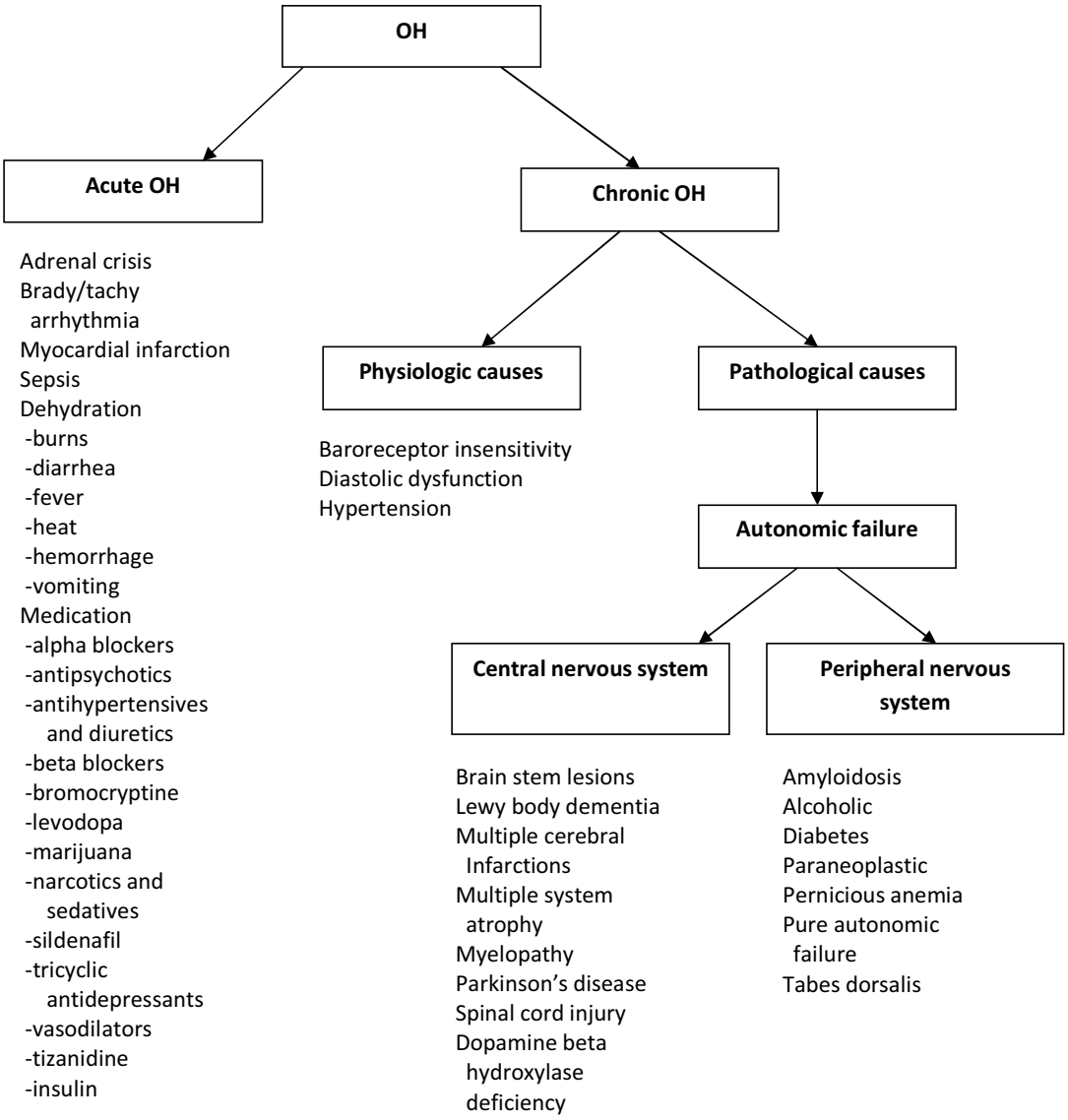

Figure 1. Etiology of orthostatic hypotension in older persons. Modified from Gupta and Lipsitz (2007), Robertson (2008) and Low and Singer (2008).

There are several factors which can increase the risk of OH e.g. age, smoking, low body mass index, hypertension, reduced kidney function, intravascular volume depletion, cardiac pump failure, venous pooling, carotid artery stenosis and carotid artery intima-media thickness, dementia, Parkinson's disease and other autonomic neuropathies (Rutan et al. 1992, Senard et al. 1997, Rose et al. 2000, Poon and Braun 2005, Andersson et al. 2008, Low 2008, Sonnesyn et al. 2009, Fedorowski et al. 2010b). In addition, reduced erythrocyte mass or the normocytic, normochromic anemia of chronic autonomic failure will also aggravate OH (Low and Singer 2008). In addition, COPD has been found to be associated with OH (Robertson et al. 1998).

Furthermore, some drugs may evoke OH, such as antihypertensive compounds, α-adrenergic blocking agents, tizanidine (Shah et al. 2006), antidepressants (e.g. tricyclic antidepressants, mianserin, paroxetine, sertraline, trazodone and venlafaxine, but not bupropion or moclobemide) (Poon and Braun 2005, Darowski et al. 2009), antipsychotics (e.g. clozapine, olanzapine, quetiapine and risperidone) (Mackin 2008), drugs for Parkinson's disease (Kujawa et al. 2000) and insulin (Madden et al. 2008). Conventional α_1-antagonists (e.g. prazosin, terazosin and doxazosin) which are used in the treatment of benign prostatic hyperplasia have been associated with OH. However, in the study of Ramdas et al. (2009), topical use of β-blocker eye drops was not associated with an increased risk in falling or dizziness when compared to the use of prostaglandin eye drops (to which no cardiovascular side-effects are known) in older patients with ocular hypertension or glaucoma. However, they stated that there may be an increased risk of OH (Ramdas et al. 2009). OH is also more common when the number of regular medications increase (Hiitola et al. 2009). In the study of Poon and Braun (2005) among veterans aged 75 years or more attending a geriatric clinic, the use of hydrochlorothiazide was associated with the highest prevalence of OH, followed by lisinopril, trazodone, furosemide and terazosin (65 % - 54 %). Patients with primary autonomic dysfunction or Parkinson's disease were excluded from the study.

2.6.3 Symptoms of OH

Symptoms of OH may vary from asymptomatic to severe. The typical symptoms of OH include lightheadedness, dizziness, blurred vision, weakness, fatigue, transient cognitive impairment, nausea, palpitations, tremors, headache and neckache (Consensus statement 1996). However, the symptoms may also be atypical such as lower extremity discomfort and backache (Arbogast et al. 2009). In fact, asymptomatic OH has been claimed to be rather common (Benvenuto and Krakoff 2011). Arbogast et al (2009) examined patients (mean age 70.8 years) with a decrease in systolic blood pressure more than 60 mmHg during a head-up tilt table test. They found that only 43 % of them had typical symptoms, while 24 % had atypical symptoms and 33 % of subjects were asymptomatic. However most patients with asymptomatic OH suffer subtle symptoms in situations where there is increased orthostatic stress, such as after a meal, during elevated ambient temperature, or after exertion (Low and Singer 2008).

2.6.4 Treatment of OH

Due to the several different causes of OH, its treatment may be challenging. Although OH is defined through strict changes in blood pressure, its treatment should not be aimed to achieve arbitary blood pressure goals. Instead, the treatment should be directed toward ameliorating symptoms, correcting the underlying causes of OH when possible, improving the patient's functional status, and reducing the risk of complications (Gupta and Lipsitz 2007). Nonetheless, severe supine hypertension should be avoided (Low and Singer 2008). Treatment of OH can be divided into nonpharmacological and, when necessary, pharmacological interventions.

2.6.4.1 Nonpharmacological therapies

When possible, the cause of OH should be treated. The first step involves careful assessment of the patient's medication and, if possible, removal of any medication that could precipitate OH. Possible conditions predisposing to OH should be corrected e.g. initiation of fluid replacement therapy to dehydrated patients; in fact a reasonable daily fluid intake is important for all older persons, in addition to salt supplementation (Low and Singer 2008).

Patient education is an important part of management of OH (Freeman 2008, Low and Singer 2008, Medow et al. 2008). Orthostatic demands are fairly constant throughout the day and if the subject is made aware of his/her orthostatic blood pressure pattern, many patients can plan their activities accordingly (Medow et al. 2008). Activities that decrease the venous return to the heart (coughing, straining, prolonged standing) should be avoided, especially in hot weather. Blood pressure may also increase with dorsiflexion of the feet before assuming upright posture, squatting and stooping forward. In addition, physical counter-manouvers (toe raising, leg crossing, thigh contraction, bending at the waist) may be helpful. Furthermore, waist high compression stockings and abdominal binders, as well as raising the head of the bed by 10-20 degrees at night have been claimed to be helpful (Gupta and Lipsitz 2007, Low and Singer 2008). Careful dietary instruction (e.g. avoiding large meals, decreasing alcohol intake and adhering to low cholesterol diets) is also important, since food evokes hypotensive responses secondary to postprandial shifts in blood flow to the splanchnic bed (Medow et al. 2008).

2.6.4.2 Pharmacotherapy

If nonpharmacological interventions fail to improve the patient's condition, a number of pharmacological agents are available to treat OH. Fludrocortisone reduces salt loss and expands blood volume (Gupta and Lipsitz 2007). It also increases the sensitivity of α-adrenoceptors (Low and Singer 2008). Midodrine (α_1-agonist) has selective vasopressor properties and it is effective in OH treatment.

However, both of these drugs cause supine hypertension (Low and Singer 2008). Baroreflex unloading occurs mainly with standing and is negligible when the patient is supine. Since neurotransmission in the autonomic ganglia is mediated by acetylcholine, it has been hypothesized that pyridostigmine (cholinesterase inhibitor) could improve ganglionic transmission primarily when the patient is standing, it should increase orthostatic blood pressure without worsening of supine blood pressure. Although in a study with older patients with severe autonomic failure pyridostigmine had no effect on OH (Shibao et al. 2010), others have indicated that it may be adequate for patients with mild OH (Low and Singer 2008).

There are also other drugs with a pressor effect, but their role in the treatment of OH is controversial (Low and Singer 2008). The vasodilating effects of prostaglandins may be blocked by prostaglandin inhibitors, and this has been beneficial in some OH patients. In addition, non-steroidal anti-inflammatory drugs reduce sodium excretion, thereby causing volume expansion (Medow et al. 2008). Caffeine inhibits adenosine-induced vasodilatation by blocking adenosine receptors. Erythropoietin may be effective in patients with anemia and autonomic dysfunction. Clonidine (α_2-adrenergic agonist) may be beneficial in patients with CNS causes of autonomic failure. Yohimbine (central α_2-adrenergic antagonist) may

also increase central sympathetic outflow in some patients with residual sympathetic nervous system efferent output (Gupta and Lipsitz 2007) and has been effective with patients with severe autonomic failure (Shibao et al. 2010). Nonselective β-blockers, particularly those with intrinsic sympathomimetic activity (e.g. pindolol) may have some effect, possibly due to the blockage of vasodilating β_2-receptors allowing unopposed α-adrenoceptor mediated vasoconstrictor effects to predominate (Freeman 2008). In addition, metoclopramide has been effective in OH treatment, probably due to vasoconstriction (Gupta 2005).

A new approach in the treatment of neurogenic OH has been the use of droxidopa. This is a prodrug that is converted by dopa decarboxylase into noradrenaline outside the CNS, therefore ameliorating the symptoms of OH in patients with neurogenic OH due to degenerative autonomic disorders (Kaufmann 2008, Mathias 2008).

When considering older persons, pharmacological treatment of OH needs to be considered with caution, especially for the drugs for which there are unconvincing results, as several drugs listed above (non-steroidal anti-inflammatory drugs, clonidine, metoclopramide) are not recommended for older persons due to their adverse effects (The American Geriatrics Society 2012 Beers Criteria Update Expert Panel). One must also bear in mind, that pharmacologic therapy alone is often inadequate, and non-pharmacological measures, including patient education, must represent the firm foundation for an overall treatment plan (Medow et al. 2008).

3 Aims of the Study

The purpose of this study was to examine some aspects (shown below) of pharmacotherapy in older persons. The specific aims were:

1. To examine which symptoms are experienced as drug-related by patients, and whether these are concordant with the judgment of the physician.

2. To find out, whether the results of the SAA assay associate with published ranked anticholinergic lists and whether SAA or ranked anticholinergic lists are applicable in determining the anticholinergic burden and anticholinergic adverse reactions during drug therapy.

3. To investigate the effect of CGA on drug use in general and on the prevalence of orthostatic hypotension in particular.

4 Materials and methods

4.1 THE GeMS STUDY

The GeMS study (Geriatric Multidisciplinary Strategy for the Good Care of the Elderly) is a multi-disciplinary population-based health intervention study that took place between the years 2004-2007. In the study, a random sample of 1000 people was drawn from all of the people ≥75 years living in the city of Kuopio (88 253 inhabitants, 5615 of whom were aged ≥75 years), Eastern Finland on 1st November 2003. They were randomized with computer-generated numbers into intervention (n=500) and control (n=500) groups. Of the randomized subjects, 162 declined to attend to the study, 55 died before the examination and 2 moved to a different municipality. The participation rate was 78 % (n=781) in the entire population, 81 % (n=404) in the intervention group and 75 % (n=377) in the control group. At baseline, 233 of the participants were men and 548 women with a mean age 81.7 years (range 75.3 – 99.0). The vast majority (n=700) were home-dwelling and 81 were living in institutionalized care.

Those 781 persons who participated in the study, underwent a structured clinical examination and an interview conducted by three trained nurses in 2004. This was repeated to all study subjects in 2005, 2006 and 2007. During the study, all participants had normal access to primary and specialized health care.

After the baseline examination by the trained nurses, the subjects in the intervention group underwent a comprehensive geriatric assessment (CGA) annually between the years 2004-2006. During the CGA, they were examined by two physicians (trainees in geriatrics), who performed an interview and clinical examination including a critical drug assessment. If needed, the physicians made new diagnoses or referred the patient to a specialist (e.g. ophthalmologist). In addition, two physiotherapists tested the patients' functional capacity, strength and balance and compiled a tailored training program for each individual. This included an opportunity to participate in supervised muscle strength and balance training once a week in a gym, with the emphasis on the lower limbs to increase mobility (Lihavainen et al. 2012). Those individuals considered to be at risk of malnutrition (short form of MNA ≤ 11, Nykänen et al. 2012) received also nutritional intervention from a nutritionist. The tailored nutritional intervention consisted of two meetings with the nutritionist in the years 2005 and 2006, and of telephone counselling at least every two months during the intervention. In this intervention, the nutritionist helped the participants draw up their own meal plan with enough energy and proteins, and aimed to reinforce the dietary advice and to give additional support. In addition, two dentists examined the oral health of the subjects at least twice during the study period (Komulainen et al. 2012). The flow of the study subjects is shown in Figure 2.

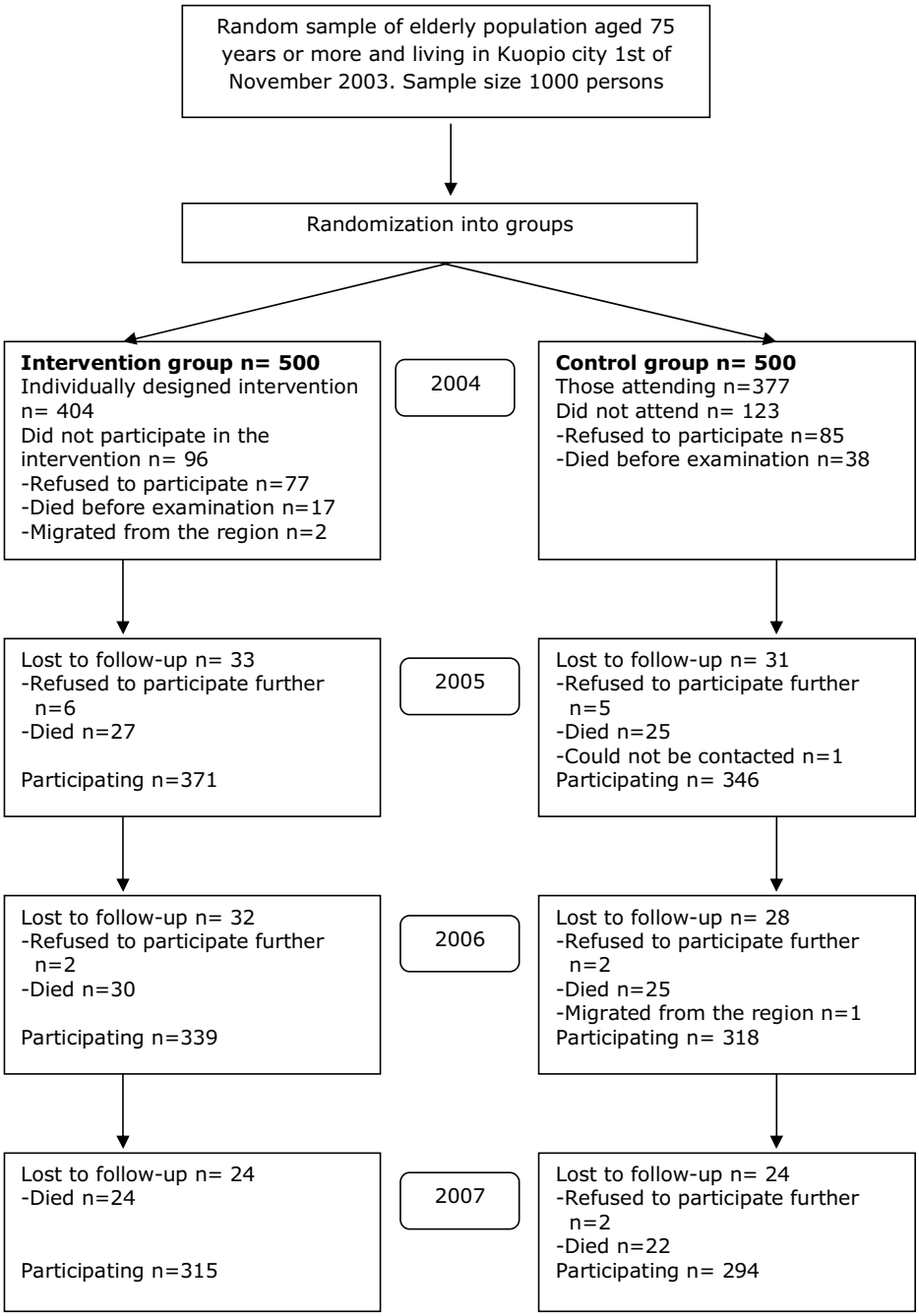

Figure 2. Flow chart of persons in the GeMS study during the years 2004-2007.

The participants of the four studies were as follows:

Study I

In the first study, the study population consisted of those subjects in the intervention group who attended into the study at 2004 (n=404). A total of 360 of those were home-dwelling at the time of the investigation, and 44 individuals were in institutionalized care. Eight patients did not respond to the question about adverse effects, mostly due to problems in cognition or difficulties in speech.

Study II

The population of the *Study II* consisted of those whose blood samples were drawn in 2004 (total n=717, n=378 and n=339 for intervention and control groups, respectively) After exclusion of the persons whose SAA samples were deemed unusable, the number of participants was 621. Most of them were home-dwelling (n=563) and the number of persons living in institutionalized care was 58. Subjects with and without dementia (n=129 and 492, respectively) were analyzed separately, since dementia may itself have an effect on some of the outcomes studied.

Study III

The population of the *Study III* consisted of the home-dwelling population in the intervention and control groups, who attended to the GeMS study in years 2004 and 2005 (n=331 and n=313 for intervention and control groups, respectively). Flow chart of persons in this study is presented in the article (**III**).

Study IV

In this study, the population consisted of persons (home-dwelling and in institutionalized care) in whom the orthostatic BP measurements were performed at least once during the GeMS study, and therefore the number of participants varied between the years. At baseline, the number of participants was 697 (n=365 and n=332 for intervention and control groups, respectively). The number of participants decreased every year of the study and at the end of the study, the number of participants tested for OH was 583 (n=304 and n=279 for intervention and control groups, respectively). Flow chart of persons in this study is presented in the article (**IV**).

4.2 DATA COLLECTION

The participants were annually interviewed by three trained nurses at the outpatient clinic. The structured interview and examination included items pertaining to sociodemographic factors, living conditions, social contacts, health behavior and state of health and also measurements of blood pressure and orthostatic tests. The protocol also included laboratory tests (serum electrolytes, complete blood count, glucose, thyroid hormone, lipids, albumin and vitamin B_{12} levels) in the years 2004 and 2006. Blood samples for

subsequent measurements of anticholinergic levels were also stored at -70°C prior to analyses. The subjects were asked to bring along their prescription forms and medication containers to the interview. If the individual could not answer the questions, the information was provided by a close relative or caregiver. Among other questions, they were asked about possible drug-related adverse effects using an open type of questioning ("Have you had problems with your medication, e.g. adverse effects or has a drug that you were using been changed or discontinued due to an adverse effect?") The researchers had also access to medical records from the municipal health centre, home nursing service, local hospitals and Kuopio University Hospital. If the subject was unable to visit the outpatient clinic, a home visit was made by a trained nurse to conduct the interview and examination and to check the use of drugs. Hospitalized subjects or those living in a nursing home were interviewed and examined in their current residence.

The physician interviewed and examined patients in the intervention group generally within two weeks after the nurse's interview and examination. The physician had access to the information recorded by the nurse. The clinical examination included a careful evaluation of cognition, mood, orthostatic reactions as well as the presence of possible adverse drug events. The physician also evaluated the indications for all drugs in use, and those drugs without an indication were withdrawn. When necessary (e.g. in case of new diagnoses as result of clinical examination), the patient's medication was adjusted.

Health experience (subjective health) was inquired during the interview by the study nurse by a question "How you describe your present health?" with 5 options to answer (1=good, 2= quite good, 3=mediocre, 4=quite poor, 5=poor).

4.2.1 SAA assay (II)

The assay was based on the method of Tune and Coyle (1980). It measures the level of unbound anticholinergic activity in serum by displacement of a radioligand from muscarinic receptors. Muscarinic receptor antagonists compete with L-quinuclidinyl [phenyl-4-^{3}H] benzylate (QNB) (Amersham Biosciences, Germany) and proportionally reduce its binding to the receptors. The binding of tritiated QNB to membranes containing muscarinic receptors from Wistar rat cerebral cortex and striatum was measured in the presence of atropine as an anticholinergic standard, and in the presence of compounds with anticholinergic activity in the serum samples.

Membranes were prepared by sonicating and centrifuging fresh Wistar rat cerebral cortex and striatum sample, after which the supernatant was frozen at -70°C. Serum samples were also stored in -70°C.

Protein concentration was assayed and adjusted to approximately 1.5 mg/ml with assay buffer. The assay was performed in a 1 ml/well 96-well plate, to which atropine standard or patient's serum was pipetted to followed by tritiated QNB. Finally, rat brain membrane preparation was added.

After incubation up to 1 h, the reaction was stopped by filtration on glass fibre filters. Samples were washed with polyethylenimine and air-dried. Scintillation mats were then melted on the filters and radioactivity measured in Wallac MicroBeta counter (PerkinElmer, USA).

Prior to the assay on human samples, the proper final concentrations and amounts of the individual components in the incubation solution were optimised. To avoid animal to animal differences on the level of muscarinic receptors on rat cortex membrane preparations, these were assayed in different samples. Saturation curves were assayed for tritiated QNB, the optimal protein concentration was determined and a suitable calibration curve was set. The concentration range of the labelled ligand was between 0.1 and 1 times the dissociation constant. In all assays, the concentration of the binding sites in the rat cortex membrane preparation added to the binding assay was between 0.2-1 mg of protein/ml. Variability of the counts per minute readings was verified to be normally distributed and despite the variance in the mean readings, the precision was comparable from between experiments. Atropine calibration curves and an internal control of known activity were included in each experiment.

4.2.2 Vision (II)

Both short- and long-distance vision were measured using E tables.

4.2.3 Measurements of cognitive capacity, mood and functional ability (II)

The focus was set separately on persons with and without dementia (n=129 and 492, respectively), since dementia may itself have an effect on some of the outcomes studied (MMSE, ADL and IADL). The cognitive capacity and mood of the participants were assessed with Mini Mental State Examination (0-30 points, higher points indicate better cognition) (Crum et al. 1993) and Geriatric Depression Scale (GDS-15) (0-15 points, higher scores are suggestive of depression) (Yesavage et al. 1982), respectively. Basic functional capacity (e.g. toileting, dressing) was assessed using Barthel Activities of Daily Living Index (scale 0-100 points, with higher points indicating better function) (van der Putten et al. 1999). Other activities like shopping and using the phone were assessed using Lawton & Brody's Instrumental Activities of Daily Living scale (0-8 points, higher points indicate better function) (Lawton and Brody 1969).

4.2.4 Anticholinergic lists (II)

In *Study II*, three different published anticholinergic lists were used. The Anticholinergic drug scale (ADS) devised by Carnahan et al. (2006) includes 536 drugs, including 419 classified as having no anticholinergic activity. The ADS includes also drug doses in the determination of anticholinergic activity. The Anticholinergic Risk Scale (ARS) was published by Rudolph et al. (2008). It includes 49 drugs which all possess anticholinergic activity and is based on the drugs most commonly prescribed within the Veterans Affairs Boston Healthcare System. The third list used in the study (Chew et al. 2008) is based on the *in vitro* affinity on muscarinic receptors and includes 107 drugs commonly used by older persons with 85 of them classified as having no or minimal anticholinergic activity.

4.2.5 Causative medication (IV)

In *Study IV*, the list of causative drugs (ie. drugs associated with OH) was compiled based on the literature (Baldessarini 2006, Baldessarini and Tarazi 2006, Gupta and Lipsitz 2007, Robertson 2008) and clinical judgment (by Professors Sirpa Hartikainen and Risto Huupponen) (Table 9).

Table 9. Classification of drugs associated with OH (ATC code) used in the study.

Cardiac therapy (C01)	Bromocryptine (G02CB01)
Antihypertensives (C02)	Sildenafil (G04BE03)
Diuretics (C03)	Tizanidine (M03BX02)
Peripheral vasodilators (C04)	Opioids (N02A)
Vasoprotectives (C05)	Dopaminergic drugs for Parkinson's disease (N04B)
β-blockers (C07)	Antipsychotics (N05A)
Calcium channel blockers (C08)	Tricyclic antidepressants (N06AA)
Drugs affecting renin-angiotensin-aldosterone system (C09)	Non-selective monoamine oxidase inhibitors (N06AF)

4.2.6 Statistics (I – IV)

Data were entered into the SPSS statistical software (SPSS Inc., Chicago, USA). Different versions of the software were used, versions 11.5 and 14.0 (**I**), and versions 17.0 and 19.0 (**IV**). In addition, SAS software, version 9.1 (**III**) and 9.2 (**II**) (SAS Institute, Inc., Cary, NC, USA) and Prism software (version 5.03, GraphPad Software Inc., USA) (**IV**) were used.

In *Study II*, the differences between anticholinergic drug use among the three lists studied were analysed with two-way ANOVA. The other results in *Study II* were not normally distributed, and therefore Kruskal-Wallis one-way analysis of variance test was used. In *Study III*, unadjusted odds ratios and their 95 % confidence intervals were calculated, and in *Study IV*, differences between groups with different OH status were tested with Pearson chi-square test for categorical variables and with Mann-Whitney U test for continuous variables.

In addition, Markov models were used in *Study IV* in the measurement of CGA on orthostatic hypotension. The manifest Markov model was used to model change over time in observed categorical variables by estimating conditional probablilities of moving from one state at one period to another state at another period. Latent Markov model permitted a more accurate estimation of stability and change by separating variability due to measurement error from true change on the latent level. In Markov models, the individual's current state was determined by his/her behaviour during the period immediately preceding the test (first-order process).

4.2.7 Ethical issues

The participants or their relatives signed written informed consent to the study. This study was approved by the Research Ethics Committee of the Hospital District of Northern Savo.

5 Results

5.1 MAIN CHARACTERISTICS OF THE STUDY POPULATION AT BASELINE

Main characteristics and the most common medical conditions of the study population at baseline (in the year 2004) in the population attending to the GeMS study (n=781) are shown in Tables 10-11. The data in Table 11 is based on the special reimbursement codes by the Social Insurance Institution of Finland.

Table 10. Main characteristics of the study population at baseline.

	Home-dwelling	**Institutionalized**	**All**
n	700	81	781
Age, mean (range)	81.3 (75.3-99.0)	85.6 (75.6-98.6)	81.7 (75.3-99.0)
Sex, n (%)			
-male	214 (30.6)	19 (23.5)	233 (29.8)
-female	486 (69.4)	62 (76.5)	548 (70.2)
Education ≤6 years, n (%)	342 (48.9)	16 (19.8)	358 (45.8)
MMSE ≤25, n (%)	221 (31.6)	68 (84.0)	289 (37.0)
GDS >5, n (%)	34 (4.9)	12 (14.8)	46 (5.9)
Barthel <80, n (%)	36 (9)	61 (75.3)	97 (12.4)
IADL ≤6, n (%)	242 (34.6)	61 (75.3)	303 (38.8)

Table 11. The most common medical conditions in the study population (n=781) at baseline.

Medical condition	**n**
Hypertension	305
Coronary heart disease	241
Cardiac failure	106
Dyslipidemia associated with coronary heart disease	74
Glaucoma	73
Asthma and COPD	68
Diabetes	56
Alzheimer's disease	51
Hypothyreosis	45
Rheumatoid arthritis, disseminated connective tissue disorders	42
Chronic cardiac arrhythmia	41

5.2 POTENTIAL ADVERSE DRUG REACTIONS ACCORDING TO PATIENTS AND PHYSICIANS (I)

At the beginning of the GeMS study, there was a marked disparity between adverse drug reactions reported by the patients (n=404) and those observed by the physician in the intervention group. Out of 404 patients, almost all (n=399, 98.8 %) were using at least one drug either regularly or on an on-demand-basis, with 390 (96.5 %) using drugs regularly at time of the clinical examination. The most widely used drug classes were cardiovascular

and nervous system drugs, drugs affecting blood or blood forming organs, as well as digestive tract and metabolism drugs. The mean number of regular drugs per patient was 5.2 (range 0-23, median 5) and on-demand drugs 1.4 (range 0-18, median 1).

Most of the patients did not have any apparent adverse drug reactions (n=215, 53.2 % of the sample). However, the physician did detect some drug-related adverse reaction at the time of the investigation in 97 patients (24.0 %), while only 46 patients (11.4 %) reported that they have or have had at least one drug-related adverse reaction.

The mean number of drugs in use increased with adverse reactions; while the mean number of drugs in those patients without either self-perceived or physician-detected adverse reactions were 5.4 (4.9-5.9) (mean (95 % confidence interval (CI))) drugs, the number increased to 7.3 (6.0-8.6) and 9.0 (8.2-9.7) with those who self-reported adverse drug reactions and in whom physician identified adverse drug reactions, respectively.

In general, the potential adverse reactions identified by the physicians and reported by the patients differed substantially. The types of adverse reactions are shown in Table 12. The physicians identified mainly adverse reactions related to the cardiovascular system, central nervous system, dry mouth, and gastrointestinal and urinary tract, while patients reported mainly adverse reactions related to skin, central nervous system and gastrointestinal tract.

Table 12. The number of potential adverse drug reactions among the study group. OH = orthostatic hypotension, EP = extrapyramidal.

Adverse reaction	**Identified by the physician (n=97)**	**Reported by the patient (n=46)**
Xerostomia	15	1
Cardiovascular	52	0
-OH	*49*	*0*
CNS	28	18
-EP symptoms	*14*	*1*
Gastrointestinal	7	14
Urinary	6	0
-retention	*4*	*0*
Skin	1	19
Others	5	6

When the patients with self-reported adverse reactions and physician-diagnosed adverse drug reactions were compared, only seven patients (1.7 % from the sample) belonged to both groups. Furthermore, only four of these subjects reported the same adverse reaction which had been identified by the physician; in the other three patients the self-perceived and physician-diagnosed adverse reactions did not coincide. One patient reported shaking, and the physician suspected a drug-drug interaction due to the concomitant use of citalopram and tramadol, which could well account for the symptom reported by the patient (increased serotonergic tone). This patient is not included in the table, since the physician had not categorized the finding as an adverse reaction.

In institutionalized care, the frequency of adverse reactions observed by the physician and self-reported by patients were 59.1 % and 4.5 %, respectively. On the other hand,

among the home-dwelling population, the corresponding numbers were 23.6 % and 15.6 %, respectively.

5.3 ANTICHOLINERGIC ADVERSE REACTIONS, RANKED LISTS AND SAA ASSAY (II)

With respect to the drugs in regular use by the study population, Carnahan's list covered 88 %, Chew's list 51 % and Rudolph's list 5 %. The SAA values of the study population varied between 2.3 – 82.7 pmol/ml (median 9.3 pmol/ml) of atropine equivalents. When the SAA values were measured against the outcomes (vision, MMSE, GDS, ADL and IADL), there was no association in either of the study groups (persons with or without dementia). In addition, there was no association between the number of regular drugs in use and SAA. When SAA was compared with scores from the anticholinergic lists, only Chew's list scores were associated with the SAA values ($p<0.05$).

The number of regular drugs in use was associated with all three anticholinergic lists in both individuals without and with dementia. In those without dementia, there was a statistically significant association with scores of all three ranked lists and short-distance vision, MMSE, GDS, ADL and IADL.

In the subjects with dementia, these associations were weaker, an association was found only for short-distance vision and lists by Chew and Carnahan as well as for ADL and IADL and lists by Carnahan and Rudolph.

5.4 EFFECT OF CGA ON DRUG USE (III)

The study physicians revealed significant adverse-effects from existing medication in 35 patients, a significant risk of a drug-drug interaction in seven patients, the evident need for modification of drug doses in 58 patients and suboptimal treatment of the disease with a potential effect on survival or functionality in 56 patients. In 24 patients, the indication why the medication had been prescribed was unclear. Three patients could not use their existing medication. In addition, study physicians found 15 previously undiagnosed subjects with Alzheimer's disease and two patients with Lewy body disease. An appropriate treatment regimen was initiated in these patients.

During the follow-up, the mean number of regular and on-demand drugs in use increased in both the intervention (from 4.7 to 5.2 and from 1.4 to 1.7, respectively) and control (from 4.8 to 5.2 and from 1.1 to 1.3, respectively) groups. In the cases with significant differences in medication changes between intervention and control groups, there was always a higher amount of changes in the intervention group. The alterations of medications are summarized in Tables 13-14.

Table 13. The therapeutic classes of regular drugs in which more statistically significant changes occurred in the intervention group compared with the control group. Grouping is based on the ATC classification (given in parenthesis).

New prescriptions	Cessations of medication	Increase of dosage	Decrease of dosage
Calcium in combination with other drugs (A12AX)	Vitamins (A11)	β-adrenoceptor antagonists (C07)	Cardiovascular system drugs (C)
Acetylsalicylic acid (B01AC06)	Calcium (A12AA)	Agents acting on the renin-angiotensin system (C09)	Nervous system drugs (N)
Antihemorrhagics (B02)			
Vitamin B12 and folic acid (B03B)			
Drugs for treatment of bone diseases (M05)			

Table 14. The therapeutic classes of on-demand drugs in which more statistically significant changes occurred in the intervention group compared with the control group. Grouping is based on the ATC classification (given in parenthesis).

New prescriptions	Cessations of medication
Cardiac therapy (C01)	Cardiac therapy (C01)
Hypnotics and sedatives (N05C)	Anxiolytics (N05B)
Ophthalmologicals (S01)	

The study physicians changed medication (regular or on-demand) in 200 patients, including 173 initiations and 55 cessations of regular medications in 114 and 41 patients, respectively (Table 15). In general, they were responsible for 35 % of new prescriptions, 16 % of drug cessations, 6 % of dose increases and 70 % of dose decreases. About 58 % of the drugs initiated by the study physicians were still in force after one year. Health experience was more frequently increased in the intervention than in the control group.

Table 15. The contribution of study physician (%) to all performed drug changes over the one-year period in the intervention group.

Therapeutic group	New prescriptions	Cessations of drugs	Increase of dose	Decrease of dose
Alimentary tract and metabolism	38.0	6.1	15.8	13.3
Blood and blood forming organs	64.0	15.4	0.0	100.0
Cardiovascular system	12.7	16.7	4.7	63.9
Genito urinary system and sex hormones	21.1	5.6	0.0	100.0
Systemic hormonal preparations, excluding sex hormones and insulins	55.6	0.0	0.0	100.0
Anti-infectives for systemic use	0.0	0.0	0.0	0.0
Musculo-skeletal system	59.1	30.4	0.0	50.0
Nervous system	40.8	29.0	7.7	105.6
Respiratory system	41.7	15.4		
Sensory organs	0.0	0.0		
TOTAL	35.4	15.6	6.4	69.9

5.5 EFFECT OF CGA ON ORTHOSTATIC HYPOTENSION (IV)

During the study, the amount of OH-positive subjects declined from 123 (35.0 %) to 77 (28.0 %) in the intervention group, while their number increased from 105 (32.8 %) to 100 (40.8 %) in the control group. The differences between the groups were statistically significant two (31.0 % vs. 39.8 %, p=0.028) and three (28.0 % vs. 40.8 %, p=0.002) years after baseline.

During the study, transitions of patients between OH-positive and OH-negative groups were frequent (Table 16). There were no statistically significant differences between intervention and control groups except in the transitions two to three years after baseline, when individuals in the control group were over two times more likely to remain OH positive than subjects in the intervention group (risk ratio (RR) 2.20, 95 % CI 1.36-3.55) and only 0.64 times as likely to stay OH-negative as those in the intervention group (RR 0.64, 95 % CI 0.45-0.90).

In the intervention group, BP was recorded for 267 subjects at every measurement point while for 98 persons at least at one measurement point was missing. In the control group, the corresponding figures were 208 and 124, respectively. Markov models were used to examine stabilities and changes in OH status over time in both groups. The manifest Markov model chain was applied, and subsequently extended to the latent Markov model (LMM), which takes the possibility of measurement error into account.

Table 16. The number of persons whose OH status remained the same for 1-3 years during the study.

	OH-positive persons			**OH-negative persons**		
	Intervention group	Control group	Total	Intervention group	Control group	Total
2004-05	45	38	83	169	135	304
2005-06	37	38	75	168	118	286
2006-07	32	53	85	144	97	241
2004-06	20	20	40	123	85	208
2005-07	14	21	35	118	77	195
2004-07	10	15	25	90	51	141

Based on the LMM, significant group differences were detected. In the intervention group, the transition probabilities to develop OH were 3.9 % lower than for the control group and the transition probabilities to recover from OH were 10.1 % higher than for the control group in each of the two consecutive waves. Transition probabilities to remain in the OH-positive group were 9.3 % higher and, to remain in the OH-negative group 5.8 % lower in the control group than in the intervention group.

According to univariate LMMs with one covariate at a time for the OH state at baseline, the odds of individuals aged 85 years or more having OH at the baseline were 1.6 times (odds ratio (OR) 1.59, CI 1.05-2.40) greater than the odds of those aged 75 to 79 years old. In addition, subjects with Parkinson's disease were 3.7 times (OR 3.71, CI 1.17-11.75) more likely to have OH during the study period. The existence of diabetes, hypertension, coronary artery disease, cardiac insufficiency or dementia or use of drugs associated with OH were not associated with having OH.

At baseline, there were 254 persons in the intervention group and 208 persons in the control group using one or more regular drugs associated with OH (Table 17). The only statistically significant difference between the groups occurred during the first year of the intervention, when there were more dosage decreases of drugs associated with OH in the intervention group.

Table 17. The number of patients in the intervention and control groups with changes in regular medicines associated with OH throughout the study period.

Drugs associated with OH	Intervention group	Control group	OR (95 % CI)
2004-2005: persons 2004	254	208	
• initiations	101	78	1.10 (0.75-1.60)
• cessations	91	66	1.20 (0.81-1.77)
• dose increases	42	27	1.33 (0.79-2.24)
• dose decreases	52	27	1.73 (1.04-2.86) *****
2005-2006: persons 2005	247	193	
• initiations	83	61	1.10 (0.73-1.64)
• cessations	62	46	1.07 (0.69-1.66)
• dose increases	38	21	1.49 (0.84-2.63)
• dose decreases	37	27	1.08 (0.63-1.85)
2006-2007: persons 2006	226	203	
• initiations	79	64	1.17 (0.78-1.75)
• cessations	58	51	1.03 (0.67-1.59)
• dose increases	33	36	0.79 (0.47-1.33)
• dose decreases	33	25	1.22 (0.70-2.13)

Statistically significant changes are shown with *.

When medication changes were measured against OH status, statistically significant changes emerged in the intervention group, as drugs associated with OH (Table 9) were cancelled more often in OH-positive than in OH-negative subjects during the second year of the intervention, and more dosage increases in the OH-associated medication occurred in the OH-positive than in OH-negative subjects during the third year of the intervention (Table 18).

Table 18. The number of patients in the intervention and control groups with changes in regular medicines associated with OH throughout the study period.

Drugs associated	Intervention group			Control group		
with OH	OH+	OH-	OR (95 % CI)	OH+	OH-	OR (95 % CI)
2004-2005: persons 2004	89	165		72	136	
• initiations	33	68	0.84 (0.49-1.43)	14	64	0.27 (0.14-0.53) *
• cessations	38	53	1.57 (0.92-2.68)	16	50	0.49 (0.26-0.95)
• dose increases	14	28	0.91 (0.45-1.84)	9	18	0.94 (0.40-2.21)
• dose decreases	23	29	1.63 (0.88-3.04)	13	14	1.92 (0.85-4.34)
2005-2006: persons 2005	63	184		50	143	
• initiations	24	59	1.30 (0.72-2.36)	14	47	0.79 (0.39-1.61)
• cessations	23	39	2.14 (1.15-3.99) *	10	36	0.74 (0.34-1.64)
• dose increases	12	26	1.43 (0.67-3.04)	5	16	0.88 (0.31-2.55)
• dose decreases	14	23	2.00 (0.96-4.18)	9	18	1.52 (0.64-3.65)
2006-2007: persons 2006	69	157		80	123	
• initiations	21	58	0.75 (0.41-1.37)	21	43	0.66 (0.36-1.23)
• cessations	16	42	0.83 (0.43-1.60)	20	31	0.99 (0.52-1.89)
• dose increases	15	18	2.15 (1.01-4.56) *	12	24	0.73 (0.34-1.55)
• dose decreases	12	21	1.36 (0.63-2.96)	10	15	1.03 (0.44-2.42)

Statistically significant changes are shown with *.

In the control group, less initiations of OH-associated regular and on-demand drugs took place in the OH-positive than in OH-negative patients with respect to OH-associated regular and on-demand drugs, respectively, during the first year after baseline (Tables 19-20). There were no other statistically significant changes between the groups and/or OH status in on-demand medication.

Table 19. The number of patients in the intervention and control groups with changes in on-demand medicines associated with OH throughout the study period.

Drugs associated with OH	**Intervention group**	**Control group**	**OR (95 % CI)**
2004-2005: persons 2004	105	63	
• initiations	54	26	1.51 (0.80-2.83)
• cessations	29	19	0.88 (0.44-1.76)
2005-2006: persons 2005	120	63	
• initiations	45	15	1.92 (0.97-3.82)
• cessations	28	14	1.07 (0.51-2.21)
2006-2007: persons 2006	112	61	
• initiations	33	14	1.40 (0.68-2.89)
• cessations	26	14	1.02 (0.48-2.13)

Table 20. The number of patients in the intervention and control groups with changes in on-demand medicines associated with OH throughout the study period.

Drugs associated	**Intervention group**			**Control group**		
with OH	**OH+**	**OH-**	**OR (95 % CI)**	**OH+**	**OH-**	**OR (95 % CI)**
2004-2005: persons 2004	36	69		22	41	
• initiations	16	38	0.65 (0.29-1.47)	4	22	0.19 (0.06-0.67) *
• cessations	9	20	0.82 (0.33-2.04)	4	15	0.39 (0.11-1.35)
2005-2006: persons 2005	28	92		18	45	
• initiations	11	34	1.10 (0.46-2.63)	6	9	2.00 (0.59-6.79)
• cessations	5	23	0.65 (0.22-1.91)	5	9	1.54 (0.43-5.44)
2006-2007: persons 2006	37	75		24	37	
• initiations	11	22	1.02 (0.43-2.41)	6	8	1.21 (0.36-4.06)
• cessations	9	17	1.10 (0.43-2.77)	4	10	0.54 (0.15-1.97)

Statistically significant changes are shown with *.

6 Discussion

6.1 METHODOLOGICAL CONSIDERATIONS

The GeMS study was a population-based intervention study with a random sample of 1000 persons aged at least 75 years living in Kuopio area at the beginning of the study in 2004. At baseline, the response rate of the study was 78.1 %, which can be considered as adequate (Jesson 2001). The population attending the study was rather heterogenous, from home-dwelling persons with no regular drugs in use to institutionalized persons with several morbidities, reflecting the health status of this age group (Cho et al. 2011). The results are therefore likely to be generalizable to older persons living in Kuopio area. As the population of Finland is ethnically homogenous and health care provided by municipalities is organized according to a national framework (Ministry of Social Affairs and Health 2008), the results are also likely to be generalizable to older persons throughout Finland. However, the generalizability of the results to countries with different health care systems may be limited.

CGA is a multi-disciplinary assessment. In addition to the physician, the team has included members (generally 4-5) from different specialities such as nurses, physiotherapists, social workers, nutritionists, occupational therapists, pharmacists, audiologists, dentists, psychologists, and pastoral carers (Ellis and Langhorne 2005). However, in some studies, the team has consisted of only a physician and a nurse (Stuck et al. 1995, Li et al. 2010). The CGA team in the GeMS study consisted of physicians, trained nurses, dentists, a physiotherapist and a nutritionist, thus representing the comprehensive CGA team.

Data collection of the study was performed by trained personnel, who conducted the study following written guidelines. The accuracy of medical and medication data was verified using patient records from the municipial health centre and Kuopio University Hospital, resulting in well-documented data about medication use. A care manager (study nurse or physiotherapist) was appointed for every patient participating in the study. The CGA team (including physicians, study nurses, physiotherapist and nutritionist) had weekly meetings with a geriatrician (Sirpa Hartikainen) to discuss about the patients and to receive guidance, ensuring continual senior support.

In addition, study physicians had separate meetings with Prof. Hartikainen to discuss about patients' medication, diagnoses, need for referrals and treatment plans. They also received training about ADRs. When assessing the medication, they focused on the appropriateness of medication, indications and dosages with special attention being paid to the use of psychotropic agents.

The individuals attending the GeMS study were old, and therefore some loss in participants during the study period was to be expected. At the end of the study in 2007, 78 % of those who participated to the study at baseline were still attending in both groups. The first three studies of this thesis concentrated on the baseline (**I, II**) or on the first year of the GeMS study (2004-2005) (**III**). The last study (**IV**) was the only one in which patient loss

would have played a role, since this examined the participants during the whole trial period (2004-2007). This loss was taken into account by using Markov models.

The instruments used in this study to measure potential anticholinergic ADEs (i.e. IADL (Barberger-Gateau et al. 1992, Landi et al. 2000, Kauppi et al. 2005, Vittengl et al. 2006), ADL (Stone et al. 1994, Landi et al. 2000, Odlund Olin et al. 2005, Venturelli et al. 2011), GDS-15 (Burke et al. 1991, Vinkers et al. 2004, Smalbrugge et al. 2008) and MMSE (Naugle and Kawczac 1989, Landi et al. 2000, Boban et al. 2012)) have been widely used in geriatric epidemiology and therefore should be applicable for our population.

The anticholinergic lists compiled in this study have been used in several studies (e.g. ADS (Nebes et al. 2012, Bhattacharya et al. 2011, Boudreau et al. 2011, Chatterjee et al. 2010, Low et al. 2009), ARS (Nebes et al. 2012, Kumpula et al. 2011, Lowry et al. 2011a, Lowry et al. 2011b, Koshoedo et al. 2012) and Chew (Ehrt et al. 2010)). However, it remains an open question whether these lists truly measure anticholinergic ADRs. There are several other items that may cause similar effects to those evoked by anticholinergic drugs (see Table 4).

However, there are also some limitations to be taken into consideration. The CGA was generally performed within two weeks after the nurse's interview, and although in some cases changes in the subject's medication or health status may have occurred, those were rare. In addition, the participants in the GeMS study were examined only once a year, and therefore data on medication and physiological status is available only on an annual basis. It is likely that during that period, there could have been short-term changes in health status and subsequently in the medication (e.g. infections treated with antibiotics, increase of cardiac failure medication as a response to decreased physiological status due to infections etc.), but no information about these events is available.

Due to the multi-disciplinary nature of the intervention, it is impossible to separate the results of one aspect (e.g. the medication assessment) from the entire CGA. It is likely that the beneficial effects seen on the study population (e.g. Lihavainen et al. 2012) result from the sum of all changes achieved during the intervention process.

Markov models were developed by statistician Piia Lavikainen. The other statistical methods used here have been widely used in this type of study.

6.2. DISCUSSION OF THE RESULTS

6.2.1 Adverse reactions as assessed by patient and physician (I)

The result of the study was that physicians discovered more potential adverse reactions (24 %) than patients reported (11 %), but there was a great disparity between what adverse reactions they reported.

In the literature, ADRs have been reported to occur in a wide range between 6.7 % - 43 %, depending on the setting (Lazarou et al. 1998, Camargo et al. 2006). However, these values may not be accurate since generally only a small amount of ADRs are actually detected (Hannan 1999). Furthermore, patients have tended to report higher amounts of ADRs than physicians (Zimmerman et al. 2010, Gäwert et al. 2011), although also opposite results have been published (Lorimer et al. 2012). The method of data collection may greatly affect the reports of the patients. The application of a 'rating-scale method', in which the patient is provided with a questionnaire listing potential side effects has increased reporting of side-

effects experienced (Sheftell et al. 2004). In the GeMS study, the adverse drug effects were inquired from the patients using an open type question "Have you had problems with your medication, e.g. adverse effects or has a drug that you were using been changed or discontinued due to an adverse effect?" It is possible that the rating-scale method would have produced more ADR reports from the patients. However, the open-type question is closer to the reality in today's clinical practice. Furthermore, the GeMS study was a multidisciplinary study, in which the medication assessment was only one component, and GeMS already involved quite large questionnaire panel to be answered by the patient. Therefore, asking the patients to answer a wide rating-scale questionnaire may not have been advisable since it would have greatly increased the number of questions to be answered by the patient.

Although the study physicians were trainees in geriatrics, they had had long clinical experience in primary care, where they had focused on geriatric patients. Thus, the physicians were experienced in treating elderly subjects and well motivated to focus on possible drug-related problems. Unfortunately the situation is not so optimal in everyday practice. It has been previously reported that physicians may under-report ADRs in clinical settings (Moride et al. 1997). It has been claimed that electronic medical records may improve detection of ADRs (Hannan 1999), and the possible utilization of National Archive of Electronic Health Records (KanTa) in the future will hopefully result in a reduction in the numbers of ADRs.

The most frequently reported ADRs by patients were related to skin, CNS and gastrointestinal tract; i.e. to readily observable ADRs. This is in agreement with a previous study with patients with rheumatoid arthritis, who most often reported gastrointestinal and skin disorders followed by general system disorders (Gäwert et al. 2011). In that study, the highest number of ADRs detected by physicians involved gastrointestinal disorders, infections and skin disorders. However, relatively good agreement in the frequencies of reports were found for vascular hypertensive disorders, oral soft tissue disorders and cardiac arrhythmias. Patients were more likely to describe general system disorders, weight changes, dizziness, headaches and vision disorders. However, despite similar overall frequencies, the highest agreement between the physician and an individual patient was still only at the level of one third for skin disorders and oral soft tissue conditions (Gäwert et al. 2011).

Therefore, it seems that physicians focus on those ADRs that may have more serious clinical consequences, but patients focus on those ADRs that they consider as harmful in everyday life. Therefore, although physicians should actively seek for possible ADRs, they should also take ADRs reported by patients into account. This would improve the quality of life of the patient.

OH was the most commonly discovered cardiovascular ADR by the physician. As previously reviewed in 2.6, OH is a common condition among older persons and may have a great impact on their quality of life. In addition, there were also several cases of extrapyramidal symptoms as well as urinary retention. These are ADRs that may be related to the use of anticholinergic drugs.

6.2.2 Association between ranked anticholinergic lists, SAA and anticholinergic adverse reactions (II)

There were two main results in this study. First, there was no association between potential adverse reactions and SAA levels. Second, the scores of the three anticholinergic ranked lists (Chew, Carnahan and Rudolph) were associated with the outcomes.

As described in the literature review (2.5.5), there is extensive heterogeneity in results between SAA levels and clinical outcomes, e.g. in some reports MMSE has (Tune et al. 1981, Golinger et al. 1987, Rovner et al. 1988, Flacker et al. 1997, Mulsant et al. 2003) or has not (Chengappa et al. 2000) been associated with the SAA results. In addition, Mangoni et al. (2012) found an association between SAA and Katz ADL index in older hip fracture patients, however no association was found between SAA and Barthel's ADL or Lawton-Brody's IADL in our study.

In the present study, a weak, but statistically significant association was detected between SAA values and Chew's list but not with the ADS or ARS. In agreement with these results, in the recent study of Mangoni et al. (2012), no association was found between SAA and any of the lists they utilized (Rudolph's ARS, Carnahan's ADS, Anticholinergic Burden Scale or anticholinergic component of Drug Burden Index). The ARS score, unlike the other lists, was associated with 3-month mortality. There do not appear to be any other studies investigating the association between the ranked lists and SAA.

However, the present study detected a significant association between the ranked lists and several potential anticholinergic ADRs in individuals without dementia. Short-distance vision, but not long-distance vision, was associated with higher scores in the three studied lists. In addition, cognition, mood and function were affected by the increasing scores. This indicates that the ranked lists of anticholinergic drugs may be useful in the determination of potential ADRs. When the three lists are compared, the results of Carnahan's and Chew's lists match quite well with each other with a logical decrease (or increase in case of GDS), however the results with Rudolph's list often produce divergent results with the highest scores. This may be due to small number of individuals with the highest scores as identified by Rudolph's list. In summary, it is likely that the ARS is less useful in our population.

Unlike the situation in individuals with normal cognition, no statistical significance was achieved in MMSE or GDS among subjects with dementia. Most likely this results from the small number of persons in this group. However, statistical significance was achieved in changes in short-distance vision and physical function as measured with ADL and IADL, indicating that patients suffering from dementia are more vulnerable to the anticholinergic ADRs than their counterparts with normal cognition. The levels of acetylcholine decrease with increasing age and especially in patients with dementia (Johnell and Fastbom 2008), resulting in greater susceptibility to anticholinergic drugs. Therefore, even drugs with mild anticholinergic effects may have dramatical effect to persons with dementia.

The ARS has been reported to be associated with both central and peripheral anticholinergic ADRs (Rudolph et al. 2008). Therefore, it is somewhat surprising that its associations with measured ADRs were poorer than with the Chew's list (based on *in vitro* measurements) or on the ADS (based on the medications' contribution to the SAA).

Although the ADS scores have been associated with SAA scores (Carnahan et al. 2006), this could not be confirmed in the present work. The SAA assay is based on biological samples and is possible that different sources of brain homogenate may have an effect on

the assay. In addition, there are issues related to the patient (e.g. endogenous anticholinergic activity, unrecognized cholinergic drugs in use binding to the muscarinic receptors) that may affect the results. This is seen also in the variety of the baseline results encountered in the patients irrespective of their anticholinergic drug use (Flacker and Wei 2001, Mulsant et al. 2003). Furthermore, although there has been an association between SAA and delirium and delirium resolution has been accompanied by a decrease in SAA, that change was often not attributable to any discontinuation or reduction in anticholinergic medication (Carnahan et al. 2002a). In addition, the different ability of different drugs to pass the blood-brain barrier (Kay et al. 2005), which is not taken into account when measuring the SAA, may have an important impact on their central anticholinergic effects.

Our results confirm the proposal that anticholinergic drugs affect negatively on cognition and short-distance vision. Unlike the SAA measurement, the ranked lists seem to be useful in clinical practice in the measurement of the risk of anticholinergic ADRs.

6.2.3 Effect of CGA on drug use and orthostatic hypotension (III – IV)

The assessment of the effects of CGA focused on two questions: how a single CGA can affect the drug use during a 1-year period, and can the prevalence of OH be reduced by using repeated annual interventions over a 3-year period.

A single CGA did not decrease the number of medicines in use, but it did reduce the number of inappropriate medication as defined by the Beer's criteria during the one-year period. When performing the medication assessment, the study physicians focused on indications of drugs in use, proper dosages and potential inappropriate medication. Basic laboratory tests were conducted in the participants in years 2004 and 2006. In addition, the study physicians focused on those conditions commonly found in older persons, e.g. dementia (Grossman et al. 2006), osteoporosis (Bonnick 2006), orthostatic hypotension (Low 2008) as well as low levels of vitamin B_{12} (Park and Johnson 2006) and folic acid (Lökk 2003). In addition, several initiations of vitamin B_{12} and folic acid as well as calcium-vitamin D combinations (with subsequent cessations of plain vitamin D preparations) were made by the study physicians. Furthermore, a substantial number of persons with OH were identified.

During the CGA, the indication for all drugs in use was carefully considered, with those drugs without an indication being withdrawn. The study physicians focused especially on CNS drugs which are commonly used by older persons even though there were no appropriate indications (Linjakumpu et al. 2002). However, these drugs had often been used for a long time, and therefore their use needed to be tapered off carefully rather than a prompt cessation and this was seen in the results. Other dosage modifications focused on the drugs affecting the cardiovascular system, common conditions in the older persons. For example, the treatment of hypertension is based on the concomitant use of several different types of drugs, therefore requiring a careful consideration on their doses. When evaluating the drugs associated with OH, there were no significant changes.

In general, the increase of medicines in use is linked with drug-related problems (Viktil et al. 2006), and therefore the decision to initiate a medication needs to be carefully considered. In this study, the number of medicines in use increased over the one-year period despite the CGA. On the other hand, old people often have several comorbidities

which do require medication. Nonetheless, the amount of inappropriate drugs (as defined by Beer's criteria) decreased, and the increases in the self-perceived health experience were more frequent in the intervention group than in the control group. In general, an increase in the number of prescribed drugs after CGA can be acknowledged as an acceptable outcome when it aims to reduce situations of under-treatment (Sergi et al. 2011).

Although the self-perceived health experience increased more frequently in the intervention group than in the control group one year after the first CGA, there were no changes in the OH status between the groups at that timepoint. The beneficial effect in the OH status in the intervention group was statistically significant only after repeated CGAs, which is in line with previous studies (Stuck et al. 2002). There are several causes for OH, some of which are irreversible (such as autonomic failure) (Figure 1). However, with proper treatment e.g. in the case of diabetes, the development of OH may be at least slowed down.

In addition, there are several other factors causing OH that can be modified, one of those being the use of medicines. There are several drugs that may evoke OH, and therefore a medication review is recommended in individuals with OH. In the present study, there were no clear changes among these drugs in either the intervention or the control groups. Thus, the decrease in prevalence of OH in the intervention group could not be explained solely by medication changes.

In addition to clinical examination and medication review, GeMS patients in the intervention group also underwent other interventions with a dentist, nutritionist and physiotherapist. These may have achieved improvements in other factors that can affect on OH e.g. nutrition, fluid balance and general lifestyle. The mobility of patients in the intervention group has been reported to improve (Lihavainen et al. 2011). It is therefore likely that it was the overall improvement in the patients' health status contributed also to the improved OH status.

In CGA, the results after changes in medication or other treatment need to be closely monitored and further adjustments should be performed based on the results of monitoring. However, due to the lack of resources, this was not possible in the GeMS study and therefore one can only speculate whether the results would have been better with more frequent monitoring of the patients. The GeMS study was able to organize patient examinations mainly only once a year. Most of the year, patients were treated by general practitioners in health centres and specialists in special health care. Therefore, the study physicians were not the primary treating physicians of the study population. The best result of a CGA is likely to be achieved when a treating physician, who ideally has been known to the patient for a long time, performs the CGA. In addition to the benefit of knowing the patient, this also would increase the adherence of the treating physician to the treatment of the patient better than just receiving a report of a CGA performed by others. This may also account for the number of 'unchanges' that were noticed during the one-year period after the first CGA. Medication review should be performed at least once a year to older persons with medications in use (Ministry of Social Affairs and Health 2007). This frequency may be suitable for older persons with relatively stable medication and medical conditions, however a higher frequency would often be beneficial e.g. when a new drug treatment is initiated.

There are some limitations to the study. Although the BP measurements were performed in a standardized manner, there were variations in the time of the measurements ranging

from early morning to afternoon. This may have affected the results, since the OH status varies over time, being most prevalent after rising up in the morning (Ooi et al. 1997). These measurements were also performed only once, increasing the possibility of a measurement error. In addition, delayed orthostatic hypotension was not assessed. As delayed OH may be a mild or early form of sympathetic adrenergic failure (Podoleanu et al. 2009), its assessment would have been interesting. Furthermore, the number of persons that could not be evaluated was rather high. Moreover, the subjects included into the study varied annually, although this could be taken into account by using the Markov model.

Some of the GeMS participants were not tested for OH. The main reason was their inability to adopt an upright posture required time for BP measurements. In general, those subjects were in poorer condition than those who participated in this trial. It is known that the prevalence of OH is even higher among demented and frail elderly individuals (Ooi et al. 1997, Passant et al. 1997), and most likely this would have been the case also in the present study. Therefore, special attention should be paid also to those individuals who cannot co-operate in the orthostatic tests.

7 Conclusions

1. Identification of adverse drug reactions

There is a disparity between patients and physician about adverse drug effects. The recognition by patients of clinically important ADRs such as OH and EP symptoms was poor. On the other hand, patients report more ADEs that are easily observable than physicians.

2. Use of SAA and anticholinergic ranked lists in determination of anticholinergic-like ADRs

SAA is not an applicable tool for measuring anticholinergic adverse effects. The ranked anticholinergic lists are more useful although their applicability in clinical practice would be enhanced if they could be embedded into electronic databases and prescribing programs. However, it is an open question whether these lists truly measure anticholinergic effects.

3. Effect of CGA on medication and OH

CGA can be used to rationalize medication, however this effect may be partially counteracted by other healthcare professionals. This harmful possibility would be decreased if electronic patient records were available to all healthcare professionals, i.e. to the personnel of municipal health centres, special health care and private practitioners. CGA can also be used to decrease the prevalence of OH among old persons, but to be sucessful this requires a time interval of years with repeated interventions.

8 Implications for the Future

PRACTICAL IMPLICATIONS

1. Assessments of medication
A medication assessment should be performed for older persons at least annually, however in cases of comorbidity or polypharmacy, it should be performed more often, e.g. after the initiation of every new treatment.

2. Identification of adverse drug reactions
Physician should actively search for possible adverse drug reactions even though the patient has not recognized and reported any drug related symptoms.

3. Identification of potential anticholinergic load on medication
Several drugs possess anticholinergic properties, and if these drugs act in an additive or synergistic manner they may cause a decrease in cognition as well as other anticholinergic adverse drug reactions. However, the anticholinergic properties of many widely used drugs are not known. For the recognized anticholinergics, a database embedded into normal practice would be useful.

IMPLICATIONS FOR RESEARCH

1. Drugs and older persons
The effects and adverse effects of drugs commonly used in older persons should be evaluated in trials with older age study groups and patients with comorbid conditions.

2. Anticholinergic effects of drugs especially in aged persons
All of the anticholinergic effects of drugs are not known. In addition, several changes occur with aging (e.g. increases in blood-brain barrier permeability) that may make older persons more vulnerable to anticholinergic ADRs, however the scientific data about these changes is greatly limited. Furthermore, a fast and reliable method is needed with which to assess an individual's anticholinergic load.

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Pasi Lampela

Improving Pharmacotherapy in Older People

a Clinical Approach

Aging is a heterogenous and individual process. Therefore, an individualized assessment of an older person's health status including assessment of his/her medication is essential. This thesis investigated the effect of comprehensive geriatric assessment, and especially the impact of a medication assessment in individuals aged ≥75 years focusing especially on the disparity on recognizion of adverse drug reactions by patients and their physician, the anticholinergic adverse reactions, and the effect of CGA on drug use and orthostatic hypotension.

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