ANTICHOLINERGIC MEDICINE BURDEN AND OLDER PATIENTS

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“Hot as a hare, blind as a bat, dry as a bone, red as a beet, and mad as a hatter.”

- Peters (1989) describing anticholinergic adverse effects

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Tiivistelmä – Referat – Abstract

Anticholinergic medicines are commonly used to treat e.g. incontinence. These medicines have side effects, which may cause and also exacerbate e.g. dryness of the mouth, increased heart rate, and even cognitive impairment. Older people may be more at risk for these side effects as they may be experiencing similar symptoms as a natural effect of aging, and because they may be using several medicines causing these effects. Older people often have a high medicine burden and also a high disease burden. Measuring anticholinergic effects to change medicine regimens and to reduce the symptoms is difficult as there is no golden standard method.

This thesis investigated the published methods available for estimating anticholinergic burden in the literature review part, and used one anticholinergic scoring system, the Anticholinergic Risk Scale, in a cross-sectional study to test the effects of anticholinergics on mortality in 1004 older institutionalised patients from Helsinki area public hospitals. Cross-tabulations and Kruskal-Wallis or Chi square methods were used to detect differences between variables such as nutritional status or certain diagnoses when the patients were stratified according to their anticholinergic use. Cox Proportional Hazard regression, the logrank test and Kaplan-Meier curve were used to investigate the effects of anticholinergics on 5-year all-cause mortality.

An *in vitro* serum assay and seven anticholinergic scoring systems were identified in the literature search. Also, 17 anticholinergic lists were identified, which covered 278 medicines, of which 21 appeared on at least eight of the lists. In the empirical study, the women's (n = 745) mean (± SD) age was 83.35 (± 9.99) years, and they were older than the men (n = 241, mean age ± SD 75.11 ± 11.48, $p < 0.001$). The 1004 patients (response rate 70 %) were using a mean (± SD) number of 7.1 ± 3.4 regular medicines (range 0-20). 455 patients used no anticholinergics, 363 had some anticholinergic burden (score 1 or 2), and 186 had a high burden, with anticholinergic scores of 3 or more. The mean ARS score (± SD) was 1.2 ± 1.5 (range 0-10). When three anticholinergic lists were compared, all three lists identified only 280/791 of patients who were anticholinergic users according to at least one list. No association was found between anticholinergic medicine use and mortality.

There are several methods available for measuring anticholinergic burden, but there is a need for a consensus method. This was highlighted by the lack of agreement on medicines on different lists and when three anticholinergic lists tested identified different patients when compared to each other. Anticholinergic use was common in this frail, older patient sample, but no effect on mortality was shown in this study setting. The cross-sectional nature of the data limits the reliability of the study, and any conclusions beyond older patients in Helsinki area must be done very cautiously. Future research should define anticholinergics better and investigate their possible effect on mortality in a prospective, randomised, and controlled setting.

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Tiivistelmä – Referat – Abstract

Antikolinergisiä lääkkeitä käytetään yleisesti mm. inkontinenssin hoitoon. Näillä lääkkeillä on sivuvaikutuksia, jotka voivat aiheuttaa tai pahentaa esim. suun kuivumista, sydämentykytystä tai jopa kognitiivisia kykyjä. Vanhukset saattavat kärsiä näistä oireista osana luonnollista vanhenemista, ja heillä saattaa olla käytössään useita antikolinergisia lääkkeitä. Tästä johtuen heillä saattaa olla suurempi riski kärsiä näistä sivuvaikutuksista. Vanhuksilla on usein suuri lääke- ja sairaustaakka. Antikolinergisten vaikutusten mittaaminen lääkehoitojen muuttamiseksi ja oireiden vähentämiseksi on vaikeaa, koska saatavilla ei ole referenssimenetelmää.

Tässä tutkimuksessa tutkittiin kirjallisuusosiossa antikolinergisten lääkkeiden taakan mittaamiseen käytettäviä menetelmiä. Erästä tällaista menetelmää, Anticholinergic Risk Scalea (ARS) käytettiin läpileikkaustutkimuksessa arvioitaessa antikolinergien käytön vaikutusta kuolleisuuteen potilasaineistolla, jossa mukana oli 1004 laitoshoidossa olevaa vanhusta Helsingin alueen julkisista sairaaloista. Ristiintaulukoinnin ja Kruskal-Wallisin sekä Khin neliö -testien avulla tutkittiin eri antikolinergisen taakan omaavien ihmisten eroja mm.ravitsemustilassa ja tietyissä diagnooseissa. Coxin suhteellisen riskin regressio-menetelmällä, logrank-testillä ja Kaplan-Meier-kuvaajalla tutkittiin antikolinergien vaikutusta kuolleisuuteen viiden vuoden tarkasteluvälillä.

Kirjallisuushaussa löytyi *in vitro* seerumimääritys sekä 7 antikolinergien pisteytysmenetelmää. Lisäksi löydettiin 17 antikolinergilistaa, joilla oli yhteensä 278 lääkeainetta, joista 21 löytyi vähintään kahdeksalta listalta.Kokeellisessa tutkimuksessa naisten (n = 745) keski-ikä oli 83.35 (± 9.99, SD) vuotta, he olivat vanhempia kuin miehet (n = 241, keski-ikä 75.11 ± 11.48 vuotta, $p < 0.001$). Tutkimuksen 1004 osallistujaa (vastaus-% 70) käytti 7.1 ± 3.4 lääkettä säännöllisesti (vaihteluväli 0-20). 455 potilasta ei käyttänyt lainkaan antikolinergeja, 363 käytti jonkin verran (pisteysaldo 1 tai 2), ja 186 käytti paljon (pistesaldo 3 tai yli). Keskimääräinen ARS-pistemäärä oli 1.2 ± 1.5 (vaihteluväli 0-10). Verrattaessa kolmea antikolinergilistaa toisiinsa, vain 280/791 potilasta tunnistettiin antikolinergien käyttäjäksi yhtä aikaa kolmen listan avulla. Antikollinergien käytöllä ei ollut tässä tutkimuksessa yhteyttä kuolleisuuteen.

Useasta antikolinergikuormitusta mittaavasta menetelmästä huolimatta tarvitaan konsensus-menetelmä. Tätä korosti tutkimuksessa havaittu vaihtelu siinä, mitkä lääkkeet olivat antikolinergisilla listoilla, ja miten eri listat tunnistivat eri potilaita antikolinergien käyttäjiksi. Tämä heikkokuntoinen vanhusväestö käytti yleisesti antikolinergeja, mutta yhteyttä kuolleisuuteen ei löydetty tässä koeasetelmassa. Tutkimuksen läpileikkausrakenne rajoittaa sen luotettavuutta, eikä tuloksia voida varauksetta yleistää muihin potilasryhmiin. Tulevissa tutkimuksissa tulisi keskittyä määrittelemään antikolinergit paremmin, ja tutkia niiden mahdollista vaikutusta kuolleisuuteen prospektiivisissa, satunnaistetuissa ja kontrolloiduissa tutkimuksissa.

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CONTENTS

Contents continued…

ABBREVIATIONS

ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive subscale
ABS	Anticholinergic Burden Score
AC	anticholinergic
ADE	adverse drug event
ADL	activities of daily living
ADS	Anticholinergic Drug Scale
AMI	acute myocardial infarction
ARS	Anticholinergic Risk Scale
AS	antimuscarinic syndrome
ATC	Anatomical Therapeutic Chemical Classification system
BVRT	Benton Visual Retention Test
CAD	coronary artery disease
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CSF	cerebrospinal fluid
DM	diabetes mellitus
DM2	type 2 diabetes mellitus
EDTA	ethylenediaminetetraacetic acid
GDS	Global Deterioration Scale
IST	Isaac's Set Test
MCI	mild cognitive impairment
MESH	medical subject heading
MMSE	Mini Mental-State Examination
MNA	Mini Nutritional Assessment

MRDD	maximum recommended daily dose
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
OTC	over-the-counter medicines
qEEC	quantitative electroencephalography
SAA	serum anticholinergic activity
SD	standard deviation
TDB	total drug burden
TMT	Trail Making Test
TQB	tritiated quinuclidinyl benzilate
WMH	white matter hyperintensities

1 INTRODUCTION

The proportion of over 65-year-olds is increasing in many developed countries, including Finland (Koskinen et al 2006; Statistics Finland 2008). Incidence rates of many diseases will most likely decline and treatments will be improved, but the sheer increasing number of the older population will require more health care resources (Koskinen et al 2006). This challenges health care services as the amount of people in need of long-term care increases.

There are several special challenges in geriatric care. Older people may have several comorbidities and a heavy ailment and medicine burden (Spinewine et al 2005). Many conditions such as Parkinson's disease, cerebrovascular changes, multiple sclerosis, and schizophrenia may increase the risk of cognitive impairment in this age group (De Ridder 2006). Sometimes changes in mental status, such as hallucinations and delirium may go unnoticed for longer periods of time in older patients as they may not be able to voice complaints about discomfort, and reversible reasons behind the changes such as certain medicines may be overlooked (De Ridder 2006; Raivio et al 2006). A patronizing or "ageist" attitude among caregivers concerning older patients may be a problem, as well as frequent changes in treating physicians, making acute care the priority while long-term treatment considerations may be overlooked (Spinewine et al 2005). Transferring medicine data of older patients between primary and secondary care may be limited, and shared decision making throughout the chain of treatment may be a challenge.

This thesis investigates the burden of anticholinergics, a group of medicines with potentially harmful side effects in older patients. Anticholinergic medicines block muscarinic receptors, and common indications for these medicines include incontinence, Parkinson's disease and glaucoma (Tune and Coyle 1980; Mintzer and Burns 2000). Dry mouth, constipation and blurred vision are common side effects caused by anticholinergics, and they have the potential to cause impairment in cognition and problems in everyday

functions of patients, e.g. dizziness and loss of balance (Mintzer and Burns 2000; Ancelin et al 2006). Older patients may be more at risk for adverse effects from anticholinergics, as they may have some of these symptoms already as a natural effect of aging. Methods for estimating anticholinergic burden i.e. the sum of anticholinergic effects or medicines are reviewed in this thesis, and one anticholinergic scoring system is used to investigate possible effects of these medicines on mortality in older nursing home patients.

2 BACKGROUND

Older people in Finland commonly use many medicines at the same time, as average nursing home residents over the age of 65 or 70 use seven to nine medicines concomitantly (Suominen et al 2005; Raivio et al 2006). Overmedication may be a problem in older patients but having several medicines at the same time may be clinically sensible (Hanlon et al 2001). Polypharmacy or having multiple medicines at the same time can be defined as using nine or more medicines concomitantly, as people with such a medicine burden are more likely to be exposed to unnecessary medicines (Hajjar et al 2005). A common problem associated with polypharmacy is undermedication, e.g. when not enough laxatives are used to treat constipation caused by opioids or no stomach protecting agents are used with non-steroidal anti-inflammatory drugs (NSAID) (Kuijpers et al 2008). Controlling for possible interactions of medicines, either pharmacodynamic or kinetic, may be more difficult in cases where there are several medicines being used for possibly several different indications.

2.1 Care of older people in Finland

The national framework for high-quality care and services for older people sets the standard and works as an aide for planning the care of older people in the municipalities of Finland (Ministry of Social Affairs and Health 2001). Local and regional authorities use the framework as a base to develop services to their local older inhabitants according to what

their needs are. The Finnish system encourages older people to live independently at home in a familiar environment for as long as possible, offering community-based or home services to support this. Nursing homes and other institutional care facilities should be as safe and home-like as possible, to maintain and promote the functional capacity of their residents.

2.2 Older people as medicine users – challenges and opportunities for better treatment

Starting from the early 40s, body composition starts to change, as muscle tissue is reduced and replaced with fat tissue, with the general fat content of the body increasing (DeVane and Pollock 1999). There are also changes in heart output, and subsequently also in intestine, renal and liver functions, partly through reduced blood flow. The overall ability of the body to adapt to changes is reduced, as homeostasis is impaired (DeVane and Pollock 1999; Hilmer et al 2007b). Clinical studies on medicines are typically performed on healthy younger individuals, so little is known about how medicines behave in older people apart from practical experience gained by individual professionals in their everyday practice. Older patients should be monitored closely to see whether a medicine has desired effects, and if it does not, it should be discontinued (Hilmer et al 2007b).

Average body weight is reduced in older people, and many older institutionalised patients are malnourished and have very low body weight (Suominen et al 2005; Suominen et al 2007). Therefore dosages appropriate for younger people may be too high for older patients. Also, frailty should be considered as a phenotype of older people, since it has significant effects on how medicines behave in the body (McLachlan et al 2009). Frail persons are typically not participants in clinical trials, and therefore form a special group of patients that need extra consideration when deciding on treatments. Rather than focusing on the genotype of the older patient, phenotypes such as frailty should be considered.

Because of diminished renal and liver clearance, and because of higher fat content in the body, many medicines have longer half-lives than in younger patients (DeVane and Pollock

1999). Oral medicine absorption may be slowed down because of slower intestinal movements and decreased gastric acid output. Reduced plasma albumin and α_1-acid glycoprotein concentrations may change the pharmacokinetics of acidic and basic medicines, respectively, as these proteins are the main binding molecules of these medicines in plasma. The hepatic P450 metabolic enzyme system may be affected by aging, making medicine dosing in older people even more difficult. Declines in hepatic clearance and metabolism are important factors to consider when prescribing for older people (Hilmer et al 2005). Older people in general are a very heterogenous group, and must be considered as individuals when deciding on treatment options (DeVane and Pollock 1999; Hilmer et al 2007b). Some very old patients have perfectly normal organ functions, while others have severe reductions.

Older patients are a group with special needs when designing treatment strategies. Medication reviews may be one good tool for evaluating the appropriateness of the medicines in use, regardless of the age of the patient. Reviews can lead to more rational medicine use, described by lower scores in tools measuring medicine inappropriateness (Stuijt et al 2008) or discontinuation of potentially harmful medicines, e.g. hypnotics (Nishtala et al 2008). They may also reduce adverse effects and events like falls (Zermansky et al 2006). Reductions in the numbers of hospitalisations and mortality (Zermansky et al 2006) or costs (Altavela et al 2008) have not been proven in clinical trials investigating the issue. However, medication reviews may offer an opportunity to discuss and manage problematic issues like adherence or suboptimal treatments (Altavela et al 2008).

2.3 Identifying potentially inappropriate medicines

There are several tools available to screen medicine regimens of older patients for potentially inappropriate medicines (Beers et al 1991; Beers 1997; Fick et al 2003; McLeod et al 1997; Naugler et al 2000; Socialstyrelsen 2003; Hanlon et al 1992 and 2004; Laroche et al 2007), but they may be difficult to adapt to care practices in other countries than those

where they were developed. A review of studies using the widely applied Beers criteria found that most studies modified the criteria to better suit their settings (Aparasu and Mort 2000). The predictive properties of the Beers criteria to estimate possible adverse healthcare outcomes also need to be improved before it can be utilized for maximum benefits (Jano and Aparasu 2007). A comparison of the Beers criteria (Beers et al 1991; Beers 1997; Fick et al 2003) and the IPET tool (Naugler et al 2000) in detecting potentially inappropriate medicines in hospitalised older people showed that the Beers criteria had improved during its development, but nevertheless all inappropriate prescribing tools would need to be updated every three to five years (Barry et al 2006). Raivio et al (2006) found no differences in mortality rates when comparing institutionalised over 70-year-old Finns who were taking potentially inappropriate medicines according to the Beers list (Beers et al 1991; Beers 1997; Fick et al 2003) or not taking them. However, effects on the quality of life of older patients may be more important than effects on mortality. The guiding thought in the care of older people should be preservation of functional independence (Hilmer and Gnjidic 2009). This means that older people should be able to live as good-quality life as possible independently, preferably not institutionalised, until as advanced age as possible. There is a clear need for better screening tools that would effectively reduce adverse events caused by medicines, be more adaptable to local circumstances, and offer guidance on how to avoid errors in geriatric care (O'Mahony and Gallagher 2008). Prescribing patterns need to be changed to better meet care goals, as older people may be more at risk for adverse events from medicines because of the high incidence of polypharmacy and changes in medicine metabolism in their age group (Hartikainen and Klaukka 2004).

Hosia-Randell et al (2008) investigated potentially inappropriate medicine use based on the Beers criteria in older Finnish nursing home residents, and a usage rate of 34.9 % was found. Most of these patients were using only one potentially inappropriate medicine, but approximately every sixteenth patient of the whole study population was using more than one. Fialova et al (2005) investigated the use of potentially inappropriate medicines in 11 countries in Europe. Their study focused on people aged 65 or older living at home, and they used the Beers Criteria (Beers et al 1991; Beers 1997; Fick et al 2003) developed in

the United States and the McLeod Criteria (McLeod et al 1997) developed in Canada to define potentially inappropriate medicines. They found a rate of 73.3 % of their Finnish sample to be using at least six medicines either regularly or when required, and 41.2 % to be using nine or more medicines. These rates observed in Finland were higher than those in the Czech Republic, Denmark, Iceland, Italy, the Netherlands, Norway and the United Kingdom. Potentially inappropriate medicines were used by 21 % (39 of 187) of the Finnish participants, which was close to the 20 % European average for all the countries in the study.

Because of the potential for adverse events and reductions in the quality of life, medicine regimens should be screened for potentially inappropriate products (Hartikainen and Klaukka 2004). This may be especially important in older patients, as they usually have a high medicine and disease burden, making any adverse effects more pronounced. Anticholinergic medicines, which block muscarinic receptors, have the potential to cause adverse effects such as dryness in the mouth, constipation, urinary retention, and problems with vision (Mintzer and Burns 2000; Lieberman 2004). Some of these symptoms may be present as a normal effect of aging, so anticholinergic medicines may exacerbate the effects. It is therefore important that clinicians screen for anticholinergic effects in their patients, and that more research is done to investigate these effects and to improve medicine treatments.

3 OBJECTIVES

The literature review part of this thesis investigates anticholinergics as a medicine group and different ways to measure anticholinergic burden, i.e. the total amount and/or effects of anticholinergic medicines of the person using the medicines. As there is currently no international consensus on which medicines are to be considered anticholinergic and which not, this review will investigate current anticholinergic medicine lists and anticholinergic burden estimation tools available and their usefulness in clinical practice.

The empirical part of this thesis investigates the use of medicines with anticholinergic properties in older people living in nursing homes in the Helsinki area with a cross-sectional sample. The main objective is to investigate if there is any association between the use of anticholinergic medicines and risk of death. Anticholinergic medicine use in this patient group is also investigated.

4 METHODS

This thesis has two parts: the literature review of peer-reviewed, published articles on methods to measure anticholinergic burden and the empirical research investigating the effects of anticholinergic medicine use on mortality in older people living in nursing homes. The research methods used in the study are described in this chapter.

4.1 Methods for the literature review

The literature review search was performed with the University of Helsinki NELLI Internet portal with the ISI Web of Science and Medline search applications. For Medline searches Ovid MEDLINE, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, BIOSIS Previews 1999 to 2008, BIOSIS Previews, Biological Abstracts, Biological Abstracts/RRM 1989 to 2008, CAB Abstracts 1973 to Present, Drug Information Full Text December 2008, PsycINFO, PsycARTICLES, Nursing@Ovid, British Nursing Index and Archive, AARP Ageline, AMED (Allied and Complementary Medicine), EBM Reviews - ACP Journal Club, EBM Reviews - Cochrane Central Register of Controlled Trials, EBM Reviews - Cochrane Database of Systematic Reviews, EBM Reviews - Cochrane Methodology Register, EBM Reviews - Database of Abstracts of Reviews of Effects, EBM Reviews - Health Technology Assessment, EBM Reviews - NHS Economic Evaluation Database, and Journals@Ovid databases were included. The time frame investigated was from the starting date of all the databases until December 2008.

4.1.1 Search strategy

Medical subject heading (MESH) terms for anticholinergics were obtained from the US National Center for Biotechnology Information's PubMed portal. Terms used for anticholinergic medicines included cholinergic antagonists, cholinolytics, cholinergic blocking agents, acetylcholine antagonists, anticholinergic agents, anticholinergics, antimuscarinics, antimuscarinic agents and parasympatolytics. These terms were combined in the Medline search engine with the terms "physical function", "cognitive function", "mortality", "serum anticholinergic activity", "definition", "elderly", and "measurement". The same terms were also used in Web of Science in different combinations.

4.1.2 Data abstraction

All titles and abstracts of articles found in the searches were screened for relevance to the thesis topic. Articles discussing anticholinergic use in older people, effects on physical and cognitive functions, and how to measure anticholinergic medicine effects were obtained and investigated further. Those articles that listed anticholinergic medicines or presented a way of estimating anticholinergic burden in medicine users were considered particularly relevant. All selected articles' lists of references were also investigated to find more related articles. No formal data abstraction tables were used in this systematic literature search, and one researcher reviewed the articles. Some articles were used in the literature review, while others were used as background information for the whole thesis. Based on the literature search, a table of anticholinergic medicines was collected from different publications. The frequency of medicines appearing on different anticholinergic lists was also investigated.

4.2 Methods used in the empirical research

The Anticholinergic Risk Scale (ARS) tool developed by Rudolph et al (2008) was used to identify medicines with anticholinergic properties and the sum score of all anticholinergics

was calculated for each patient. This score can be used to estimate anticholinergic burden, and its association with mortality was investigated.

4.2.1 Patient sample

The study population were all the residents in 53 long-term care wards in the city of Helsinki public hospitals in September 2003. These hospitals serve, among other patients, both older patients with acute health concerns and a need for rehabilitation, and also nursing home residents, with a total patient base of 200,000 inhabitants (Soini et al 2004; Raivio et al 2007). At the time of the data collection, there were 1444 patients staying in the hospitals, and all the hospitals in the area were included in the study. Data collection was performed as part of nutrition status studies (Soini et al 2004; Suominen et al 2005; Suominen et al 2007). Trained nurses evaluated their patients' nutritional status and filled out a questionnaire, which was based on the National Resident Assessment Instrument for Nursing Homes (Morris et al 1990), which was modified and translated to Finnish (Soini et al 2004). The questionnaire used in their study had two sections: the nutrition status section with 18 items (forming the Mini Nutritional Assessment, MNA), and the background information section with 21 items (Appendix 1). The patients' age, gender, marital status, level of education, problems with eating (e.g. dry mouth), diagnoses and prescription medicine use were recorded as part of the background information data (Soini et al 2004). The Hospital District of Helsinki and Uusimaa ethics committee approved the study.

As part of the background data, Charlson Comorbidity Index scores were calculated for patients. The Charlson Comorbidity Index is a method for describing the total comorbidities in a patient (Charlson et al 1987). It combines the effects of diseases, which are given scores weighted by their seriousness, i.e. likelihood to increase mortality and morbidity. It also takes into account the patient's age, giving extra points on the Index score for more advanced age. The higher a Charlson Comorbidity Index score a patient has, the poorer their overall condition is thought to be. The index has been validated to predict long-

term mortality, and also to predict short-term (six month) hospitalisations and mortality in older nursing home patients (Buntinx et al 2002).

Mini Nutritional Assessment (MNA) scores were also calculated for patients. The MNA is a validated screening tool that attempts to identify older patients at risk for malnutrition (Guigoz et al 1996; Guigoz et al 2002). It investigates self-perceived health and markers of malnutrition, e.g. dietary intake, mobility, depression, weight loss, BMI, calf circumference, and mid-arm measurements with an 18-item questionnaire. A low score in the MNA means that the patient may be malnourished or at risk for it, and scores below 17 are considered malnourished.

4.2.2 Medicine data

All patients' prescription medicine use was recorded in an Excel file, and the data was coded to the level of ATC codes (Anatomical Therapeutic Chemical Classification system) and medicinal substances, and the medicines were marked as being used regularly or only when required. During the coding process misspelled names for medicines were corrected and different brand names for the same medicinal substance were coded to mean the same medicine. Medicines marked in the records as "taken when required" were excluded from the analysis, as were topical, ophthalmological, and otologic products. The total number of medicines in regular use was calculated from the file for every patient.

4.2.3 Identifying anticholinergic medicines

The ARS scoring system (Rudolph et al 2008) was used to identify medicines with anticholinergic properties. This list of anticholinergic substances includes 21 medicines that give three points in the scoring system, 14 medicines contributing two points, and 14 medicines giving one point (Table 2). The higher points a medicine has, the more anticholinergic it is considered, and the more anticholinergic burden it adds to the patient's total score. Of these 49 medicines, 34 were commercially available in Finland in 2003

when the study material was collected (Lääketietokeskus 2002 and 2003). The data were coded to give ARS points for all medicinal substances ranging from zero to three (Table 2), and total ARS scores were calculated for each patient by adding up all their ARS points.

Three different lists of anticholinergics were used to classify all patients as either users or non-users of anticholinergics. If a patient was using a medicine on a given list, they were considered to be anticholinergic users according to that particular list. One of the lists was chosen because it is based on SAA measurements (Tune et al 1992 combined with its update, Lu and Tune 2003), one because it is based on literature (Rudolph et al 2008), and one because it is based on Finnish patients and medicines (Uusvaara et al 2009).

Table 2. The ARS list (Rudolph et al 2008) of anticholinergic medicines and their availability in Finland in 2003.

ARS points	**Medicines in the ARS list (those available in Finland in 2003 underlined)**
3	amitriptyline, atropine, benztropine, carisoprodol, chlorpheniramine, chlorpromazine, cyproheptadine, dicyclomine, diphenhydramine, fluphenazine, hydroxyzine, hyoscyamine, imipramine, meclizine, oxybutynin, perphenazine, promethazine, thioridazine, thiothixene, tizanidine, trifluoperazine
2	amantadine, baclofen, cetirizine, cimetidine, clozapine, cyclobenzaprine, desipramine, loperamide, loratadine, nortriptyline, olanzapine, prochlorperazine, pseudoephedrine-triprolidine, tolterodine
1	carbidopa-levodopa, entacapone, haloperidol, methocarbamol, metoclopramide, mirtazapine, paroxetine, pramipexole, quetiapine, ranitidine, risperidone, selegiline, trazodone, ziprasidone
0	all other medicines

4.2.4 Statistical methods

Patient characteristics were analysed with statistical methods and possible differences between groups of varying load of anticholinergics were investigated. Characteristics were cross-tabulated to obtain patient numbers in each group and the differences between groups were tested. Categorical variables were tested with the chi-squared test. These included being bed bound, nutritional status as defined by an MNA category, gender, being widowed, having studied only at primary school level, having diabetes mellitus (DM), coronary artery disease (CAD), acute myocardial infarction (AMI), stroke, dementia, depression, other psychiatric illness, Parkinson's disease, other neurological illness, rheumatic disease, chronic obstructive pulmonary disease (COPD), gastric or duodenal ulcer, hip fracture, cancer, and the number of medicines in regular use in three categories. Continuous variables were tested with the Kruskal-Wallis test (comparing at least three variables) test, which does not require the data to be normally distributed. The continuous variables investigated included the length of stay in the ward, age, Charlson Comorbidity Index score, and the absolute number of medicines in regular use. The null hypothesis in all analyses was that there was no difference in these variables between patient groups with differing anticholinergic load. All statistical analyses were performed with the NCSS 2007 software, and p-values less than 0.05 were considered statistically significant.

The Kruskal-Wallis one-way analysis of variance (also called the H test) tests whether three or more independent populations are the same according to some characteristic and its sample distribution, or if they differ from another (Chan and Walmsley 1997). The test does not show which specific population group may differ or how, only if there is a difference in distributions between the groups compared. Sample and population distributions are investigated in the test, and it shows whether any observed differences are by chance or real differences between populations. The test is nonparametric, so it does not assume any distributions for the data, but it does assume that the observations analysed are independent. An expert must critically examine any observed differences to see whether they are meaningful from a clinical point of view.

The risk of death over a five-year time period was investigated. The null hypothesis was that there was no difference in survival between patient groups with varying anticholinergic load. Causes of death were not known for the patients, so all cause mortality was used as the end-point. Effects of several independent explanatory variables on the risk of death were investigated with the Cox Proportional Hazard method. This model estimates the sizes of differences between groups with logistic regression, and hazard ratios with 95 % confidence intervals for the included explanatory factors are obtained. Hazard ratios provide an estimate of how much the factors affected the risk of death, and with logistic regression the combined effects on risk of death could be investigated in the Cox model (Spruance et al 2004). The cumulative rate of mortality during the two-year follow-up was investigated by drawing a Kaplan-Meier curve. The Kaplan-Meier curve shows calculations of survival at time intervals and estimates the probability that patients who were alive at the beginning of a time interval were still alive at the end of it (Bland and Altman 1998). The logrank test was used to analyse patient data. It compares the survival of patient groups, in this case groups with a different anticholinergic load, and takes the whole follow-up period into account in the analysis (Bland and Altman 2004). The test does not give the size of any observed difference in survival between groups, but it shows if the difference is statistically significant. Clinical significance must again then be considered.

5 LITERATURE REVIEW: METHODS FOR ESTIMATING ANTICHOLINERGIC BURDEN

Anticholinergic medicines are a modifiable risk factor for morbidity, and identifying those at need for medicine regimen changes is important (Rudolph et al 2008). Estimating the total burden of anticholinergic medicines to a patient’s system would be useful e.g. for clinicians reviewing a medicine regimen or investigating patient complaints of side effects typical of anticholinergics. An ideal burden estimation system would take into account all

clinically significant anticholinergic medicines in use and their dosing (Hilmer et al 2007a). The patient's clinical status and all its implications, and also individual variance in e.g. medicine metabolism should be considered when estimating anticholinergic burden. Developing such a system that would suit every patient situation is a challenge, as currently there is not even a universal, all-inclusive list of anticholinergic medicines available. An internationally accepted definition for an anticholinergic medicine is lacking as well. Rudd et al (2005) recommend in their review of methods to estimate anticholinergic burden that lists of anticholinergic medicines combined with clinical judgment are currently the best choice despite the lists' lack of objectivity. This literature review chapter introduces some methods for determining anticholinergic burden.

5.1 Anticholinergic medicines and their use in the elderly

The effects of anticholinergic medicines on the body, both intended effects and side effects are described in the following chapters. Some of the problems with adverse effects are reviewed, focusing on cognitive effects and older people as the medicine users.

5.1.1 Anticholinergic medicines

Anticholinergic medicines block either nicotinic or muscarinic acetylcholine receptors either in the peripheral or central nervous system synapses or both (Peters 1989). The most clinically relevant are the muscarinic blockers, which can be used for a variety of clinical indications, e.g. to relax smooth muscle tissue. Some indications include intestinal pain, overactive bladder, obstructive respiratory diseases, and also prevention of extrapyramidal side effects in Parkinson's disease.

Muscarinic receptors are G-protein coupled receptors distributed throughout the body (Caulfield and Birdsall 1998). There are five receptor subtypes, and the M_1 subtype is mainly found in the brain, sympathetic ganglia and glands. M_2 is mainly found in the heart, hindbrain and smooth muscle, while M_3 is located in smooth muscle, glands and to some extent the brain. M_4 can mainly be found in the striatum and basal forebrain, and M_5 in

substantia nigra and in peripheral tissues. The selectivity of anticholinergics for these five receptor subtypes determines whether they have adverse effects.

Other medicines than actual muscarinic blockers have anticholinergic properties too (Tune and Coyle 1980). Some commonly used medicines that are examples of these include digoxin, furosemide, prednisolone, and theophylline (Tune et al 1992). Their effects are less well understood, but may be clinically relevant. Anticholinergic medicines are usually directed at peripheral targets where their effects would be useful, but depending on their ability to cross the blood-brain barrier, they may also block central nervous system muscarinic receptors, possibly leading to confusion and delirium (Tune and Egeli 1999). Whether central anticholinergic effects are clinically relevant may depend on individual variability in pharmacokinetic factors, baseline cognitive status, and the total sum of all anticholinergic effects (Roe et al 2002).

Anticholinergics, defined as true antimuscarinics and other medicines with anticholinergic properties, are quite commonly used in older populations. Estimates of prevalences of using one or more anticholinergic medicine range from 15 % (262/1777 patients, Lechevallier-Michel et al 2004) to 40 % (144/364 patients, Landi et al 2007) to 63 % (342/544 patients, Han et al 2008) in older patients, depending on the sampled population.

5.1.2 Anticholinergic side effects

Because only a few anticholinergics are highly specific to their intended target organs, they will also block muscarinic receptors in other tissues. This blocking may cause unwanted side effects. Typical anticholinergic side effects with varying severity of symptoms according to Mintzer and Burns (2000) and Lieberman (2004) are presented in Table 1. With increasing anticholinergic load and receptor blocking, symptoms may worsen from mildly irritating (e.g. dry mouth) to severe (e.g. dental decay).

These side effects may be more common in older than in younger users, and the symptoms may be attributed to other factors than medicines (Pollock 1999). And as they are common, they may be considered unavoidable, a "part of growing old". Even mild anticholinergic effects may exacerbate some common ailments like constipation, dry mouth, glaucoma and urinary retention in older people (Pollock 1999), and difficulties in chewing may lead to malnutrition as the patient may be unable to finish her/his meal (Suominen et al 2005). Of particular concern is the potential for causing tachycardia in older patients with pre-existing myocardial ischemia (Pollock 1999). Central effects such as amnesia, delirium, or memory impairment are potentially more harmful for the patient, but even mild peripheral effects like urinary hesitancy may become important issues because they reduce the quality of life.

However, anticholinergic side effects are usually reversible, and may have harmful but potentially avoidable effects on quality of life. For many medicines that have anticholinergic side effects, there is an equally effective non-anticholinergic alternative, and any observed side effects should warrant re-evaluations of the medicines in use (Mintzer and Burns 2000). When e.g. antipsychotics cause these side effects, decreasing the dose may be the first step, or eliminating or reducing the doses of other medicines with anticholinergic properties, but changing to a primary medicine with less anticholinergic effects may be necessary and advisable (Lieberman 2004; Mulsant et al 2004). Also, choosing an alternative that is more M_3 receptor subtype specific may be wise. M_3 receptors are distributed more in the periphery than in the CNS, and therefore binding to them does not disturb cognitive functions so easily. When treating incontinence, darifenacin, a specific M_3 blocker had fewer side effects than oxybutynin, a M_1 and M_3 specific blocker that is more likely to have central anticholinergic effects (Scheife et al 2005; Kay et al 2006). Long-term medicines should ideally be chosen so that the anticholinergic activity would be low to begin with, thus reducing the likelihood of having to change medicines during therapy because of unwanted effects. There needs to be a change in prescription practices, and clinicians should be more alert to anticholinergic side effects, especially in the most vulnerable, older demented patients.

Table 1. Typical anticholinergic side effects ranging from mild to severe (Mintzer and Burns 2000, Lieberman 2004).

Mild	Moderate	Severe
Dryness of mouth (modest)	Moderately disturbing dry mouth or thirst Speech problems Reduced appetite	Difficulty chewing, swallowing, speaking Impaired perception of food texture and taste Mucosal damage Dental decay, periodontal disease, denture misfit Malnutrition Respiratory infection
Mild dilatation of pupils	Inability to accommodate Vision disturbances Dizziness	Increased risk of accidents and falls, leading to decreased function, Photophobia Exacerbation/precipitation of acute angle closure glaucoma
	Oesophagitis Reduced gastric secretions, gastric emptying (atony) Reduced peristalsis, constipation	Faecal impaction (in constipation patients) Altered absorption of concomitant medications Paralytic ileus, pseudo-obstruction
Urinary hesitancy		Urinary retention, urinary tract infection (in patients with urinary hesitancy)
	Increased heart rate	Conduction disturbances, supraventricular tachyarrhythmias Exacerbation of angina Congestive heart failure, Myocardial infarction
Decreased sweating		Thermoregulatory impairment leading to hyperthermia
Drowsiness	Excitement	Profound restlessness and disorientation, agitation
Mild amnesia	Memory impairment	Exacerbation of cognitive impairment
Inability to concentrate	Confusion	Ataxia, muscle twitching, hyperreflexia, seizures Hallucinations, delirium

Ness et al (2006) investigated the prevalence of anticholinergic symptoms and burden, and adverse drug events (ADEs) from anticholinergics in 532 community-dwelling older veterans (97.9 % were men). Their patient sample was older than 65 years of age, using at least five medicines regularly, and cognitively intact. This group was thought to be at high risk for ADEs because of their high medicine use. Altogether 27.1 % (n = 144) of the study participants were using at least one anticholinergic medicine. No statistically significant difference was found in ADE occurrence rates reported between those who were using no anticholinergics and those who were using one or more. Those who used anticholinergics had a significantly higher mean number of anticholinergic symptoms than those who did not (3.1 vs. 2.5, $p < 0.01$). The prevalences of dry mouth and constipation were also higher

in the group that used anticholinergics than in those using none (57.6 % vs. 45.6 % and 42.4 % vs. 29.4 %, for dry mouth and constipation, respectively).

5.1.3 Increased risk of cognitive impairment in older people

Anticholinergic medicines are often prescribed to treat common ailments such as incontinence, but they may also have a negative impact on cognitive functions despite their supposed peripheral only mode of action (Kay et al 2005). They usually target mostly peripherally located muscarine receptor subtypes (M_3) to actuate their effect, and either do not enter the CNS at all or do not bind to the CNS receptor subtypes (M_1, M_2), which affect memory and cognition. This would ensure that there are no unwanted effects on cognitive functions. However, it is becoming more and more apparent, that these unwanted effects do occur when these medicines are used, possibly because of cumulative effects, often in patients with multiple comorbidities.

Older people may be more at risk of adverse effects on cognition caused by anticholinergic medicines (Kay et al 2005). Several factors may cause normally only peripherally acting medicines to cross the blood-brain barrier into the CNS and cause unwanted side effects (Figure 1). New medicines are mainly tested on younger people, so these negative effects may not show in clinical trials before the product comes to the market. Normal age-related decline in memory functions may cause older people to be more vulnerable to any effects on cognition that anticholinergic medicines may have. Because anticholinergics are frequently used in this older age group, the potential for adverse effects exists, especially since polypharmacy is common in older people, leading to possible cumulative effects from e.g. several very mildly anticholinergic medicines.

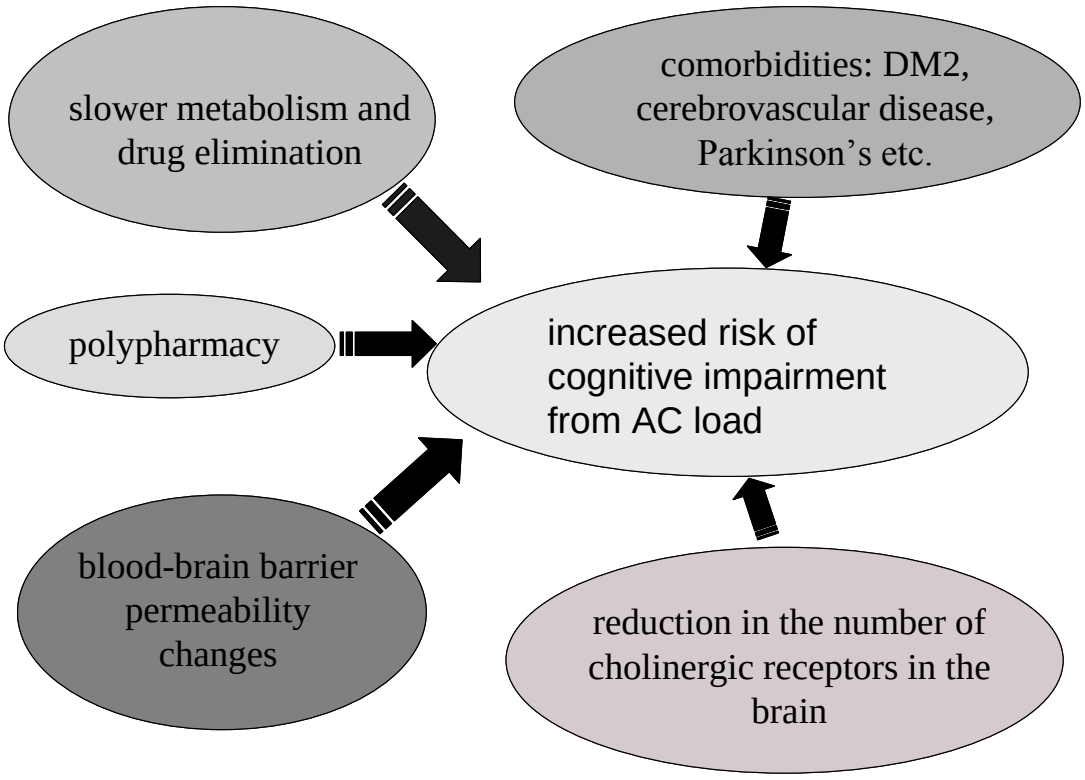

Figure 1. Reasons for the increased risk of cognitive impairment in older people (adapted from Kay et al 2005). All these cumulative issues may lead to increased sensitivity to anticholinergics and subsequently to an increased risk of cognitive impairment. AC = anticholinergic medicine, DM2 = type 2 diabetes mellitus.

As the body ages, blood flow to many tissues and organs may be reduced (DeVane and Pollock 1999). Reduced liver and kidney functions and an increased body fat content may lead to slower medicine metabolism and elimination, thus prolonging the desired but also the unwanted effects in the body. Liver P450 enzymes make medicines more water-soluble, and as aging may reduce the enzyme activity, medicine molecules may stay more lipid-soluble for longer, and may cross the blood-brain barrier more easily. The blood-brain barrier also becomes more "leaky" with advancing age, allowing bigger and more water-soluble molecules through than in younger individuals (Kay et al 2005). Comorbidities such as diabetes mellitus and Parkinson's disease may also make the barrier weaker, having an additive effect on medicine permeability, making it easier for agents to get into the CNS.

If an older person also has multiple medicines in use, the potential for additive anticholinergic effects in the CNS increases.

Muscarinic receptor numbers in the brain decline with aging (Kay et al 2005). This may make the fewer functioning receptors more vulnerable to muscarinic blocking, as a small amount of an anticholinergic agent may then block a larger percentage of the total amount of receptors than in a younger brain. When this vulnerability is combined with the effect-prolonging factors described in the previous paragraph, the net effect may be that older people are more at risk for adverse effects from anticholinergics. Also, because some of the less M_3 specific medicines may not normally cross the blood-brain barrier, their effects on CNS muscarinic receptors and cognition may not be identified in clinical trials using younger people as study subjects. They may become clinically relevant in older patients though, when the medicines cross the barrier and block CNS muscarinic receptors. Here again the receptor subtype selectivity of the medicine determines, how harmful (if at all) the blocking may be for cognitive functions.

There are data available for the possible role of anticholinergics in cognitive decline, although no study so far published can be described as a large-scale, prospective, randomised clinical trial. Drimer et al (2004) studied the cognitive effect of discontinuing biperiden, an anticholinergic agent in a small-scale study. They investigated 21 older (mean age 65.7 years, range 60-78) institutionalised people with schizophrenia, who had been using the medicine for over one year. There were improvements in several tests of the Alzheimer's Disease Assessment Scale – Cognitive subscale (ADAS-Cog), a battery of tests that measures different cognitive functions. The total score of the ADAS-Cog test battery was significantly lower (20.0 vs. 21.7, $p < 0.03$), showing cognitive improvement ten days after the discontinuation of biperiden. Cancelli et al (2008a) investigated anticholinergic medicines as a possible risk factor for psychosis in 230 non-randomly selected older Alzheimer disease patients (mean age 77 ± 6 years, range 60-93). The participants were stratified into anticholinergic users and non-users, and the users were older and taking more medicines than the non-users. The investigators determined after

adjusting for confounders that there was a relative risk of 2.13 (95 % confidence interval (CI) 1.03-4.43, p = 0.042) for psychosis for users compared to non-users. This cross-sectional study may have overestimated the risk though, as those most likely to develop a psychosis may have been more likely to come to the clinic because of their symptoms.

5.1.4 Effects on tools measuring cognitive function

Several studies have investigated the effect of anticholinergics on overall mental capabilities, measuring effects with the Mini-Mental State Examination tool (MMSE). Lu and Tune (2003) studied the two-year effect of anticholinergic medicine use on MMSE scores in Alzheimer's disease patients (n = 53 for non-users, n = 16 for users) in a small-scale study. The results of the MMSE test at baseline and at one year did not differ between users and non-users, but there was a decline in MMSE results for the user group at two years (p = 0.032). The study was not randomized, however, and the patient groups were small. When Bottiggi et al (2007) replicated the same study in a bigger, unselected patient group (n = 300) they found no association.

Lechevallier-Michel et al (2004) investigated the effects of anticholinergics on the risk of poor cognitive performance in 1780 older, community-dwelling individuals (mean age 77.3 years, range 67.3-102.5 years) in a cross-sectional study. Their study did not find statistically significant higher odds ratios for performing more poorly in MMSE and two other measures of cognitive function, Benton Visual Retention Test (BVRT, measuring immediate visual memory) and Isaac's Set Test (IST, assessing verbal fluency) if the person was using anticholinergics, compared to those who were using none. Jewart et al (2005) compared the MMSE scores of Alzheimer's disease patients taking anticholinergic incontinence medicines and without them in a small-scale study. The same nine patients in the study were observed with and without the medicines, with appropriate three-week washout periods in between. There was a difference in MMSE scores, as they were higher when the patients were not using the incontinence medicines (p = 0.017). However, no difference was observed in another mental state assessment tool, the Alzheimer's Disease

Assessment Scale (ADAS-Cog). The same patients were analysed twice in the study, and the patient number in the study was small, so again this could only be seen as a preliminary study calling for more research on the subject.

Bottiggi et al (2006) examined the effect of long-term use of anticholinergics on several cognitive measures. MMSE results did not get poorer during the six-year follow-up, but there was a statistically significant difference in another tool, the Trail Making Test (TMT) parts A and B, measuring attention, processing speed, hand-eye coordination, visual scanning abilities and executive function. Those who did not use any anticholinergics performed better in the TMT than those who were using anticholinergics. However, the study did not take dosage into account, and during a six-year longitudinal study it may be difficult to control for all over-the-counter (OTC) medicines or herbal products that the patients may use, when interviews were performed only once a year.

Cancelli et al (2008b) tested anticholinergic medicine use as a potential risk factor of cognitive decline in 750 randomly chosen older individuals (mean age 75 ± 7.0 years, range 65-99). Use of anticholinergics was more common with advancing age, growing from 13.0 % in the age group 65-69 to 27.4 % in the 80+ group. Anticholinergic medicine users were older (76.7 vs. 74.4 years, $p < 0.001$) than those who used no anticholinergics. They were also using more medicines (mean number of medicines 4 vs. 1, $p < 0.001$) than the non-users, and were more likely to have poorer results in the MMSE and another cognitive test, Global Deterioration Scale (GDS), having an OR of 2.30 (95 % CI 1.19-4.45, $p = 0.013$) in the MMSE and 2.59 (95 % CI 1.25-5.38, $p = 0.011$) compared to the non-users.

Similar results were found in the study by Ancelin et al (2006), where 372 older patients (at least 60 years old) were recruited by randomly chosen general practitioners. Their medicines were recorded at 0, 1 and 2 years time points and patient anticholinergic scores were assigned, and an assessment of cognitive performance and a standardised neurological examination were done to detect mild cognitive impairment (MCI) and dementia. The

cognitive assessment was also performed 8 years after the start point of the study to investigate long-term effects. Included in the analysis were 297 patients who had never during the previous year used anticholinergics, and 30 patients who were considered consistent users. Anticholinergic medicine use and age were the only highly significant predictors of mild cognitive impairment (OR 5.12; range 1.94-13.51, p = 0.001). Anticholinergic medicine users (those with a score of 1 or greater) did have poorer results in many cognitive measures, but some measures showed no effect. Comparing those with the highest anticholinergic score (3) with non-users did not change the situation. The study showed that older patients taking anticholinergic medicines had an increased risk for mild cognitive impairment, but not of dementia at an 8-year follow-up. The attributable risk of anticholinergic agents to cause MCI was 19 % in this study. This effect may not have been caused by anticholinergics alone, as not all known MCI risk factors were taken into account in the study. Also, only the general practitioners referring the patients were randomly chosen, the patients were not.

It is difficult to interpret the results of all these different studies as most are very small-scale and have several methodological limitations, but they seem to suggest that anticholinergics may have some effects on global cognitive functions as measured by the MMSE. These effects seem mild, however, and more studies are needed to estimate actual effects in patient situations, as very small changes in MMSE scores may not be clinically relevant.

5.1.5 Delirium and possible effects of anticholinergics

Another clinical state that may be affected by anticholinergics is delirium. Delirium involves transient changes in cognition, concentration and orientation (Clary and Krishnan 2001). Several diagnostic tools have been developed to diagnose delirium, but different tools measure different aspects of the condition, making diagnosis and comparisons difficult (Clary and Krishnan 2001; Laurila et al 2004). Reduced ability to focus, sustain or shift attention and disorientation are commonly used as diagnostic criteria (Clary and

Krishnan 2001). The transient or fluctuating nature of the cognitive disturbances can also be used to identify delirious states.

Lemstra et al (2003) propose the term Cholinergic Deficiency Syndrome (CDS) to describe a condition where central cholinergic activity is reduced. This may happen because of anticholinergic medicines in the CNS. The clinical symptoms, e.g. restlessness and anxiety, are caused by loss of attention, impaired concentration and reduced capacity to detect and select relevant stimuli from the surroundings. This description matches the symptoms of delirium well. Snow et al (2007) propose a different term, Antimuscarinic Syndrome (AS) to describe the same state. Their group found that an anticholinergic agent, propofol, given as a sedative, caused extreme inexplicable agitation and aggressiveness in a 20-year-old man. The symptoms cleared only after administration of physostigmine, a cholinesterase inhibitor, which counteracted the effects of propofol by prolonging the effect of acetylcholine in the synapses. This isolated case-study offers some evidence to support the possible connection of anticholinergics with the development of delirium.

Delirium is a very complex state, with many precipitating factors like substance intoxication or withdrawal, infections and trauma, some of which may be rare conditions that are difficult to diagnose, as noted by Laurila et al (2008) in their study of Finnish acutely ill patients aged 70 years and older. Their study found that anticholinergic medicines were often involved in the development of delirium. Caeiro et al (2004) investigated the role of anticholinergic medicines in delirium in 22 acute stroke patients. As controls they had 52 non-delirious stroke patients, matched by age and gender, as older people generally take more medicines and because the male gender may be a risk factor of delirium. Delirious patients were using more anticholinergic medicines before the stroke (4 vs. 1, $p = 0.03$) and during hospitalisation (15 vs. 14, $p = 0.001$). The investigators' predictive model had a specificity of 86.4 % (true negatives identified correctly for delirium, i.e. 13.6 % of false positives) and sensitivity of 100 % (all true positives identified correctly, no false negatives). However, despite isolated case reports (Snow et al 2007) and

these small-scale studies showing a possible connection with delirium and the use of anticholinergics, no large-scale, conclusive evidence has been presented yet.

5.1.6 Concurrent use of anticholinergics and cholinesterase inhibitors

Acetylcholine levels and the numbers of cholinergic neurons and receptors decrease with advancing age and in Alzheimer's disease (Johnell and Fastbom 2008). To boost cholinergic nerve and memory functions cholinesterase inhibitors (anticholinesterases) are sometimes used. These medicines inhibit the cholinesterase enzyme that breaks down acetylcholine in the synapses, thus prolonging its effect, as metabolism is the main pathway to end this neurotransmitter's activity. Anticholinergics affect the acetylcholine nerves in the opposite way, as they block the binding of acetylcholine. They may then counteract any beneficial effects that cholinesterase inhibitors may have, as if the increased acetylcholine in the synapse cannot bind to its receptors, its action is of no use. Concurrent use of anticholinergics and cholinesterase inhibitors may be a potential risk factor for suboptimal treatment results (Ancelin et al 2006; Johnell and Fastbom 2008). As cholinesterase inhibitors are used to treat Alzheimer's disease, where the amount of cholinergic neurons is already reduced, any anticholinergics even in small amounts and with low affinities may have harmful effects.

Johnell and Fastbom (2008) found in their register-based study of 731,105 Swedish individuals who were at least 75 years old, that anticholinergic medicine use was more common among those who were using cholinesterase inhibitors than those who were not ($p < 0.001$). Logistic regression that controlled for age, type of residential area and number of dispensed medicines showed an OR of 1.23 (95 % CI 1.13-1.35) for concurrent use for men and 0.88 (0.83-0.94) for women, so men were at risk to take both of these types of medicines at the same time. The study was cross-sectional in nature and the medicines use registry did not include residents in nursing homes or hospitals. OTC medicines were also not included. No information was available on diagnosis or possible comorbidities. Still the large amount of study participants was a strength of this study. Bottiggi et al (2007) found

in their unselected patient group (n = 300, all patients with any cholinesterase inhibitor included) no association with the concomitant use of anticholinergics and cholinesterase inhibitors and progression of Alzheimer's disease. Their conclusion was that caution should be maintained but that these medicines with opposing effects do not automatically mean that the disease worsens. It is therefore still unclear, whether the use of anticholinergics should categorically be advised against in patients taking cholinesterase inhibitors.

5.1.7 Anticholinergic effects on physical function

Anticholinergic medicines may also affect physical function because of the side effects they cause, and the potential medical conditions that these effects may cause. Dizziness or poor depth perception caused by dilation of the pupils may make falls more likely (Pollock 1999). Aizenberg et al (2002) investigated the risk of falls in older psychiatric inpatients in a small-scale study and how anticholinergic burden might affect the risk. Their 4-year study included consecutive patients admitted to a psychiatric ward, with 34 patients using anticholinergics (case group) and 68 controls using none. Altogether 8.2 % of all patients suffered a fall during their hospitalization, and those that suffered a fall did not differ from those who did not in mean age or distribution of psychiatric diagnosis. There were more women among those who fell, however, with 68 % in the case group and 39 % in the control group ($p < 0.02$). There was also a difference between the groups regarding anticholinergic burden score (ABS, defined as the sum of anticholinergic medicine scores, and each medicine was graded from one to five according to its anticholinergic potency). The mean ABS was 2.68 ± 1.8 for all patients in the study, and 3.25 ± 2.2 for those that fell ($p = 0.03$). This preliminary finding suggests that having a higher anticholinergic load may predispose a person to falls.

Landi et al (2007) and Nebes et al (2007) found in their studies that anticholinergic use affected physical function negatively. They tested walking speed, response times, balance, hand grip strength, and everyday living activities, and found that having a higher anticholinergic burden, defined as having more anticholinergic medicines (Landi et al

2007) or higher serum anticholinergic activity (Nebes et al 2007) was statistically significantly associated with poorer performance in the tests. This may mean that the quality of life of older people may decrease as everyday tasks become more difficult. Cao et al (2008) tested the effects of anticholinergics (based on Mosby's Drug Consult and the list of Peters 1989) on mobility in 932 older women. A higher anticholinergic burden was associated with more mobility difficulty, slower gait, more difficulty in rising, and more difficulty in activities of daily living (ADL), as well as poorer results in the MMSE test.

5.2 Measuring individual *in vitro* serum anticholinergic activity

Tune and Coyle (1980) were the first to develop a method for measuring *in vitro* anticholinergicity in individual patient serum samples. This radioreceptor assay called the Serum Anticholinergic Activity (SAA) assay, developed for measuring the combined anticholinergic effects in the blood, has become a gold standard over recent years despite its limitations (Carnahan et al 2002a).

5.2.1 Serum anticholinergic activity assay – basic methodology

The SAA assay uses serum as the sample matrix, and 200 µl samples are run in triplicate or in some cases in duplicate if the assay procedure has been well optimised in a laboratory (Tune and Coyle 1980). In the assay, displacement of a radiolabelled, potent anticholinergic antagonist tritiated quinuclidinyl benzilate (TQB) from muscarinic receptors by other anticholinergic agents is measured by reductions in radioactivity. TQB has affinity for all muscarinic receptor subtypes. Specific binding of TQB is reduced in proportion to the concentration of the displacing agents, giving an estimate of the total anticholinergic agent content in the sample.

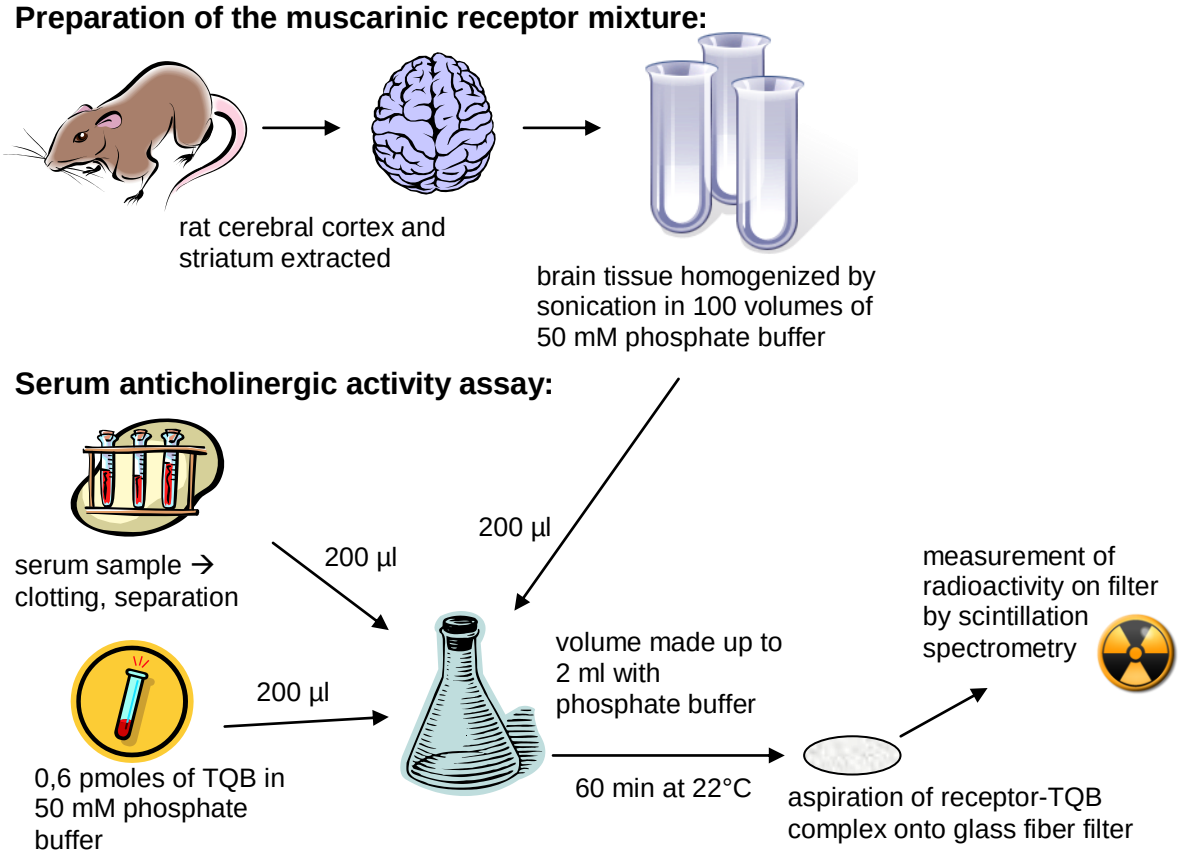

Figure 2. A description of the Serum Anticholinergic Activity (SAA) assay developed by Tune and Coyle (1980). Briefly, rat brain tissue is homogenized and a sample is incubated together with a serum (patient) sample and some tritiated quinuclidinyl benzilate (TQB). After filtration radioactivity is measured and reductions in activity reveal the presence of anticholinergic agents that displace the radioactive TQB in the serum sample investigated.

In the SAA assay, rat brain homogenate is used as a source of muscarinic receptors, and Chew et al (2008) report using 200-225 g of rat brain tissue at a time. 200 µl of the homogenate is mixed with 200 µl of serum sample and 200 µl of the TQB preparation (Figure 2). The assay mix is then made into 2 ml volume with buffer, and the mix is incubated at 22°C for 60 min (Tune and Coyle 1980). Then the mix is aspirated onto a glass fibre filter, which lets all free material run through but retains complexes containing the receptor with a bound molecule. These complexes may be radioactive if TQB is bound, or

non-radioactive if the bound agent is an anticholinergic substance from the serum sample (Figure 3). Radioactivity on the filter is measured by scintillation spectrometry, and results are compared to a standard curve made with known amounts of atropine, a potent anticholinergic agent that also displaces TQB. The levels of radioactivity represent levels of TQB displacement (the less radioactivity, the more TQB displaced), and the amount of displacing (anticholinergic) agent equals that of the amount of atropine used in a sample creating a similar radioactivity level. Because atropine is used as a reference molecule in all assays, results are given as atropine equivalents, and they are comparable between different anticholinergic compounds and laboratories.

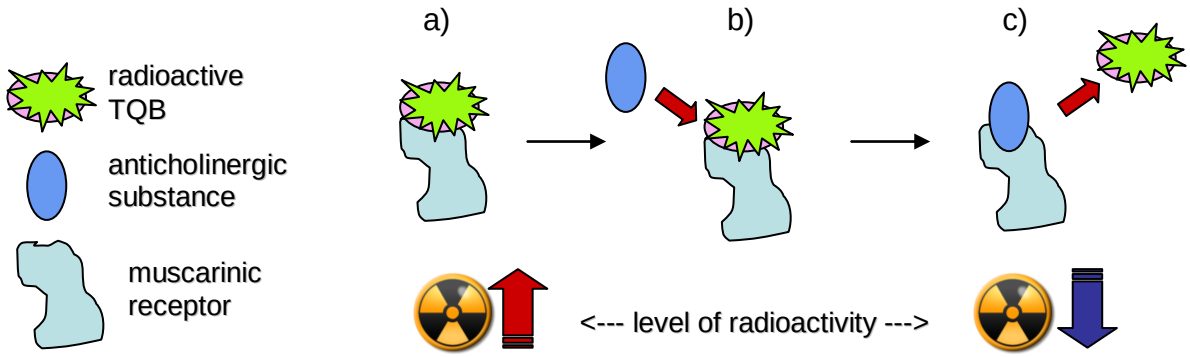

Figure 3. Displacement of bound tritiated quinuclidinyl benzilate (TQB) in the SAA assay. a) TQB bound to a muscarinic receptor in the rat brain preparation. b) An anticholinergic agent may displace TQB from the receptor. c) Displacement leads to reduced radioactivity, as unbound TQB is filtered out.

5.2.2 Using the Serum Anticholinergic Activity assay in practice

Several studies have used the SAA assay to estimate anticholinergic burden (Carnahan et al 2002a; Chew et al 2005). Results of the studies have often been conflicting, and the distribution of SAA levels is skewed, i.e. there are more people with low values (Nebes et

al 2007). Dose-dependent increases in SAA have been observed with anticholinergic medicines, but developing a tool for clinicians to e.g. estimate possible anticholinergic effects expected for any given dose of a medicine is difficult because of inter or intra-individual variation (Chew et al 2006). When Mulsant et al (2003) measured the SAA values of 201 randomly chosen older (mean age 78.2 years) community-dwelling adults, they measured detectable values in 89.6 % of the cases, the median SAA value being 1.25 nM (range 0 - 5.6 nM). MMSE test results were available for all subjects, and there was an association between SAA and cognition, with lower scores being associated with high SAA in the blood (OR 19.12; 95% CI 2.15-169.85; p = 0.008)

5.2.3 Estimating central anticholinergic effects with the Serum Anticholinergic Activity assay

The SAA assay attempts to describe the total anticholinergic burden in peripheral blood, but it is not clear how well if at all it can be used to estimate central anticholinergic burden. Plaschke et al (2007a) investigated the correlation between plasma (ethylenediaminetetraacetic acid, EDTA plasma) and cerebrospinal fluid (CSF) SAA levels in 15 non-randomly selected pre-surgical urological patients (mean age 70.4 ± 6.0 years, range 58-78 years). Some of these patients were using anticholinergic medicines while others were not, but there were no statistically significant differences between the two groups. Mean levels in the SAA radioreceptor assay were 2.4 ± 1.7 nM of atropine equivalents (range 0-5 nM) in plasma samples and 5.9 ± 2.1 nM (range 2-12 nM) in CSF samples. CSF levels of anticholinergic activity were 2,5 times higher than those in plasma, but there was a significant correlation between the two ($R = 0.86$, $p < 0.001$) so the assays in the two sample matrices were likely to be measuring the same parameter. Therefore the investigators concluded that SAA could be used to estimate central anticholinergic activity. Miller et al (1988) also found a correlation in their study.

Thomas et al (2008) also investigated whether the SAA correlates with cerebral cholinergic function. Quantitative electroencephalography (qEEG) was chosen as a means to measure

CNS function. The qEEG measures the brain's electric function, and centrally acting anticholinergics affect the alpha rhythm in the qEEG. 61 consecutive patients aged over 80 admitted to an acute health ward were recruited to the study, and their medicines, cognitive test results, and qEEGs were recorded for analysis. The patients were evaluated for dementia, and stratified according to their mental status: cognitively unimpaired (n = 15), dementia (n = 31), and delirium with dementia (n = 15). No statistically significant differences could be found between these groups in their SAA levels, and SAA did not correlate with cognitive impairment (MMSE) or qEEG, even though these two reference parameters correlated together ($p < 0.005$). Based on this study SAA does not describe the CNS anticholinergic activity or enable detection of delirium in the acutely ill older people.

Both the Plaschke et al (2007a) and Thomas et al (2008) studies are limited by a small patient sample. Both studies also used only a limited battery of cognitive tests to determine the mental status of the patients. More research is needed on SAA measurements from CSF as a potential tool for estimating central anticholinergic effects.

5.2.4 Association of Serum Anticholinergic Activity with cognitive functions

Chew et al (2005) reviewed previous studies on SAA relationship with cognition. Most studies had a very small patient population. There were conflicting results, but most studies found a relationship with higher SAA and a poorer cognitive status, even if the association was weak. Nevertheless, their conclusion was that treatments with anticholinergics should be used with caution in older, demented patients. Nebes et al (1997) hypothesized that SAA might in part explain the observed inter subject differences in cognitive performance, especially memory, that are common in depressed older patients. Their finding of effects on memory in patients with even a low measurable SAA level may mean that the anticholinergic burden needs to be taken into account when assessing cognitive performance in older patients.

Patients with dementia had significantly higher levels of SAA in the study of Mussi et al (1999). Another type of cerebrovascular disease affecting memory, white matter hyperintensities (WMH), also had a correlation to SAA levels (Nebes et al 2005). Miller et al (1988) compared different cognitive tests when analysing mild cognitive impairment in older patients of whom one half was taking and the other half was not taking scopolamine, a potent anticholinergic. Serum and CSF samples were analysed with the SAA assay, and anticholinergic activity levels were significantly higher in the scopolamine group compared to the placebo group with both samples. There were no differences between groups in the MMSE score, or the Symbol Digit Modalities score (measuring timed visual-motor performance), but with the Delirium Checklist score developed by the authors, scores were poorer for anticholinergic users. Miller et al state that in its early stages mild cognitive impairment is more easily managed than if it is allowed to progress to gross impairment. They therefore recommend SAA measurements and cognitive tests as a part of care for older people. Larger scale studies are needed to investigate the usefulness of SAA.

5.2.5 Serum Anticholinergic Activity levels and delirium

Central anticholinergic measurements have the potential to be useful diagnostic or even treatment guiding tools, and several studies have investigated the association of SAA with delirium (Chew et al 2005). SAA can be used as a delirium disease marker according to Marcantonio et al (2006). Milbrandt and Angus (2005) also mention SAA as a potential means for detecting critical illness-associated cognitive dysfunction, as several medicines not commonly considered to have anticholinergic properties can show such effects. The SAA in their opinion would better describe the total anticholinergic burden at any given time than calculations from a dose, as there are intra- and inter-individual differences in medicine metabolism.

Hori et al (2005) described a 75-year-old man with Alzheimer's disease, who was showing signs of dementia and delirium. When his anticholinergic medicine was stopped, his SAA levels dropped, the delirium resolved, and his MMSE score increased from 7 to 21 in the

following 28 days. Hori et al commented, that none of the medicines the patient had before the intervention were considered particularly anticholinergic, but nevertheless he had a high enough SAA value to measure. The changes in his medicine regimen had a positive effect on his clinical status and quality of life. The SAA assay may therefore be useful in detecting those patients with delirium who may benefit from medicine changes, as especially subclinical delirium may be hard to diagnose otherwise.

Tune et al (1981) found an inverse correlation between SAA and MMSE in delirious patients. Mach et al (1995) found that delirium was more likely to be resolved in those patients who had high SAA at entry but whose anticholinergic medicines were then discontinued and whose SAA levels dropped. Flacker et al (1998) found the occurrence of delirium to be increasing as SAA levels increased. Plaschke et al (2007b) found no differences in SAA levels between delirious and non-delirious patients, when qEEG was used as a reference method to detect delirium. Also, SAA did not correlate with the qEEG. All these studies had limitations, as they had been not been fully randomised and they were very small scale, with only 77 (Flacker et al 1998), 37 (Plaschke et al 2007b), 29 (Tune et al 1981), or 11 (Mach et al 1995) patients. Since anticholinergic medicines are not a clear risk factor for delirium but rather there is an association between the two, interpretation of results is difficult (Carnahan et al 2002a). Delirious patients may be sicker and using more medicines, so SAA may not be independently associated with delirium (Tune and Egeli 1999). As a conclusion, the SAA test cannot be used as a diagnostic tool to detect the presence or absence of delirium, but may be useful as a tool to identify delirious patients whose symptoms may be medicine induced (Mach et al 1995).

5.2.6 Limitations of the Serum Anticholinergic Activity assay

There are some methodological problems with the SAA assay, as it is not internationally standardised and it is not clearly defined, what it is that the assay is measuring (Carnahan et al 2002a). The assay measures binding to central muscarinic receptor subtypes more than to peripheral, M_3 and M_5 subtypes (Chew et al 2006). Reductions in SAA levels do not always

coincide with discontinuation of anticholinergic medicines, and this clouds the issue further, as there are other factors affecting SAA as well (Carnahan et al 2002a). It is also not available as a commercial kit, and the rat brain preparation needs to be prepared in-house before performing the assay. This may generate differences in assay performance, as every laboratory needs to validate the method in their own respective conditions. This makes reproducibility and precision an issue, as if within day and between days variation in reproducibility is not limited, results may vary between assay runs and laboratories (Bylund and Toews 1993; Junghans 1996). Also, since the TQB tracer is radioactive, it has a limited shelf life, and batch-to-batch variations in the commercial product may add to possible reproducibility problems.

The reported limit of detection (lowest theoretical, or in some cases actual concentration that can be measured) for the SAA assay ranges from 0.25 nM (pmol/ml, Mulsant et al 2003) to 0.5 nM (Thomas et al 2008). The assay linear range has been reported to range from 0.50 to 25.00 nM (Mulsant et al 2003), but also a much broader measuring range from 0.5 to 250 nM has been reported (Chew et al 2008). Intra-assay reproducibility (CV %) has been reported to be less than 12 % (Mulsant et al 2003) or less than 9 % (Thomas et al 2008). Inter-assay reproducibility is reported as less than 12 % (Mulsant et al 2003). Mussi et al (1999) report a precision of 4.1 % but do not report which parameter they are describing. Intra- and inter-assay accuracies (i.e. recovery of spiked standard from serum) have been reported to be 93-109 % and 95-105 %, respectively (Thomas et al 2008). Tune and Coyle (1980) describe in their original article that they use a total volume of 2 ml for the assay, but in a following report (Tune et al 1981) they use a total volume of 1.2 ml. This may or may not affect TQB binding and assay results as in the larger assay volume serum is diluted more and the concentration of proteins is lower. Other groups using the SAA assay often do not mention, which total volume they are using. Carnahan et al (2002b) compared SAA parameters from different studies, and the results were showing clear differences between laboratories. However, as an atropine standard curve is always run in parallel with the assay, changing parameters may be controlled for through the standard.

One of the problems with a lack of standardisation is that some researchers use plasma samples rather than serum (e.g. Plaschke et al, 2007a: EDTA-plasma, Flacker et al 1998: heparin plasma). This may cause differences in receptor binding, as Tune and Coyle (1980) noticed a matrix effect even in their original article, and they believed this effect to be caused by proteins in serum. Proteins may reduce the binding of TQB, potentially leading to more displacement and subsequently an overestimation of anticholinergicity in the sample. Plasma contains all clotting factors which serum does not, so the protein content and possibly also binding interference may be higher in plasma samples (Toldy et al 2005). This may cause discrepancies between results in different laboratories as noted by Carnahan et al (2002b), especially if a medicine molecule tends to bind to serum proteins in a living human subject, and its binding affinity (anticholinergic activity) is being determined in a sample of pure medicinal substance. Aaltonen et al (1984) tested the sample matrix effect while developing a similar TQB binding assay for atropine, and found plasma proteins to reduce binding by only up to 2 %. Plasma interference may therefore not be relevant in practice.

Because results from the SAA assay are an estimate of total displacement of TQB from the receptors, interfering agonists in the sample may affect the results by falsely increasing measured displacement, and the number of potentially anticholinergic medicines does not necessarily correlate with measured anticholinergic activity (Tune et al 1981; Carnahan et al 2002a; Mulsant et al 2004; Plaschke et al 2007a; Chew et al 2008). Flacker and Wei (2001) found endogenous anticholinergic substances that are likely to exist in older, acutely ill patients. They measured the SAA of ten older patients admitted to a health clinic, and who had not been using any anticholinergic medicines for the past seven days, which was considered a long enough time for any interfering anticholinergic metabolites to be eliminated. Patient samples and buffer samples spiked separately with therapeutic concentrations of all the medicines that the patients were using were analysed with the radioreceptor assay. Eight of the ten patients had measurable SAA levels (mean 0.69 ± 0.52 nM, range 0.23-1.72 nM) even though none of the buffer samples that were spiked with the medicinal substances they were using had measurable SAA. The measured levels were very

low and close to the detection limit of the assay, however, so the results may not be reliable and reproducible. However, according to literature there are some endogenous substances that can bind to cholinergic receptors and block the binding of other molecules. These include dynorphin A, myelin basic protein, and protamine. If substances like these interfere with the assay, it may explain e.g. some of the conflicting results in studies where the relationship between anticholinergic medicine use and delirium was investigated.

Determining SAA value tables for standard medicine solutions as published by Tune et al (1992) can be misleading, as having two medical substances with different SAA values does not mean that the other one is more anticholinergic, even if it has a higher SAA value (Carnahan et al 2002a). The same 10 nM standard solutions that have been used for every medicinal substance to determine "reference" SAA values may not occur in clinical practise or be clinically meaningful. Different medicinal substances have different degrees of protein binding, metabolism, and elimination, and do not appear in same concentrations as others in the blood. Medicine penetration into the CNS is a confounding factor too, as it is not known how well certain medicines and their metabolites penetrate the blood-brain barrier, and there are likely to be changes in penetration rates with advancing age and between-person variation. As the rat brain preparation in the assay contains mostly M_1, M_2 and M_4 muscarinic receptors, which are located mostly in the brain in humans too, the assay may be less sensitive to those medicines that bind to the more peripherally distributed M_3 and M_5 subtypes (Chew et al 2008). The blockade of these two more peripheral subtypes does not seem to harm cognitive functions as much as blockade of the others, so this binding to M_3 and M_5 could be considered a desirable feature in medicine molecules. The usefulness of the SAA assay for measuring this binding in clinical research is unsure, however.

Despite its limitations, the SAA assay has been widely used in studies. The reason behind this may be its ease of use when only a blood sample is required from the patient, despite the assay requiring special instruments and radioactive reagents. Its clinical usefulness

remains unclear despite decades of investigational use, as it has not been used in routine clinical practice.

5.3 Anticholinergic medicine scoring systems and lists

A simple assessment method of anticholinergic burden is needed, but serum measurements have limitations, as the rate of brain penetration of many medicines is unknown. Taking samples from CSF or other CNS tissue is difficult and time-consuming, sometimes impossible or ethically unacceptable because of the risks involved in sampling (Minzenberg et al 2004). The SAA assay is far from perfect, and it requires blood samples and a laboratory to analyse them, which may not always be practical. It is still currently a relatively widely tested method despite its limitations, and it is often used as a comparison method when alternative tools are being developed to estimate anticholinergic burden. Simply summing up the amount of anticholinergic medicines a person has does not describe their anticholinergic burden accurately enough, as different medicines have different anticholinergic effectiveness (Carnahan et al 2002a). Many tools have been developed and published fairly recently, and they have attempted to solve this problem by grading anticholinergics. These tools have not yet been tested thoroughly for usefulness in everyday clinical practise with unselected patients. Some of these tools are presented in the following chapters.

5.3.1 Anticholinergic rating scale

Carnahan et al (2002b) developed an anticholinergic rating scale and compared it with the SAA assay by assessing 98 older nursing home residents (mean age 86.8 ± 7 years, range 68-106) with both tools. The investigators based their work on an anticholinergic scoring system developed previously by Han et al (2001). This previous scoring system was updated and modified by three psychiatric pharmacists if there was a need for change arising from recent literature. The modified scores were significantly associated with SAA ($p < 0.01$), but the scores only explained 7 % of the variance in SAA levels. This low level

of explanation was thought to be because medicine dosage was not included in the scoring. Taking the dose into account is difficult, however, as the serum levels of any given medicine are not constant, and dose alone does not describe the situation in the blood. Medicines on this developed list were given scores of 0, 1, 2 or 3 depending on their anticholinergicity, but the authors note that this probably does not describe the actual relative potencies when these medicines are compared to each other. Also, since the list is based on expert opinion as well as the literature, it may not be free of bias.

5.3.2 The combined pharmacological and clinical index

Minzenberg et al (2004) developed a method where they combined a pharmacological and a clinical index to estimate the relative anticholinergic potency of psychotropic medicines. In their study they enrolled 106 outpatients with diagnosed schizophrenia, and used cognitive tests to evaluate their mental status. As a comparison they used a matched group of 50 healthy volunteers with no history of schizophrenia. Based on a thorough literature review the investigators calculated the relative benztropine (a centrally acting anticholinergic agent) equivalents for all the medicines for which they could find a brain tissue muscarinic receptor affinity value. This benztropine equivalence would serve as the Pharmacological Index. The Clinical Index was developed by having ten psychiatrists rate the same medicines by comparison to 1 mg of benztropine, based on their experiences of patient complaints of anticholinergic symptoms such as dry mouth. A mean anticholinergic potency value was then calculated from these gradings for each medicine. When these two indexes were compared to each other in the patient population, a good correlation was found ($R = 0.80$; $p<0.0001$). Both indexes were significantly related to inferior performance in the cognitive tests used, and no significant difference was observed between the indexes. There were limitations in the study, e.g. the ten psychiatrists had prior knowledge of *in vitro* receptor binding activities for the medicines, which may have introduced bias. Patient selection was not randomised, so people who were less likely to participate in studies for e.g. various personal reasons may have been underrepresented. Also, the Clinical Index is

based on peripheral symptoms, not central, as there is no accepted measure of central anticholinergic activity. This limits its usefulness in estimating central effects.

5.3.3 The Anticholinergic Drug Scale (ADS)

Carnahan et al (2006) proposed a scoring method, the Anticholinergic Drug Scale (ADS) for estimating anticholinergic burden. They proposed it for specifically choosing which medicines could be considered for discontinuation in those cases where a high anticholinergic load was present. In this study the previously published anticholinergic drug rating scale (Carnahan et al 2002b) was updated to reflect dosage, and its functionality was tested with the same patient sample as in the original article, using the SAA as a reference method. Anticholinergic scores were calculated for the 201 older patients (mean age 86 ± 7 years, range 64-102 years) based on their regular and when required medicines taken on the day of the blood sampling. If a medicine was mentioned as being taken regularly and when required, it was included twice in the scoring.

As an update to the previous scoring system, dose was taken into account for the more potent level 2 and 3 anticholinergics. FDA maximum recommended daily doses (MRDD) for adults were used as a basis for grading, and no special dosing measures for geriatric patients were taken into account. This was a limitation of the study, as older patients may be prescribed lower doses, and this leads to underestimations of the dose weights. Patients' scores for level 2 or 3 medicines were weighted based on the ratio of their daily dosage compared to the MRDD. For level 0 or 1 medicines there was no adjustment for dose. If the daily dose was less than or equal to one third of the MRDD, the dose weight was 1. If it was more than one third but less than or equal to two thirds of the MRDD, the dose weight was 2. If the dose was greater than two thirds or equal to the MRDD, the weight was 3. For doses greater than the MRDD the weight was 4. Dose-adjusted scores were calculated for level 2 and 3 medicines by multiplying the anticholinergic score by the determined dose weight.

The ADS total scores were significantly associated with SAA ($p < 0.0001$). The median ADS total score was 2 (range 0-11), and the median dose-adjusted ADS total score was 3 (range 0-25). Adjusting for dose did not offer any improvements in how well the score predicted SAA levels, and the 0-1-2-3 grading used in the older version (Carnahan et al 2002b) was ultimately deemed adequate for analysis. The authors thought that the ADS's low level of explaining variance in SAA (7 %) was due to differences in medicine potencies within scoring groups, as not all medicines in e.g. level 3 medicines have the same anticholinergic potency. A scoring system of 0-1-2-3 may not be optimal or reflect real relative potencies. Their previous conclusion (Carnahan et al 2002b) of the importance of dose was thus discarded. These new ADS scores were associated with SAA, and could be applied to any medicine list, depending on availability in any country. Also, this method did not require blood samples to be taken as the SAA assay does. The ADS could be used as an aide to choose which medicines to target to reduce anticholinergic burden, but the authors concluded that this warranted more study.

Low et al (2008) tested the ADS developed by Carnahan et al (2006) in their study of 2058 randomly selected young-old (aged 60-64 at baseline) community-dwelling individuals. This was a longitudinal cohort study, with a follow-up time of 4 years. Participants were tested with several tools measuring cognitive functions (Mini Mental-State Examination, speed of information processing, simple reaction time, verbal intelligence, immediate and delayed recall) at baseline and at 4 years. Patients with dementia, brain tumours, brain infections, stroke and cancer were excluded from the study, as they were considered to be especially vulnerable to anticholinergic effects. These excluded participants were using more anticholinergics then those included in the study analysis (22.6 % vs. 15.9 %, $p = 0.037$), which limits the study reliability. This analysis found evidence that anticholinergic medicine use, measured by the ADS score, was more common in women than in men (56.1 % of users were women vs. 46.8 % of non-users), and that the prevalence of use in the whole study population was approximately 15 %. Use of anticholinergic medicines was not associated with greater decline in any cognitive tests, but complex attention was affected negatively in one of the tests ($p = 0.005$). This small difference

detected may not be clinically relevant though, as the authors note. This study used the previously developed ADS to identify patients using anticholinergics, but whether the ADS was used to its full extent as participants were only divided by use/non-use only remains unclear. The random nature of the patient sample and the large number of participants are the strengths of this study, as they mimic real life clinical situations.

5.3.4 The Ancelin anticholinergic scoring system

Ancelin et al (2006) developed an anticholinergic scoring system based on anticholinergic potency values available in the literature for medicines in the SAA assay, combined with an expert group (pharmacologist, physician, and biologist) clinical opinion of anticholinergic potency. The result scoring system gives individual patients a score from 0 to 3, 0 meaning no anticholinergic medicines in use, 1 meaning medicines in use with no likely anticholinergic effect, 2 meaning medicines in use with a low effect, and 3 meaning that there are medicines with high anticholinergic effect in use. This system of scoring patients rather than medicines is different to the other grading tools.

To test the tool, all prescription, OTC and herbal and other medicine use of a group of patients over 60 years of age were recorded at 0, 1 and 2 years time points (Ancelin et al 2006). Those who had an anticholinergic score of one or greater had poorer test results in some tests measuring cognitive performance. The functionality of the tool was good in this study as its developers were using it, but more usage is needed to estimate its usefulness in routine practice.

5.3.5 The Han anticholinergic scoring system

Han et al (2008) evaluated an anticholinergic medicine scoring system based on clinical evaluations by geriatricians. Their study included 544 men aged 65 and older with diagnosed hypertension requiring constant pharmacotherapy, typically with several medicines at the same time. Cumulative exposure to anticholinergics over the preceding

12 months was determined, and the anticholinergic medicines were given scores from 0 to 3 according to the literature and how strong their anticholinergic effects were considered by a group of three independently evaluating geriatricians. This new list was an update of their previous study where a similar scoring system and list was created based on expert opinion of three geriatric psychiatrists (Han et al 2001).

During the 2-year follow-up period, total anticholinergic burden (defined as cumulative anticholinergic scores) over the previous year was significantly associated with poor performance in tasks that tested memory and executive function ($p = 0.002 - 0.04$, depending on the model used) (Han et al 2008). The adverse effect would amount to a 0.30-point deficit in the memory test and 0.10 point deficit in the executive decision test per one unit (score point) of anticholinergic burden per 3 months of medicine use. The clinical significance of these deficits was not explored. This would be important, because clinical importance and statistical significance do not always mean the same thing (Altman and Bland 1995). This deficit effect was three times (memory task) or one times (executive task) greater than the effect of non-anticholinergic medicines. Limitations of this study included the selected patient population (hypertension patients from a Veteran's Affairs clinic in Connecticut, USA) that may not be representative of other population groups. Also, the anticholinergic scoring system was based on three geriatricians' opinions only, and not on e.g. a consensus panel. Expert opinion may have been formed based on clinical evidence, but for some medicines with suspected anticholinergic effects there is not much peer-reviewed, published evidence available to form an opinion.

5.3.6 The Anticholinergic Risk Scale (ARS)

Rudolph et al (2008) developed a scoring system for anticholinergic medicines, the Anticholinergic Risk Scale (ARS). The tool was developed by having a geriatrician and two specialist geriatric pharmacists grade the anticholinergicity of 500 most prescribed medicines in the Veterans Affairs Boston Healthcare System with a score of either 0 (no anticholinergic effect or a limited effect), 1 (moderate effect), 2 (strong effect) or 3 (very

strong effect). Grading was done based on affinity data of the medicines for muscarinic receptors, FDA-published rates of their anticholinergic side effects, and literature regarding the adverse effects. Literature values of affinity constants mostly give values only for affinity to the M_1 receptor, which is found in the CNS, and constants for the more peripheral M_3 and M_5 are not given (Kwatra 2008). This may limit the usefulness of the ARS score, as it makes estimation of peripheral effects more difficult. Median scores were given if there was disagreement on a medicine's score among the raters. All topical, ophthalmologic, otologic, and inhaled medicines were excluded. The finished scores could then be used to give points for all medicines that the analysed person was using, and a total sum of these would be the final ARS score.

The ARS system was tested on older patients. The study combined a retrospective cohort of 132 consecutive patients (mean age 78.7 ± 5.3 years) of a health clinic, and a prospective cohort of 117 male patients (mean age 71.5 ± 11.6 years), attending primary care clinics in the same settings (Rudolph et al 2008). Each patient's medicines were used to give her/him an ARS score. All anticholinergic adverse side effects were also recorded in interviews. Each effect was given a score of 1 (hence not necessarily describing their relative severity), and the sum of adverse effects was calculated for each patient, with peripheral and central effects summed separately.

In the studied patients, higher ARS scores were associated with increased risk of both peripheral and central anticholinergic adverse effects in the prospective cohort, and an increased risk of central adverse effects in the retrospective cohort (Rudolph et al 2008). After the results were adjusted for age and total number of medicines, in the retrospective patients the relative risk of any anticholinergic adverse effects was 1.3 (95 % CI 1.1-1.6) and in the prospective patients it was 1.9 (95 % CI 1.5-2.5). The study showed the ARS to be a useful tool in identifying possible problems with anticholinergic burden in older patients. The ARS scoring does not take into account dosage, however, and as the authors state, doing the ARS calculations during a patient encounter can be difficult as it is time-consuming. It could be used in electronic databases though, e.g. in medicine records.

Because most of the patient sample was male, and the patients were a select group, veterans from the Boston area with hypertension, further studies are recommended by the authors to establish its usefulness in unselected patients in clinical situations. Hilmer and Abernethy (2008) commented that the ARS weighting of the medicines into classes of 0 to 3 was done based on data from all kinds of patients. Therefore it is more strongly associated with effects in stronger primary care patients rather than frail patients in geriatric care.

5.3.7 The Drug Burden Index

Hilmer et al (2007a) devised a drug burden index that incorporates both anticholinergic and sedative burden. The total drug burden (TDB) is calculated by summing anticholinergic and sedative effects of medicines. Their group used two US pharmacopoeias to identify medicines with clinically significant anticholinergic or sedative properties. Anticholinergic or sedative burden was calculated for each medicine by a hyperbolic function ranging in value from 0 to 1, which takes dose into account and also the recommended daily dose. The model assumes linear, additive effects for medicines, and no synergism, and comorbidities are controlled for in the analysis.

The TBD index was tested in a sample of 3075 community-dwelling older Americans (mean age 73.6 ± 2.9 years) who were interviewed and assessed both at home and at a clinic (Hilmer et al 2007a). Physical function, attention and concentration were tested, and the association of TDB with these measures was determined. Increasing anticholinergic and sedative burden were associated with poorer physical and cognitive functions. Adding one unit of medicine burden affected physical function as much as three or four physical comorbidities would have, and a greater or half the effect of anxiety, depression, or cognitive impairment, depending on the measure used. The model is only an estimate of actual effects, as the authors note, but simply calculating a total sum of comorbidities may not describe participants with complex health problems, as noted in the editorial for this article (Agostini 2007). Also, the study participants were independently living older people apparently in relatively good condition, so the results may be quite different in e.g. frail,

institutionalised populations. A strength of the study is that the TDB index takes dose into account. Still the calculation of the index seems rather complex, as recommended and taken doses need to be determined. If it could be made into a computer program, the process would be easier and the advantages of the model could be fully utilized to give a more comprehensive estimate of total medicine burden.

5.4 Anticholinergic lists based on SAA measurements

Tune et al (1992) investigated 10 nM dilutions of 25 commonly used medicines with the radioreceptor assay, and measured anticholinergic activity for each, giving a list of SAA values and medicines. Included were quite a number of commonly used medicines that are not generally considered anticholinergic, but which showed low SAA levels in the assay. The cumulative effect of these medicines when taken together may have clinical implications. Whether the 10 nM dilutions of the parent compounds without their metabolites reflect reality, especially when there are inter-individual differences in medicine absorption and metabolism, is not known. But, as a comment to the article pointed out, the metabolites of these medicines may not matter from the central cholinergic blockade point of view, as metabolites are usually more water-soluble than their parent compounds, and therefore may not penetrate the blood-brain barrier so well (Ball 1993).

Chew et al (2008) measured the anticholinergic activity of 107 medicines with the Tune and Coyle (1980) SAA assay to publish their anticholinergic list. They diluted the standard medicine preparations with medicine free serum to six clinically relevant concentrations that are commonly used in older people in long-term care facilities (as according to a pharmacy provider in the US). Their goal was to help clinician decision making by offering anticholinergic activity values for these medicines at different doses, as medicine use alone (yes/no) does not give enough information to find those at risk for adverse effects from anticholinergics.

Pure preparations of the investigated medicines were dissolved and then diluted to the desired concentrations in commercial, medicine-free human serum (Chew et al 2008). Interfering effects from the solvents were investigated, and solvents were used only at concentrations known not to disturb binding of TQB. Of the investigated 107 medicines, 22 had dose-dependent anticholinergic activity with all tested concentrations, and 17 only at the highest concentration. The resulting *in vitro* activities may be used in clinical practice, but it is unclear, how well stable concentrations of these medicines measured *in vitro* can ever describe the effects in living human patients, especially as blood-brain barrier penetration of medicines may change with advancing age.

5.5 Combining different anticholinergic lists

During the literature search, 17 anticholinergic lists were obtained. Some of these lists were based on published literature (Peters 1989; Flacker et al 1998; Mintzer and Burns 2000; Roe et al 2002; Caeiro et al 2004; Han et al 2008; Uusvaara et al 2009), some were based on SAA measurement values (Tune et al 1992; Mulsant et al 2003; Chew et al 2008), some were based on expert opinion (Carnahan et al 2006; Laroche et al 2007), and some were based on a combination of expert opinion and either literature or SAA assay values (Han et al 2001; Lu and Tune 2003; Minzenberg et al 2004; Ancelin et al 2006; Rudolph et al 2008). Most of these lists were not complete, meaning that they only listed medicines, which were used by the patient population in their study, or that they listed medicines most commonly used in a defined population. When the 17 lists were combined, a table of anticholinergic medicines was obtained (Appendix 2). Some medicines appeared only on one list like e.g. timolol, while for others there was more consensus, with amitriptyline appearing on 16 lists of the 17 investigated. Medicines appearing on at least eight lists are listed in Table 3. Altogether 278 medicines were listed on these published lists combined, and of those almost half (126) appeared only on one of the lists. 131 medicines appeared on two to seven lists, and 21 appeared on at least eight lists.

Table 3. Anticholinergic medicines most often mentioned on 17 lists of anticholinergic medicines (Peters 1989; Tune et al 1992; Flacker et al 1998; Mintzer and Burns 2000; Han et al 2001; Roe et al 2002; Lu and Tune 2003; Mulsant et al 2003; Caeiro et al 2004; Minzenberg et al 2004; Ancelin et al 2006; Carnahan et al 2006; Laroche et al 2007; Chew et al 2008; Han et al 2008; Rudolph et al 2008; Uusvaara et al 2009).

	appears on how many lists?
amitriptyline	**16**
diphenhydramine	**12**
imipramine	**12**
oxybutynin	**12**
thioridazine	**12**
hydroxyzine = hydroxine	**11**
atropine = L/D-hyoscyamine	**10**
chlorpromazine	**10**
doxepin	**10**
ranitidine	**10**
benztropine	**8**
chlorpheniramine	**8**
codeine	**8**
diazepam	**8**
digoxin	**8**
furosemide	**8**
meclizine = meclozine	**8**
nortriptyline	**8**
olanzapine	**8**
promethazine	**8**
trihexylphenidyl = benzhexol	**8**

6 RESULTS OF THE EMPIRICAL RESEARCH

The patient data were analysed with Excel and NCSS 2007 and medicine use and anticholinergic use were quantified. This data and the mortality analysis are presented in the following chapters.

6.1 Patient sample

Of the 1444 eligible patients in the 53 long-term care wards included in the study, 1004 residents (70 %) were included in the analysis (Figure 4). Of the total patient population, 357 residents (25 %) did not give consent to participate, and medicine or mortality data was not available for 83 patients (5 %). The women in the study (n = 745) were older ($p < 0.001$) than the men (n = 241), as tested with the t-test, which assumes normal distribution for the patient sample ages. The mean (± SD) age was 83.35 (± 9.99) years for the women and 75.11 (± 11.48) for the men.

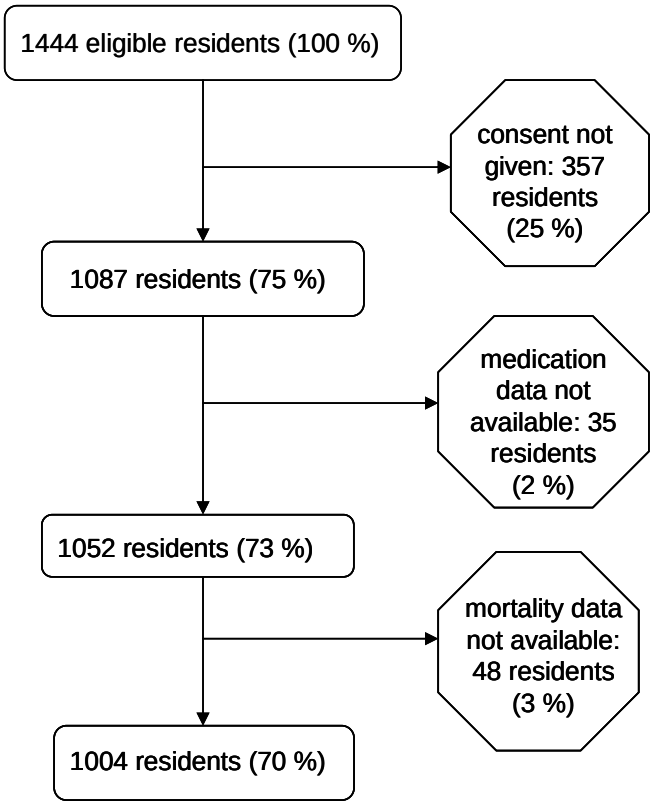

Figure 4. The sampling frame of patient information in the current study. From the original 1444 residents, 70 % were included in the final analysis.

6.2 Medicine use in the patient sample

Medicine use among the 1004 patients included in the analysis was investigated. The 1004 patients in the study were using a mean (± SD) number of 7.1 ± 3.4 medicines regularly (median 7 medicines, range 0-20). The distribution of medicine use is shown in Figure 5. Altogether 65.0 % (n = 653) were using at least six medicines or more regularly and 31.5 % (n = 316) were using at least nine medicines. When those medicines that are taken when required were also counted, the rates were 86.7 % (n = 870) using six or more medicines and 60.6 % (n = 608) using nine or more medicines.

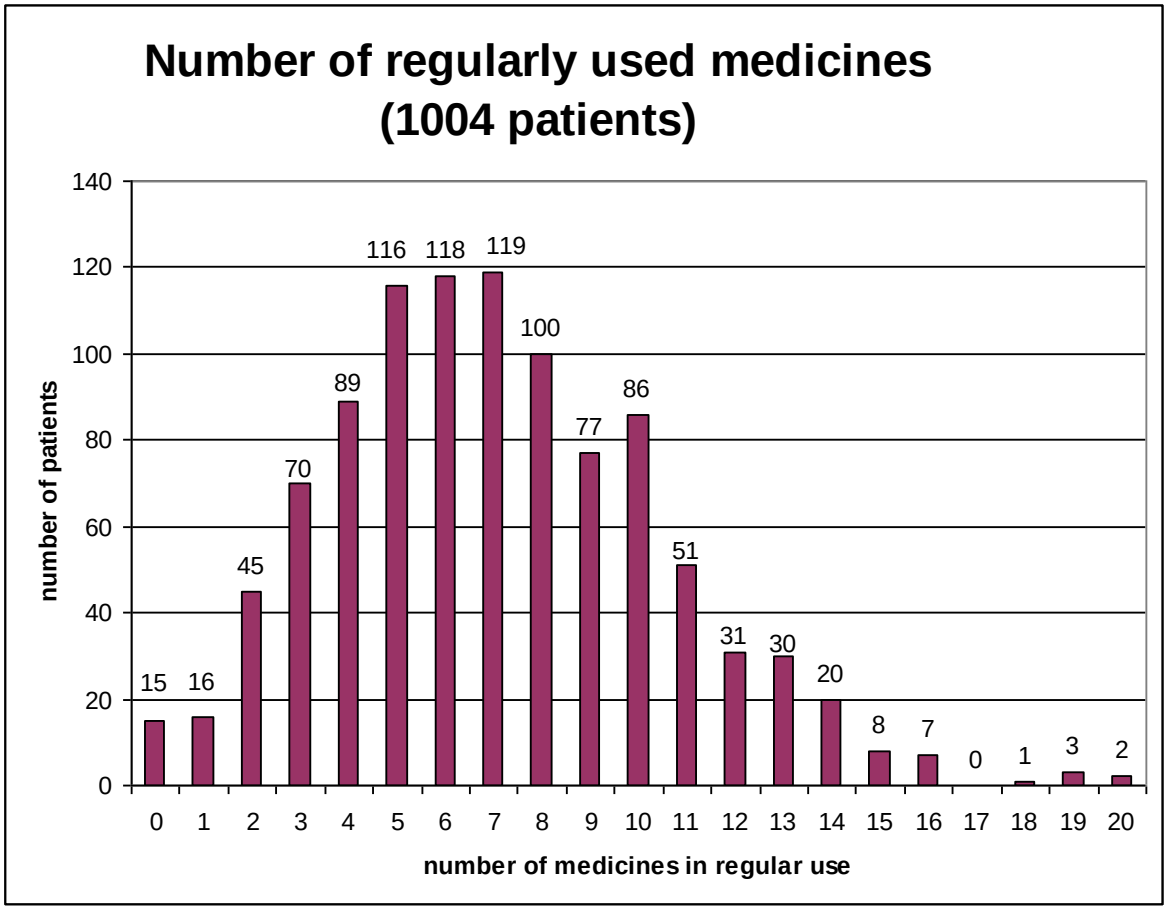

Figure 5. Medicine use in the study population. The 1004 patients were using a mean (± SD) number of 7.1 ± 3.4 regular medicines (median 7.0, range 0-20 medicines).

6.3 Use of anticholinergic medicines in the patient sample

The study participants were using 29 different medicines that are listed as anticholinergic in the ARS tool (Rudolph et al 2008). The numbers of people using them either regularly or when required are shown in Figure 6. These medicines and their ARS scores and official indications according to the Finnish National Agency of Medicines website are listed in Table 4.

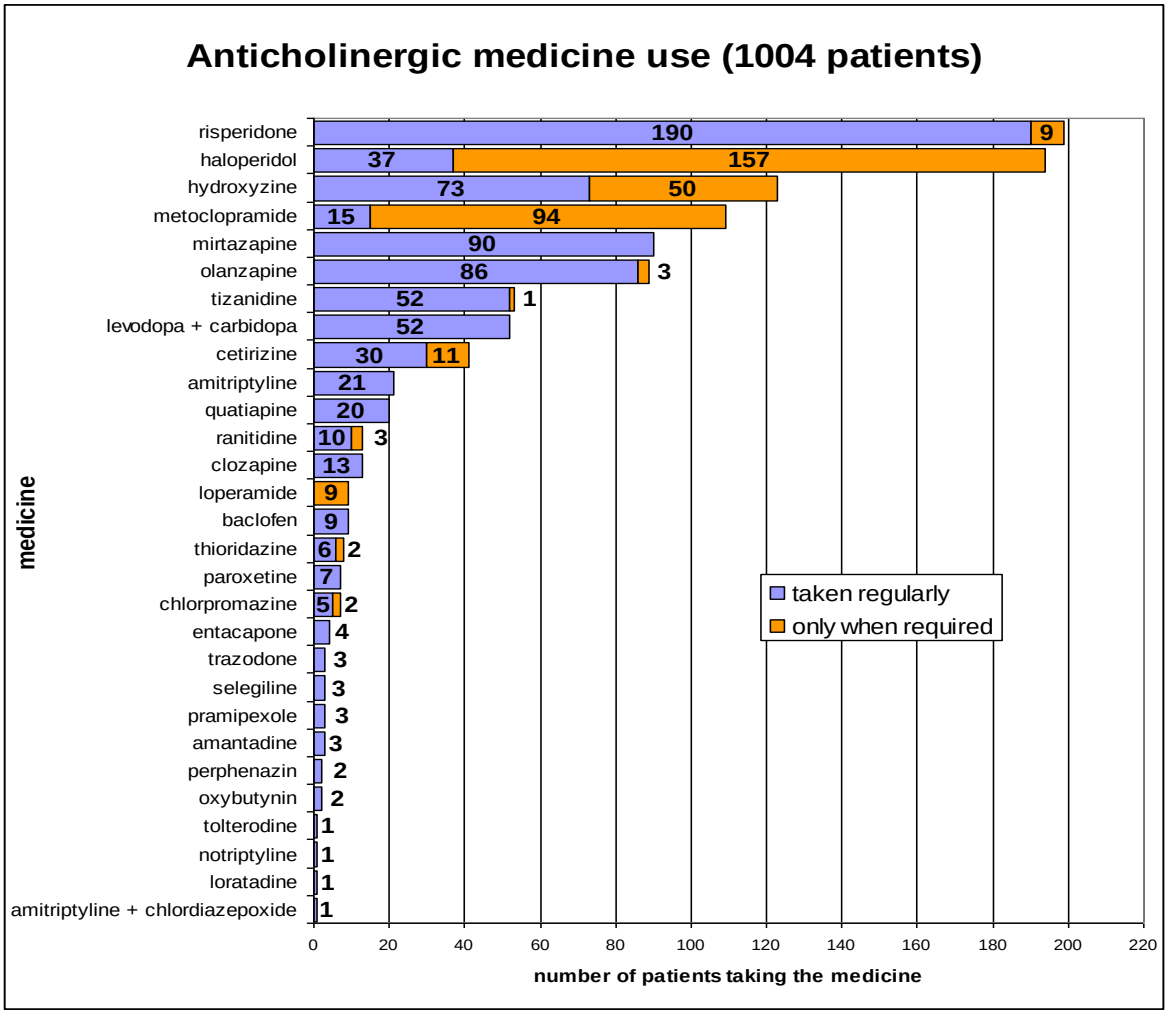

Figure 6. Anticholinergic medicine use in the study population. The numbers of people using a medicine regularly are shown with the blue bars, and the people using the medicine when required are shown with the orange bars.

Table 4. Anticholinergic medicines used by the study participants. Official Finnish indications and the ARS scores (Rudolph et al 2008) are listed for each medicine.

medicine	ARS score	indications
amantadine	2	Parkinson's disease, prevention and treatment of influenza type A
amitriptyline	3	depression, sleeplessness with depressive symptoms, chronic pain (e.g. fibromyalgia, neuropathic pain), prevention of migraine and tension headache
amitriptyline + chlordiazepoxide	3	mild depression with sleeplessness
baclofen	2	spasticity
cetirizine	2	allergy
chlorpromazine	3	psychosis, acute restlessness, agitation, severe nausea, adjuvant treatment for severe pain
clozapine	2	treatment resistant schizophrenia, treatment resistant psychotic disturbances in Parkinson's disease
entacapone	1	Parkinson's disease
haloperidol	1	long-term care of psychoses
hydroxyzine	3	adult anxiety, urticaria and itching, sleeplessness with allergic symptoms
levodopa + decarboxylase inhibitor	1	Parkinson's disease
loperamide	2	acute and chronic diarrhoea
loratadine	2	allergy
metoclopramide	1	nausea, gastro-oesophageal reflux
mirtazapine	1	depression
nortriptyline	2	unipolar and bipolar depression
olanzapine	2	schizophrenia, bipolar disorder
oxybutynin	3	incontinence
paroxetine	1	severe depression, compulsive disorder, panic disorder fear of social situations, anxiety, acute stress reactions from trauma
perphenazin	3	psychosis, schizophrenia, severe nausea
pramipexole	1	Parkinson's disease, Restless legs syndrome
quetiapine	1	schizophrenia
ranitidine	1	ulcers, reflux oesophagitis, gastro-oeasophagal reflux, gastrinoma
risperidone	1	schizophrenia, bipolar disorder, psychotic symptoms in dementia, severe behavioural disturbances in children
selegiline	1	Parkinson's disease
thioridazine	3	schizophrenia
tizanidine	3	muscular spasms, spasticity
tolterodine	2	incontinence
trazodone	1	depression, schizoaffective psychosis, sleeplessness with depressive symptoms

Anticholinergic medicines in regular use were identified from the patient medicine lists with the ARS tool and each patient's ARS score was calculated. As in the original Rudolph et al (2008) article, patients were stratified by the ARS score into groups of score zero, score one to two, and score three or more. Of the 1004 patients in the study, 455 individuals (45.3 %) were not using any anticholinergic medicines, and had an ARS score of zero. More than half of the patients (54.7 %) were using at least one anticholinergic medicine. Altogether 363 patients (36.2 %) had a mild anticholinergic load, i.e. an ARS score of one or two, and 186 patients (18.5 %) had a high load with an ARS score of three or higher. The distribution of the ARS scores in the study population is shown in Figure 7. The mean ARS score (± SD) was 1.2 ± 1.5, the median score was one and the mode score of the sample was zero. The range of the scores was 0-10.

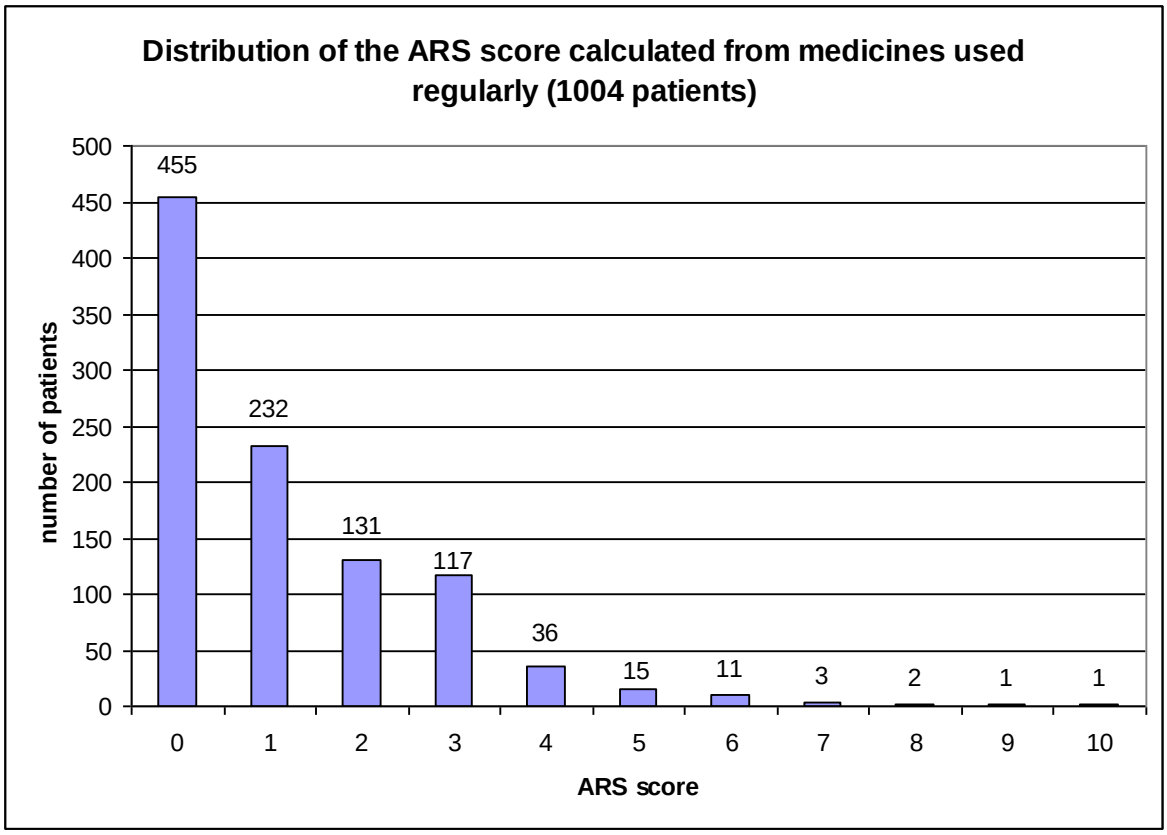

Figure 7. Anticholinergic risk scale (ARS) score distribution in the study population. More than half (54.7 %) of the patients were using at least one anticholinergic medicine.

Three anticholinergic lists (Tune et al 1992 combined with Lu & Tune 2003; Rudolph et al 2008; Uusvaara et al 2009) were used to classify the study patients into anticholinergic users or non-users based on having one or more of medicines in the list in their regular medicine regimen. Patient groups identified as users (having one or more anticholinergic medicine on a given list) or non-users (having no anticholinergic medicine listed) and overlapping of patient groups identified with different lists are shown in Figure 8.

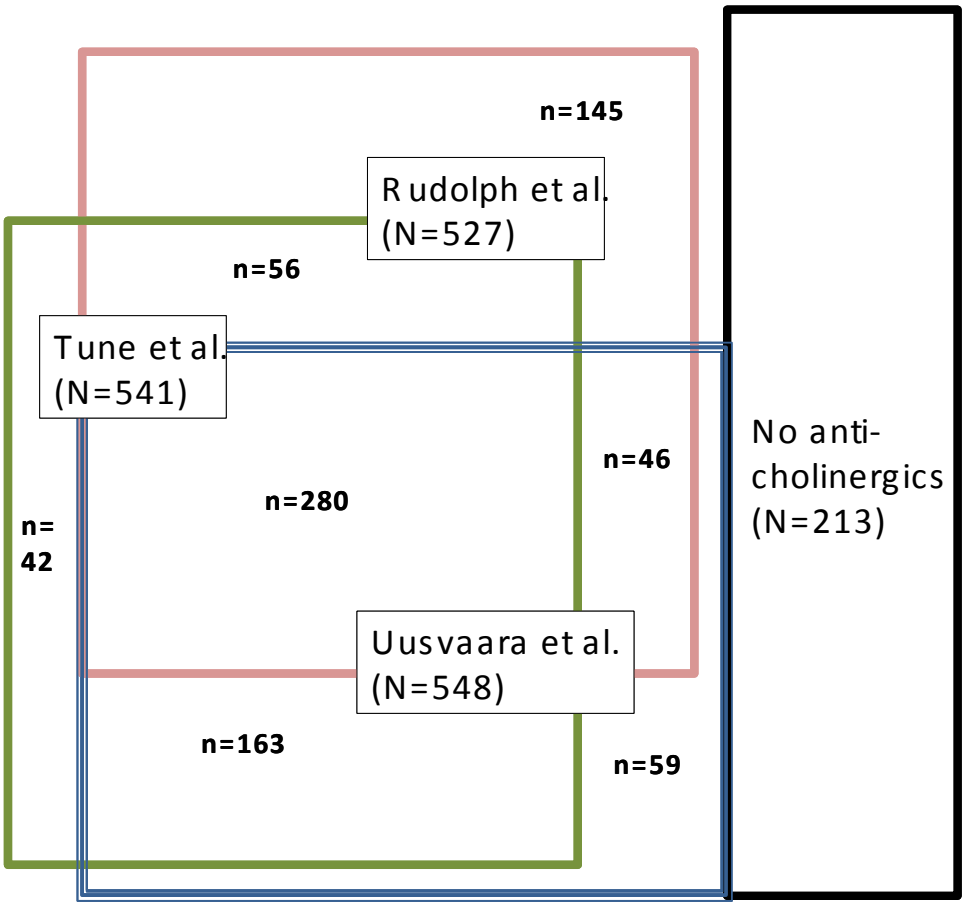

Figure 8. The patient population as divided into anticholinergic users and non-users according to three anticholinergic lists (Tune et al = Tune et al 1992 combined with Lu and Tune 2003; Rudolph et al 2008; Uusvaara et al 2009). Altogether 213 patients were not identified as users by any list. All three lists overlap and define 280 patients as anticholinergic users, and there is some overlap with any two lists together. However, there are 246 patients (145 + 42 + 59) who are only classified as users by one list, leading to different interpretations in any clinical studies that the lists might be used in. This figure highlights the problem of having no international consensus list of anticholinergics.

Altogether 213 patients were not identified as anticholinergic users by any of the three lists. There was overlapping of patient groups identified by different lists, and 280 patients were identified as anticholinergic users by all three lists. The Rudolph et al (2008) list identified 56 patients who were also identified by the Tune et al 1992 and Lu and Tune 2003 list. There was a 56 patient overlap between Rudolph et al (2008) and Uusvaara et al (2009), and 163 patient overlap between Uusvaara et al (2009) and the Tune et al 1992 and Lu and Tune 2003 lists. Altogether 246 patients (145 + 42 + 59) were identified as anticholinergic users by only one list.

6.4 Comparison of Anticholinergic Risk Scale score groups

For all subsequent analysis, patients were stratified into three groups according to their ARS score. Patients with a score of zero were considered to have no anticholinergic burden and formed the first group. Patients with an ARS score of one or two formed the "some anticholinergic burden" group. The "high anticholinergic burden" group was formed by patients with scores of three and higher.

6.4.1 Descriptive statistics

Patient descriptive characteristics are presented in Table 6. Not all information was available for all patients, and the numbers of patients in each analysis are mentioned in the table. There was a statistically significant difference in patient ages between the burden groups, and as can be seen from the age ranges, there were also some younger patients among the study population. Nevertheless, mean and median ages were high and very close to each other.

There were no differences between the anticholinergic burden groups in gender, being widowed, education, nutritional status as measured by MNA, and some diagnoses. There were differences in Charlson Comorbidity Index scores, the mean duration of

institutionalised care, and mobility. The Chi-square and Kruskal-Wallis tests do not tell, which of the groups differs or by how much, however, only that there is a difference between the three groups. Stroke, depression, other psychiatric illness, Parkinson's disease and hip fracture were diagnoses, for which there was a difference between patient groups.

When medicine use was investigated between anticholinergic burden groups, there was a difference in the total number of regularly taken medicines (Table 5). The patients in the studied population were using up to 20 medicines regularly. Polypharmacy, defined as using at least nine medicines at the same time (Hajjar et al 2005), was present in half of the patients with an ARS score of zero, 23 % of those with an ARS score of one or two, and 17 % of those with an ARS score of three or more. There was a difference between the ARS groups for the number of medicines in use, both with the mean number of regular medicines and when stratified by having zero, one to eight, or more than eight medicines in regular use.

Table 5. Medicine use of the study participants (n = 1004) stratified by anticholinergic burden based on their Anticholinergic Risk Scale (ARS) score.

	ARS score 0 No burden (n = 455, 45 %)	ARS score 1-2 Some burden (n = 363, 36 %)	ARS score ≥ 3 High burden (n = 186, 19 %)	p-value
Number of regular medicines				
Mean (± SD) (n = 1004)	5.8 (± 3.1)	7.8 (± 3.0)	8.8 (± 3.7)	**<0.01**
median	5	8	8	
range	0-16	2-16	1-20	
0 medicines in regular use	12 (3 %)	0	0	**<0.01**
1-8 medicines	220 (48 %)	278 (77 %)	155 (83 %)	
More than 8 medicines	223 (49 %)	85 (23 %)	31 (17 %)	

Table 6. Descriptive characteristics of the study participants (n = 1004) stratified by anticholinergic burden based on their Anticholinergic Risk Scale (ARS) score.

	ARS score 0 No burden (n = 455)	ARS score 1-2 Some burden (n = 363)	ARS score ≥ 3 High burden (n = 186)	p-value
Age (years) (n = 988)				
Mean (±SD)	83.0 (± 10.0) (n = 449)	80.5 (± 11.0) (n = 356)	78.7 (± 12.4) (n = 183)	**<0,01**
median	84	82	80	
range	49-104	23-99	36-99	
Gender (%): Female (n = 1002)	353 (78 %)	269 (74 %)	133 (72 %)	0.21
Marital Status (%)				
Widowed (n = 1004)	99 (22 %)	69 (19 %)	48 (26 %)	0.18
Education (%)				
Primary school or less (n = 1004)	224 (49 %)	164 (45 %)	92 (50 %)	0.45
Documented diagnosis (%)				
Diabetes (n = 828)	67 (18 %)	51 (17 %)	38 (25 %)	0.12
Coronary artery disease (n = 818)	118 (31 %)	74 (26 %)	40 (27 %)	0.32
Acute myocardial infarction (n = 777)	40 (11 %)	32 (12 %)	16 (11 %)	0.97
Stroke (n = 829)	180 (46 %)	119 (42 %)	86 (56 %)	**0.02**
Dementia (n = 978)	345 (78 %)	269 (75 %)	131 (73 %)	0.39
Depression (n = 794)	75 (21 %)	87 (31 %)	45 (32 %)	**<0.01**
Other psychiatric illness (n = 779)	29 (8 %)	62 (22 %)	33 (23 %)	**<0,01**
Parkinson's disease (n = 784)	10 (3 %)	38 (14 %)	13 (9 %)	**<0.01**
Other neurological disease (MS, ALS, etc.) (n = 785)	38 (10 %)	22 (8 %)	16 (11 %)	0.45
Rheumatic diseases (n = 788)	37 (10 %)	35 (13 %)	21 (14 %)	0.35
COPD (n = 796)	57 (15 %)	50 (18 %)	27 (19 %)	0.61
Stomach or duodenal ulcer (n = 768)	15 (4 %)	15 (6 %)	4 (3 %)	0.47
Hip fracture (n = 807)	103 (27 %)	87 (31 %)	25 (18 %)	**<0.02**
Cancer (n = 783)	36 (10 %)	29 (11 %)	20 (14 %)	0.44
Charlson Comorbidity Index score, mean (± SD) (n = 1002)	2.57 (± 1.51) (n = 454)	2.40 (± 1.64) (n = 362)	2.75 (± 1.64) (n = 186)	**<0.03**
median	2	2	3	
range	0-8	0-9	0-9	
Mean duration of institutional care (months) (± SD) (n = 786)	39.1 (± 34.1) (n = 357)	32.7 (± 32.0) (n = 280)	39.4 (± 34.5) (n = 149)	**<0.01**
median	30	24	31	
range	1-182	1-217	1-193	
Mobility - wheel chair/bed bound (%)	407 (89.5 %)	301 (83 %)	154 (83 %)	**<0.01**
MNA (% of those with same ARS)				
<17	4 (1 %)	12 (3 %)	6 (3 %)	
17-23.5	178 (39 %)	135 (37 %)	67 (36 %)	
<23.5	273 (60 %)	216 (60 %)	113 (61 %)	0.14

MS = multiple sclerosis, ALS = amyotrophic lateral sclerosis, COPD = chronic obstructive pulmonary disease, MNA= Mini Nutritional Assessment.

6.4.2 Investigating the effect of anticholinergic use on risk of death

The ARS score was included as an explanatory variable, a comorbidity in the Cox Proportional Hazard model (Table 7). Other coexisting variables or comorbidities included AMI, stroke, COPD, diabetes, age, sex, MNA, cancer and mobility. The model estimates the risk of death caused by a given comorbidity while controlling for the effects of the other comorbidities included in the analysis. The Charlson Comorbidity Index score could not be included in the model, as it also incorporates anticholinergic medicines and some comorbidities like AMI (Charlson et al 1987). Therefore the model would not be able to control for the contributions of other overlapping comorbidities to give estimates to only one comorbidity at a time. The logrank test showed no statistical significance for the model ($p = 0.3779$), and only age, gender, and nutritional status (MNA) were shown to be comorbidity variables that affected the five-year mortality that was tested. When a Kaplan-Meier curve of patient survival in days was plotted from the data, it showed no differences between the anticholinergic burden groups, as also shown by the Cox analysis (Figure 9). The percentages of patients still alive and those who were dead after a five-year period are presented in Table 8. There was no statistically significant difference between the ARS score groups. About 80 % percent of all the patients were dead after five years.

Table 7. Adjusted risk of mortality using the Cox Proportional Hazard Model

Independent variable	Hazard Ratio (95% CI)	p-value
Anticholinergic Risk Scale score	0.99 (0.89-1.10)	0.83
Acute myocardial infarction	1.02 (0.78-1.35)	0.87
Stroke	1.03 (0.87-1.22)	0.74
COPD	1.03 (1.02-1.04)	0.76
Diabetes mellitus	1.22 (0.97-1.53)	0.09
Age	1.04 (1.03-1.05)	< **0.01**
Gender	1.36 (1.11-1.67)	< **0.01**
MNA	1.50 (1.26-1.77)	< **0.01**
Cancer	1.20 (0.91-1.57)	0.20
Mobility (bed bound/wheelchair)	1.30 (0.996-1.71)	0.05

COPD= chronic obstructive pulmonary disease, MNA= Mini Nutritional Assessment

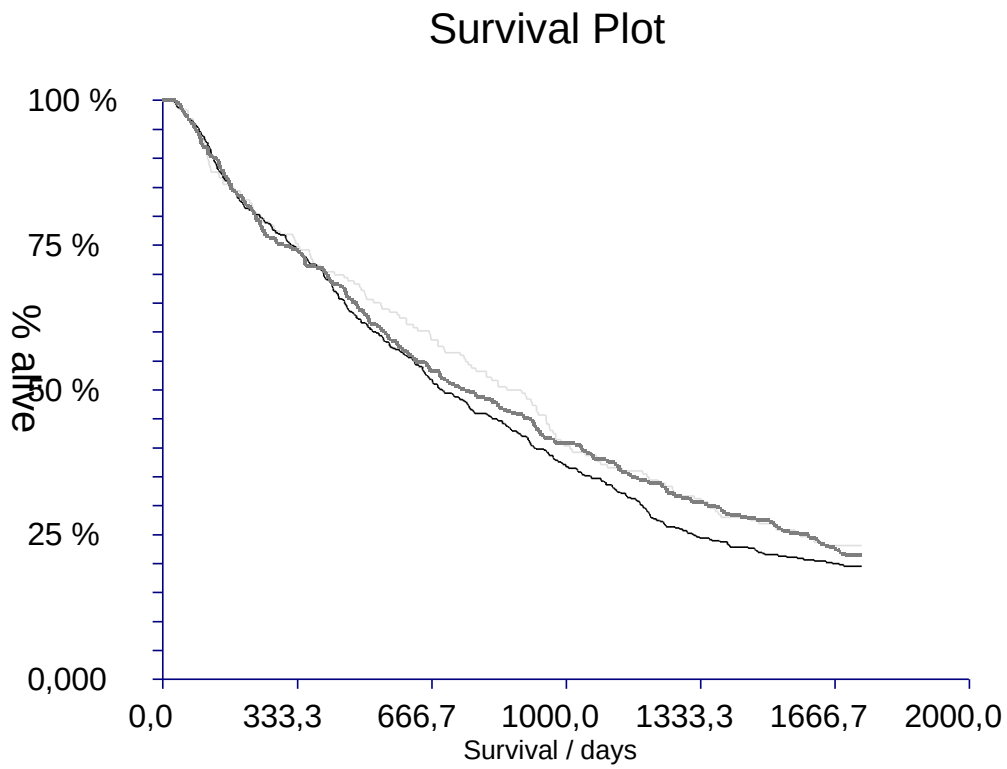

Figure 9. The Kaplan-Meier curve of the Cox mortality analysis, with a five-year observation period. The probability of still being alive after a certain time (given in days on the x-axis) is very similar in all anticholinergic burden groups (differently coloured grey lines).

Table 8. The percentage of study participants (n = 1004) dead and alive at five years. Patients have been stratified by their anticholinergic burden based on their Anticholinergic Risk Scale (ARS) score.

	ARS score 0 No burden (n = 455, 45 %)	ARS score 1-2 Some burden (n = 363, 36 %)	ARS score ≥ 3 High burden (n = 186, 19 %)	p-value
% of patients dead or alive (n = 1004)				
Alive at 5 years	20	22	23	**0.57**
Dead at 5 years	80	78	77	

7 DISCUSSION

The most important findings in both the literature review and the empirical research are discussed in these following chapters. Methodological and other limitations are discussed.

7.1 Estimating anticholinergic burden

Several methods for estimating anticholinergic burden were identified from peer-reviewed, published literature. The SAA radioreceptor assay developed by Tune and Coyle (1980) measures a total sum effect of anticholinergic agents present in the blood, giving a rough estimate of individual anticholinergic burden. This estimate can be used to investigate peripheral anticholinergic burden, but because it only measures blood content of these agents, conclusions about central nervous system burden can only be made with caution. Peripheral anticholinergic side effects can limit a patient's quality of life, but central effects have the potential to cause cognitive effects, possibly cognitive impairment (Ancelin et al 2006). The SAA is only a rough estimate of anticholinergic burden, as agonists can cause false positive results by reducing the binding of TQB (Carnahan et al 2002a). Any results obtained with the SAA assay must therefore be considered in the context of the patient's overall clinical status.

Of the anticholinergic scoring systems identified in the literature review, four levels of anticholinergic medicine potency (0, 1, 2, 3) were used in systems developed by Carnahan et al 2002b, Carnahan et al 2006, Ancelin et al 2006, Han et al 2008, and Rudolph et al 2008. These four categories of potency attempted to describe relative potencies in a user-friendly manner, as small scores are easy to add up e.g. during patient encounters. These categories do not describe relative anticholinergic potencies in detail, however, as even within category three anticholinergics in any given list, there are bound to be differences in potencies. A continuous potency scoring system might better describe the situation. The Minzenberg et al (2004) indexes have scores ranging from zero to over 1400, so its practical usefulness may be limited by comprehending huge differences in scores. But these

indexes attempt to better describe the actual differences in potencies of anticholinergic medicines, and this is a step in a possibly more clinically useful direction. The Hilmer et al (2007a) Total Drug Burden index takes also doses of the medicines into account, and additive effects of sedatives too. It calculates effects in relation to the dose used, so low doses contribute less to the burden, as seems likely to also happen in real life. Calculations such as these are complex, however, and are not suitable for quick, face-to-face encounters with patients. The Total Drug Burden index does seem promising despite that, as it could be automated in a computer program, making analysis quicker and easier for a clinician to perform.

All of these scoring systems assume a linear relationship in anticholinergic burden, assuming that anticholinergic medicine effects add up in a linear way. The possibly synergistic effect has not been taken into account in any system, as it is very difficult to predict. This would be an interesting topic for future research, as with better computers and a better understanding of body functions, mathematical models of individual medicine elimination could possibly be combined with an index like this, giving better estimates of how medicines behave in the body, and how likely they may be to cause adverse effects.

Many studies used the SAA assay as a comparison, and all its limitations were also then affecting interpretations in those studies. The MMSE tool was commonly used to measure cognitive abilities. It does describe the overall cognitive status of an individual, but it is only a rather crude measure of memory functions (Thomas et al (2008). This limits interpretations made from changes in MMSE scores.

Combining the 17 anticholinergic lists identified in the literature review showed that there is very little agreement globally, which medicines are to be considered anticholinergic. This highlights the need for an international consensus definition of an anticholinergic medicine or an official, validated reference method of measuring anticholinergic potency. Differences in medicines available in countries around the world make it more difficult to develop a global list, as if a medicine is not available in a given country, clinicians in that

country may not be familiar with its use and e.g. frequency of anticholinergic effect complaints. Some medicines are generally agreed on to be anticholinergic, as shown by the 21 medicines identified that are listed on at least eight of the 17 anticholinergic lists. Some medicines that appeared only on one list were very old medicines that may not be used widely anymore, e.g. some older antihistamines. Anticholinergic lists should therefore be updated to better mirror developing formularies in future projects.

As a conclusion from all the literature studied, there is no perfect method available at present to estimate anticholinergic burden. Clinical judgment needs to be executed, and all these methods should be used with caution. This study offers a glance on currently available methods for estimating anticholinergic burden, and highlights some of their properties.

7.2 Patients in the empirical study

Our study investigated the medicine use and mortality of patients staying in the Helsinki area public hospitals in long-term care wards in September 2003. Generalisations to any other patient groups in any other setting must therefore be done with caution. The patient sample represented 70 % of all patients in these wards at that time point, which is a good percentage. Because some of those patients who were not included in the study declined to participate at all (n = 357, 25 %), their data was not available to investigate any differences between those that declined and those that agreed to participate. Missing data was the reason for exclusion of 83 patients (5 %), so they could not be investigated for differences either. Nevertheless, 70 % of the total gives a reasonably good estimate of the whole potential population of 1444 patients. Generalising this data to other patient populations with matching characteristics may be considered, as the number of patients investigated was fairly large, 1004. Other long-term care facilities in different parts of Finland or abroad may have different care practices though, so caution must be maintained when drawing conclusions.

7.3 Medicine use in the patient sample

The observed rates of using six or more (65.0 %) or nine or more (31.5 %) medicines either regularly or when required are similar to the rates found by Fialova et al (2005) in Finland, as they found that 73.3 % of their sample were using at least six medicines either regularly or when required, and 41.2 % were using at least nine. Their study was done on home-dwelling patients when ours was a study on institutionalised patients, but still the results are in the same range.

Because this study was cross-sectional, we have no way of knowing whether the patients were still using these prescription medicines the next day, or for how long they had been using them before data collection. Interpretations of effects with long time frames like 2-year mortality must be done with caution because of this. Also, no data was available on any OTC medicines or herbal remedies that the patients may have been using on their own. However, since the patients were institutionalised, their medicine use is likely to have been known by their nurses who filled out the data collection questionnaires. Medicines that were recorded as being taken only when required were excluded from the study. This was done because there was no information available for how long and how often the patients might then have been using them. These exclusions may limit reliability, as the frequency of their use was not known, and it could have been very often. Also, excluding topical, ophthalmological and otological preparations may have limited the reliability of the study in the case of e.g. potentially anticholinergic eye drops. It is difficult to estimate, to what extent they will have systemic effects, and therefore they were categorically excluded. All in all this study shows how common it is that institutionalised patients are using several medicines at the same time. These long medicine lists reflect the high total disease burden that these frail, older patients have. This finding of commonly using many medicines may warrant more research into the rationality of such medicine use.

7.4 Anticholinergic medicine use in the patient sample

We used the Rudolph et al (2008) list to identify anticholinergic medicines. The most frequently used anticholinergic medicine was risperidone, which was used almost always regularly. A total of 19 % (n = 190) of the patients were using it, which is higher than the 10 % that was reported by Raivio et al (2007) in their study of older institutionalised patients. The laxative loperamide was used only when required in this patient sample, and haloperidol and metoclopramide were used mainly when required. Hydroxyzine was used quite commonly (7 % of the patients) as a regular medicine rather than only when required. This is twice as much as observed by Raivio et al in 2006 (3.5 %) in their study of institutionalised older patients. Hydroxyzine has quite strong anticholinergic and sedative properties, and should be used with caution especially in older people (Beers et al 1991; Beers 1999; Fick et al 2003; Fialova et al 2005). Hydroxyzine is officially indicated in Finland for treatment of anxiety in adults, as well as urticaria and itching. It is also indicated for sleeplessness if there are also allergic symptoms. Our data does not include actual individual indications for any medicines in the study population, making it difficult to draw conclusions on reasons for using any given medicine. Stroke, depression, other psychiatric illness, Parkinson's disease and hip fracture were diagnoses, for which there was a difference between patient groups stratified by their ARS score. Anticholinergic medicines are used in the treatment of Parkinson's disease and some psychiatric medicines have anticholinergic side effects, so the number of anticholinergic medicines may be affected by having those diagnoses.

An overall anticholinergic medicine usage rate of 54.7 % was found in the patient population. This is in the same range as rates of 15 % (Lechevallier-Michel et al 2004), 40 % (Landi et al 2007), or 63 % (Han et al 2008) observed in previous studies. The patients were stratified according to their ARS score, with score zero forming the "no burden" group, scores one and two forming the "some burden" group, and scores of at least three forming the "high burden" group. This was the same stratification as Rudolph et al (2008) had used, so it was chosen in this study as well for ease of comparison. They

showed in their analysis how there was a statistically significant difference in the occurrence of anticholinergic side effects when patients were grouped according to the stratification described above. It is unclear, however, whether these stratifications are clinically sensible apart from having people with no listed anticholinergics form a group.

The ARS list is limited by several factors. It does not take dose into account, and the four categories of potencies do not describe relative potencies, as described in a previous chapter. Taking dose into account did not seem to matter when comparing an anticholinergic scoring system to SAA levels (Carnahan et al 2006), but the SAA has limitations here also, as it does not seem to be dose-dependent, as increased doses do not always increase measured SAA values. It seems likely that having a higher dose would worsen any adverse effects. The ARS list was constructed from 500 most prescribed medicines in a health care provider system in Boston, so it does not necessarily describe medicines used in any other setting. E.g. biperiden, an anticholinergic agent, is missing from the list. It was only used by one of our 1004 patients, so effects of it missing in this analysis may not have been dramatic, but still it highlights the problem of different formularies in different countries and constructing anticholinergic lists based on only those medicines that were used by a given patient population. Adjustments need to be made when using tools developed in other countries (Gallagher et al 2007).

Grading of the ARS list was done based on affinity data of the medicines for muscarinic receptors, FDA-published rates of their anticholinergic side effects, and literature regarding the adverse effects. But as Kwatra (2008) commented on the article, affinity results are usually only given for the M_1 receptor, limiting reliability. Also the ARS list's predictive value has not been established, as it was only recently published. It has not been used in any published studies yet since being introduced to the scientific community.

When the three anticholinergic lists (Tune et al 1992 combined with Lu & Tune 2003; Rudolph et al 2008; Uusvaara et al 2009) were used to identify anticholinergic users, the problem of having no international consensus was again highlighted. Only 280 patients

(28 % of all patients) were identified by all three lists as users, and 213 patients (21 % of all patients) were identified as non-users. The other patients were identified as users by only two or one list, so of those identified as users, only 35 % were identified by all three lists. The lists that were used were chosen based on their different source material, either SAA (Tune et al 1992 combined with Lu & Tune 2003), or literature and an American (Rudolph et al 2008) or Finnish (Uusvaara et al 2009) formulary. This was done to highlight the differences in anticholinergic lists, so this comparison may reflect a worst case scenario. Nevertheless, international co-operation is needed to build a consensus anticholinergic list and/or scoring system to avoid the problems highlighted by this comparison.

7.5 Statistical analysis of different patient characteristics

Patients were stratified according to their ARS score into three groups: ARS score zero, ARS score one to two and ARS score three or more. This stratification was done for ease of comparison with the original Rudolph et al (2008) paper, but whether the jump from score two to score three is a clinically relevant threshold is unknown at this point. There was a difference in the mean number of medicines used by the three groups. People with a higher score seemed to also be using more medicines, although definite conclusions cannot be drawn from a Kruskal-Wallis analysis, only that there is a statistically significant difference between the groups investigated.

All patients staying in the wards in the study were included in the sampling, and patients were not excluded because of their age or having dementia, as done in the study by Low et al (2008). They excluded patients who had dementia, as they may be especially vulnerable to adverse effects of anticholinergic medicines. A large proportion, 76 % of our institutionalised patient sample had diagnosed dementia. The mean (± SD) age of our patient sample was 83.35 (± 9.99) years for women and 75.11 (± 11.48) for men, and the ages ranged from 23 to 104. In general, people in the age group of 65 to 74 have a prevalence of 4.2 % and people between ages 75 and 84 have a prevalence of 10.4 % for dementia, with over 84-year-olds having a prevalence of 35.0 % (Koskinen et al 2006). The

high prevalence of dementia in our sample can be explained by the patients being institutionalised, as those with advanced stages of dementia need constant care.

The observed difference in hip fractures between groups, which seems to suggest that patients with a zero ARS score had more hip fractures. There was a difference in being bed bound, and those with ARS score zero seemed to be more mobility-challenged. Both of these effects may be because these zero ARS score patients' medicine load had been lightened when their disabilities developed.

These observed differences in patient characteristics offer comparison points for future studies. Also, from these comparisons, explanatory factors were chosen for the mortality analysis.

7.6 Mortality analysis

Since we had exact dates of death for all participants included in the analysis, those who were still alive at the two-year mortality cut-off time were not censored by just knowing that they survived beyond the study time frame, a phenomenon called end-of-study censoring (Altman and Bland 1998; Leung et al 1997). The Kaplan-Meier estimator describes survival when there is one sample of people, and the analysis is adjusted for whether or not an observation in the study is censored. Kaplan-Meier may either overestimate or underestimate survival, depending on whether the survival time and the censoring time (i.e. end of study) are positively or negatively correlated, respectively. Because only times of death were obtained for the patients, they may also have had a competing mortality effect, i.e. they died from other reasons than because of the investigated cause (Altman and Bland 1998), the use of anticholinergics. In our study, most patients were very old, as shown by the medians of ages also being high, not just the means as the ranges showed also some very young individuals. Mortality in this old age group is quite high, approximately 43 to 46 % 2-year mortality (Raivio et al 2006; Raivio et al 2007), so most of these old patients would have died by the five-year time point. The cross-

sectional structure of our study is a limitation to researching mortality effects, as detecting and showing an addition to “normal” mortality caused by anticholinergics is very difficult. Therefore the results must be interpreted with caution as direct causality cannot be shown, only if there are differences in the mortality rates of ARS score groups.

The logrank test that was used in our analysis compares survival functions of samples of people. It was used to test whether there were differences in the rate of an event occurring, in this case death (Bland and Altman 2004). The logrank test is most likely to detect a difference between groups when the risk of an event is consistently greater for one group than another. It is unlikely to detect a difference when survival curves cross. When analysing survival data, the survival curves should always be plotted. As it could be seen from our data, the curves did in fact cross several times, as there were no clear differences between curves of different groups. The logrank test showed no statistically significant difference.

When covariates were taken into account, Cox proportional hazard model was used to see how different factors might affect the risk of death. Age, gender, and nutritional status were significant contributors to the risk of death in our Cox model. Being older, male and undernourished increased the risk of death, as seems logical, so the model did work. The ARS score failed to affect mortality in our analysis. This could be because using anticholinergics is so intertwined with some comorbidities because they are used to treat those conditions, and this would limit the power of the prediction tool. This lack of effect was also shown in the Kaplan-Meier survival plot, where patient groups with differing anticholinergic burden did not differ from each other in survival probability.

Our data included 70 % of the eligible residents in Helsinki nursing homes in September 2003. The 30 % censored were not included in the analysis. The available data may or may not describe them, and any loss of participants means some degree of loss of reliability and validity for the study (Altman and Bland 2007). In general, a 70 % response rate is considered rather good, but still there is the possibility of bias, rising from the possibility

that certain type of people may have been more likely to be excluded from the analysis. This would happen if exclusion from the analysis was not random but rather caused by e.g. one ward having all their data missing and therefore being totally excluded. This seemed to be the case in this study, as when patient identifiers of those excluded were investigated, 26 patients with consecutive identifiers were found. This may or may not mean, that a defined group was excluded. Also, since the patient data were obtained from previous nutritional status studies and not from a study design specifically made for mortality analysis, it should be considered a convenience sample.

Our cross-sectional study found no association between the use of anticholinergics and mortality in our sample of older institutionalised people from the Helsinki area. This may mean that there is no effect, or that the possible effect was not shown by our study design (Altman and Bland 1995). Because of the limited information available on the duration of medicine use offered by our cross-sectional data, it may be that our analysis did not have enough power to show a possible effect. Raivio et al (2007) found no association with mortality for atypical or conventional antipsychotics in their study, and even when investigating the effects of potentially inappropriate medicines as defined by the Beers criteria (Beers 1997) for older patients, no association was found (Raivio et al 2006). To our knowledge, this is the first study investigating association of anticholinergic medicine use with mortality, so it can be seen as a study showing a need for more research into the area. Future research should focus on establishing international guidelines or recommendations for listing which medicines are anticholinergic, and with those guidelines a method for summing up the anticholinergic effects of a patient's anticholinergic medicines could be either devised or updated and developed from the previously published methods. With an improved anticholinergic burden tool possible morbidity and mortality effects should be studied in a randomised, controlled prospective clinical study. Anticholinergics do have adverse effects, but it may be that their effects are not easily separated from other factors to estimate any direct effects on mortality that they may have.

8 CONCLUSIONS

The literature review showed that there are many methods for estimating anticholinergic burden. Anticholinergics are widely used for common ailments, but they may cause potentially harmful side effects. Therefore it is important that their use is monitored. A simple method for estimating a person's total anticholinergic burden would be a useful tool in clinical practice. One of the most used methods for research purposes is the Serum Anticholinergic Activity assay (Tune and Coyle 1980), which measures the total anticholinergic burden in blood samples. Correlation between peripheral SAA measurements and anticholinergic burden in the CNS has not been proven in large clinical trials yet, despite the assay having been available for research for decades. Many studies use the SAA as a reference method despite its limitations, as there is no reference method for measuring anticholinergicity at present time.

Several anticholinergic scoring systems have been developed in recent years, but none of them have become accepted widely. Only some medicines are generally agreed on to be anticholinergic, while for some there is conflicting evidence, which makes interpretations more difficult. Simply listing medicines as anticholinergic or not is usually not sufficient for clinical purposes, as not all medicines are as potent anticholinergics as others. Therefore many lists or scores have adopted an approach where at least some form of grading is given to medicines to mimic real life differences in potencies. Taking dose into account matters perhaps most for modestly anticholinergic medicines, where a high dose may make otherwise negligible effects clinically relevant. Factoring dose into a scoring system is difficult, however, as the need for calculations and background information increases. No list or scoring system so far has become universally accepted, and there are only small studies on their use. There is a lot of interest in anticholinergics currently, and scoring systems are being developed. More research is needed to establish truly useful tools for clinicians for everyday practice. But no matter how good a tool is, sound clinical judgment cannot be replaced, as all patients are individuals and their special circumstances need to be considered.

No association was found between the use of anticholinergics and the risk of death in the cross-sectional sample in the empirical research. Anticholinergics may contribute to accidents and falls, but it is unclear whether they affect mortality directly. Our study population of frail, older institutionalised patients was using a number of anticholinergic medicines, and their mean age was high. Because older people may have reductions in cognitive and bodily functions as a natural effect of aging, any anticholinergic medicines enhancing these reductions may be harmful. The high medicine burden and also the high anticholinergic burden in institutionalised older patients found in this study as in many others is a potentially alarming trend. More research is needed to investigate the effect of this burden, and prescribing practices need to be updated to reduce the unnecessary use of medicines.

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APPENDIX 1. The original questionnaire (in Finnish) developed by Soini et al (2004) and used in the study where the data used in the empirical part of this thesis were collected.

Liite 1 POTILAAN RAVITSEMUSTILAN ARVIOINTI (MNA) 28.5.2003

Potilaan sukunimi, etunimi_____ sotu_____
Tk-sairaala: _____Osasto: _____
Päivämäärä: _____
Pituus _____ cm
Paino nyt _____ kg, paino keväällä 2003 _____ kg
Kantapää-polvi _____ cm
Milloin potilaan hoitojakso on alkanut? PVM_____ Kesto: vuotta ____ kuukautta____päivää____

Seuraavissa kysymyksissä ympyröi yksi vastausvaihtoehdoista ja kirjaa ympyröimäsi numero kysymyksen oikealla puolella olevaan ruutuun.

SEULONTA

1. Onko ravinnonsaanti vähentynyt viimeisen kolmen kuukauden aikana ruokahaluttomuuden, ruoansulatusongelmien, puremis- tai nielemisvaikeuksien takia?
   0 = Kyllä, ravinnonsaanti on vähentynyt huomattavasti
   1 = Kyllä, ravinnonsaanti on vähentynyt hieman
   2 = Ei muutoksia ☐

2. Painonpudotus kolmen viime kuukauden aikana?
   0 = Painonpudotus yli 3 kg
   1 = Ei tiedä
   2 = Painonpudotus 1-3 kg
   3 = Ei painonpudotusta ☐

3. Liikkuminen?
   0 = Vuode- tai pyörätuolipotilas
   1 = Pääsee ylös sängystä, mutta ei käy ulkona
   2 = Liikkuu ulkona ☐

4. Onko viimeisen kolmen kuukauden aikana ollut psyykkistä stressiä tai akuutti sairaus?
   0 = Kyllä
   2= Ei ☐

5. Neuropsykologiset ongelmat?
   0 = Dementia, depressio tai neuropsykologinen ongelma
   1 = Lievä dementia, depressio tai neuropsykologinen ongelma
   2 = Ei ongelmia ☐

6. Painoindeksi eli BMI (=paino / (pituus)^2 kg/m^2)
   0 = BMI on alle 19
   1 = BMI on 19 tai yli, mutta alle 21
   2 = BMI on 21 tai yli, mutta alle 23
   3 = BMI on 23 tai enemmän ☐

Pisteet yhteensä (1. sivu) ☐☐

APPENDIX 1. The original questionnaire (in Finnish) developed by Soini et al (2004) and used in the study where the data used in the empirical part of this thesis were collected.

ARVIOINTI

7. Asuuko haastateltava kotona?
   0 = Ei
   1 = Kyllä ☐

8. Onko päivittäisessä käytössä enemmän kuin 3 reseptilääkettä?
   0 = Kyllä
   1 = Ei ☐

9. Painehaavaumia tai muita haavoja iholla?
   0 = Kyllä
   1 = Ei ☐

10. Päivittäiset lämpimät ateriat (sisältää puurot ja vellit)?
    0 = 1 ateria
    1 = 2 ateriaa
    2 = 3 ateriaa ☐

11. Sisältääkö ruokavalio vähintään

	Ei	Kyllä
• Yhden annoksen maitovalmisteita (maito, juusto, piimä, viili)	__	__
• Kaksi annosta tai enemmän kananmunia viikossa (myös ruuissa, esim. laatikot)	__	__
• Lihaa, kalaa tai linnun lihaa joka päivä	__	__

    0 = Jos 0 tai 1 kyllä –vastausta
    0.5= Jos 2 kyllä -vastausta
    1 = Jos 3 kyllä –vastausta ☐

12. Kuuluuko päivittäiseen ruokavalioon kaksi tai useampia annoksia hedelmiä tai kasviksia?
    0 = Ei
    1 = Kyllä ☐

13. Päivittäinen nesteen juonti?
    0 = Alle 3 lasillista
    0.5 = 3-5 lasillista
    1 = Enemmän kuin 5 lasillista ☐

14. Ruokailu
    0 = Tarvitsee paljon apua tai on syötettävä
    1 = Syö itse, mutta tarvitsee hieman apua
    2 = Syö itse ongelmitta ☐

15. Oma näkemys ravitsemustilasta
    0 = Vaikea virhe- tai aliravitsemus
    1 = Ei tiedä tai lievä virhe- tai aliravitsemus
    2 = Ei ravitsemuksellisia ongelmia ☐

16. Oma näkemys terveydentilasta verrattuna muihin samanikäisiin
    0 = Ei yhtä hyvä
    0.5 = Ei tiedä
    1 = Yhtä hyvä
    2 = Parempi ☐

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17. Olkavarren keskikohdan ympärysmitta (OVY cm)
    0 = OVY on alle 21 cm
    0.5 = OVY on 21-22 cm
    1.0 = OVY on yli 22 cm ☐

18. Pohkeen ympärysmitta (PYM cm)
    0 = PYM on alle 31 cm
    1 = PYM on 31 cm tai enemmän ☐

Pisteet yhteensä (2+3. sivu) ☐☐
Pisteet yhteensä 1. sivulla

Kokonaispistemäärä ☐☐

APPENDIX 1. The original questionnaire (in Finnish) developed by Soini et al (2004) and used in the study where the data used in the empirical part of this thesis were collected.

POTILAAN TAUSTATIEDOT

Kysymyksien vastausvaihtoehdoista ympyröidään sopivin numero (vain yksi).

19. Ikä: _____ vuotta

20. Sukupuoli?
    1 = Nainen
    2 = Mies

21. Siviilisääty?
    1 = Naimaton
    2 = Leski
    3 = Eronnut
    4 = Avio- tai avoliitossa

22. Koulutus?
    1 = Kansakoulu tai vähemmän
    2 = Ammattikoulu
    3 = Keskikoulu
    4 = Lukio
    5 = Opistoasteen ammattikoulutus
    6 = Korkeakoulu

23. Minkälaisessa työssä potilas on toiminut pääsääntöisesti elämänsä aikana?
    1 = Maanviljelys, karjanhoito, metsätyö, emännän työt
    2 = Tehdas-, kaivos-, rakennus-, tai muu vastaava työ
    3 = Toimistotyö, henkinen työ, palvelutyö
    4 = Muu, mikä? _____

24. Mikäli yksikössä on käytössä RAI, mitkä ovat potilaan viimeisimmän RAI – mittauksen tulokset?
    1 = CPS _____
    2 = BMI _____
    3 = ADL _____
    4 = Kipuskaala _____
    5 = Masennusskaala _____

25. Onko potilaalla joku erityisruokavalio? (voit valita useita vaihtoehtoja)

	Ei	Kyllä
1 = Laktoositon	1	2
2 = Keliakia	1	2
3 = Diabetes (insuliini)	1	2
4 = Diabetes (ei insuliini)	1	2
5 = Sappi	1	2
6 = Kihti	1	2
7 = Kasvis	1	2
8 = Muu, mikä _____	1	2

27. Millainen on potilaan ruoan rakenne?
    1 = Nestemäinen
    2 = Sosemainen
    3 = Pehmeä
    4 = Kiinteä

APPENDIX 1. The original questionnaire (in Finnish) developed by Soini et al (2004) and used in the study where the data used in the empirical part of this thesis were collected.

26. Minkä verran potilas syö pääaterioiden suositellusta annoskoosta keskimäärin?
    1 = Vähemmän kuin puolet
    2 = Puolet
    3 = Lähes kaiken
    4 = Kaiken

28. Syökö potilas välipaloja?
    1 = Ei
    2 = Kyllä

29. Käytetäänkö potilaalla täydennysravintovalmisteita (esim. Nutrison, Semper, Fortimel, Ensini, Additene jne.)?
    1 = Ei
    2 = Kyllä

30. Saako potilas kalkkivalmistetta
    1 = Ei
    2 = Kyllä

31. Saako potilas D-vitamiinivalmistetta
    1 = Ei
    2 = Kyllä

32. Kuinka usein potilaan paino mitataan keskimäärin?
    1 = Ei koskaan
    2 = Kerran vuodessa tai harvemmin
    3 = Kahdesti - kuudesti vuodessa
    4 = Yli kuusi kertaa vuodessa

33. Kirjataanko potilaan vatsantoiminta?
    1 = Ei
    2 = Kyllä

34. Onko potilaalla seuraavia ruokailuun ja suuhun sekä ruoansulatuselimistöön liittyviä ongelmia? (voit valita useita vaihtoehtoja)

	Ei	Kyllä
1 = Puremisongelmia	1	2
2 = Kuiva suu	1	2
3 = Kipua suussa	1	2
4 = Nielemisongelmia	1	2
5 = Ummetusta	1	2
6 = Ripulia	1	2
7 = Oksentelua	1	2
8 = Ruoalla sotkemista/ruoan pois työntämistä tai sylkemistä/malttamattomuutta syödessä	1	2
10= Muita ongelmia, mitä _____	1	2

35. Mikä on potilaan hampaiston tila syödessä?
    1 = Hampaaton, ei proteesia
    2 = Kokoproteesi sekä ylä- että alaleuassa
    3 = Hampaaton, mutta joko ylä- tai alaleuan kokoproteesi ja/tai muita osaproteeseja
    4 = Omia hampaita ja yksi tai useampia proteeseja
    5 = Vain omia hampaita

APPENDIX 1. The original questionnaire (in Finnish) developed by Soini et al (2004) and used in the study where the data used in the empirical part of this thesis were collected.

36. Onko potilaalla seuraavia sairauksia tai onko potilas sairastanut aikaisemmin?

	Ei	Kyllä
1 = Sokeritauti	1	2
2 = Sepelvaltimotauti	1	2
3 = Sydänveritulppa eli sydäninfarkti	1	2
4 = Aivohalvaus tai aivoverenkiertohäiriöitä	1	2
5 = Dementia	1	2
6 = Depressio	1	2
7 = Muu psykiatrinen sairaus	1	2
8 = Parkinsonin tauti	1	2
9 = MS, ALS, muu neurologinen sairaus,	1	2
10 = Reuma tai muu nivelsairaus	1	2
11 = COPD, astma tai muu keuhkosairaus	1	2
12 = Maha- tai pohjukaissuolen haavauma	1	2
13 = Muu krooninen suolistosairaus	1	2
• Jos on, mikä _____		
14 = Lonkkamurtuma	1	2
15 = Syöpä	1	2
• Jos on, mikä _____		
• Jos on, milloin todettu _____		
16 = Krooninen infektio	1	2
• Jos on, mikä _____		
17 = Jokin muu pitkäaikainen sairaus	1	2
• Jos on, mikä _____		

37. Potilaan säännöllisesti käyttämät, lääkärin määräämät lääkkeet ja vitamiinit. Tulosta lääkelista Pegasoksesta ja niittaa se tämän lomakkeen perään.

38. Onko potilas mielestäsi ylipainoinen?
1 = Ei
2 = Kyllä

39. Onko potilas mielestäsi aliravittu?
1 = Ei
2 = Kyllä

Lomakkeet palautetaan yhdessä osastonhoitajan täyttämän lomakkeen kanssa ____/____2003 mennessä yh Sirkka Virtaniemi, Herttoniemen sairaala, PL 6300.

APPENDIX 2. Anticholinergic medicine lists combined.

a) Based on a literature review / national reference books. b) Based on in vitro measurements of SAA. c) Only medicines used by study participants included. / List not complete. d) Based on Tune et al 1992. e) Based on expert opinion. f) Based on Han et al 2001. z = definite central anticholinergic effect, y = possible central anticholinergic effect. Relative potencies as defined by authors are given in numbers or descriptions, and the maximum score for each scoring list was 3.

Authors:	Peters 1989[a) c)]	Tune et al 1992[b) c)]	Flacker et al 1998[a) c)]	Mintzer & Burns 2000[a) c)]	Han et al 2001[a) e)]	Roe et al 2002[a) c)]	Mulsant et al 2003[b) c)]	Lu and Tune 2003[c) d) e)]	Mintzen-berg et al 2004[b) e)]	Caeiro et al 2004[a)]	Ancelin et al 2006[b) c) e)]	Carnahan et al 2006[e) f)]	Laroche et al 2007[e)]	Han et al 2008[c) e) f)]	Chew et al 2008[b)]	Rudolph et al 2008[a) c) e)]	Uusvaara et al 2009[a) c)]	**appears on how many lists?**
acamprosate calcium										x								**1**
acepromazine = acetylpromazine											3							**1**
acepromazine											3		x					**2**
acetazolamide										x								**1**
alimemazine = trimeprazine											2		x					**2**
alizapride										x			x					**2**
alprazolam		x					y	x			3	1		1			detectable	**7**
alverine											2							**1**
amantadine		x						x		x		1				2		**4**
ambutropium + oxazepam										x								**1**
amilsulpride = sultopride										x								**1**
amineptine = maneon										x								**1**
amitriptyline	x	x	x	x		x	z	x	x	x	3	3	x	3	3	3	high	**16**
amitriptyline + perphenazine										x								**1**
amoxapine	x			x		x			x		3		x					**6**
amoxicillin															0,5			**1**
ampicillin		x						x				1						**3**
atenolol					1									1				**2**
atropine = L/D-hyoscyamine	x	x		x		x		x		x		3		3	3	3		**10**
azatadine						x												**1**
azathioprine		x						x				1						**3**
baclofen										x				2		2		**3**
belladonna alkaloids	x			x		x				x	3		x	3				**7**
benazepril														1				**1**
benzoctamine										x								**1**
benztropine	x		x	x		x			x	x		3				3		**8**
betaxolol														1				**1**
biperiden				x		x			x	x				1				**5**
bromocriptine												1						**1**
brompheniramine						x	y					3	x					**4**
buclizine													x					**1**
bupropion = amfebutamone							y			x				1				**3**
butaverine										x								**1**
butylscopolamine = butilescopolamine										x								**1**
cabergoline										x								**1**
captopril		x					y	x				1					detectable	**5**
carbamazepine												2		1				**2**
carbidopa														1				**1**
carbinoxamine						x						3	x					**3**
carisoprodol																3		**1**
cefamandole		x						x				1						**3**
cefoxitin = mefoxin		x						x				1						**3**
celecoxib															0,5			**1**

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cephalexin															0,5			**1**
cephalothin		x						x				1						**3**
cetirizine														2		2		**2**
chlordiazepoxide		x						x		x		1		1				**5**
chlorpheniramine				x		x	z				3	3	x	3		3		**8**
chlorpromazine	x			x		x			x	x		3	x	3	2	3		**10**
chlorthalidone		x					y	x				1						**4**
cimetidine		x	x				y	x				2				2		**6**
cinnarizine										x								**1**
cisapride										x								**1**
citalopram										x					1			**2**
clebopride										x								**1**
clemastine = meclastin				x		x						3						**3**
clidinium	x			x						x							high	**4**
clidinium-chlordiazepoxide													x					**1**
clindamycin		x						x				1						**3**
clomipramine				x		x				x	3	3	x					**6**
clonazepam												1						**1**
clorazepate = chlorazepate		x					y	x			3	1						**5**
clozapine				x		x			x	x		3			3	2		**7**
codeine		x	x		1			x			2	1		1			detectable	**8**
colchicine			x				y				3							**3**
corticosterone		x						x										**2**
cortisone												1						**1**
cyamemazine										x			x					**2**
cyclizine				x		x												**2**
cyclobenzaprine	x			x		x						2		1		2		**6**
cyclopentolate	x			x														**2**
cycloserine		x						x				1						**3**
cyclosporine		x						x				1						**3**
cyproheptadine	x					x						2	x			3		**5**
dantrolene										x								**1**
darifenacin												3						**1**
Deadly Nightshade (myrkkykoiso)																		**1**
desipramine = desmethylimipramine	x	x						x	x			3		2		2		**7**
dexamethasone		x						x				1						**3**
dextromethorphan														1				**1**
diazepam		x			1		y	x				1		1	0,5		detectable	**8**
dicyclomine = dicycloverine				x		x				x		3			3	3		**6**
digitoxin												1						**1**
digoxin		x	x				y	x			3	1			0,5		detectable	**8**
dihexyverine													x					**1**
diltiazem		x						x				1						**3**
dimenhydrinate				x	3	x						3	x					**5**
diphenhydramine		x	x	x		x	z	x	x			3	x	3	2	3		**12**
diphenoxylate				x											0,5			**2**
diphenoxylate-atropin													x					**1**
dipyridamole		x					y	x				1					detectable	**5**
disopyramide	x			x		x	y					2	x				detectable	**7**
distigmine										x								**1**
domperidone										x								**1**
donepezil															0,5			**1**
dosulepin = dothiepin										x			x					**2**
doxepin	x			x		x			x	x		3	x	3	3		detectable	**10**

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doxylamine						x							x					**2**
duloxetine															0,5			**1**
Echinacea angustifolia										x								**1**
emepronium										x							high	**2**
empracet® = paracetamol-codeine					2													**1**
entacapone																1		**1**
escitalopram															1			**1**
estazolam												1						**1**
ethopropazine = profenamine				x														**1**
ethylbromide = bromoethane										x								**1**
etoperidone										x								**1**
famotidine			x									1						**2**
felbamate										x								**1**
fentanyl					1							1			0,5			**3**
fexofenadine														2				**1**
flavoxate	x			x		x				x		3						**5**
flunitrazepam		x						x										**2**
fluoxetine										x		1		1	1			**4**
flupentixol										x								**1**
fluphenazine	x			x					x	x		1	x			3		**7**
flurazepam		x						x				1						**3**
fluticasone-salmeterol												1						**1**
fluvoxamine					1					x		1						**3**
furosemide		x	x				y	x			3	1			0,5		detectable	**8**
gentamycin		x						x				1						**3**
glutethimide				x														**1**
glycopyrrolate	x																	**1**
guaifenesin														1				**1**
haloperidol	x		x		2				x	x						1		**6**
Henbane (hullukaali)				x														**1**
homatropine	x			x						x				3				**4**
hydralazine		x					y	x				1						**4**
hydrochlorthiazide								x										**1**
hydrocodone														2	0,5			**2**
hydrocortisone		x					y	x				1						**4**
hydroxyzine = hydroxine		x	x	x		x	z	x			3	3	x			3	high	**11**
hyoscyamine = L-atropine				x		x	z					3			3	3		**6**
imipramine	x	x		x		x		x	x	x	3	3	x	3		3		**12**
indapamide										x								**1**
ipratropium (inhaler)	x		x	x			z			x							detectable	**6**
isosorbide												1						**1**
isosorbide dinitrate		x	x				y	x				1					detectable	**6**
isosorbide mononitrate												1					detectable	**2**
ketorolac														1				**1**
ketotifen ophthalmic												1						**1**
lansoprazole															0,5			**1**
levodopa + carbidopa										x						1		**2**
levofloxacin															0,5			**1**
levomepromazine = methotrimeprazine										x	3	2	x				high	**5**
lithium															1			**1**
loperamide					1							1		1		2		**4**
loratadine														1		2		**2**
lorazepam												1						**1**

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loxapine									x			2						**2**
maprotiline	x			x						x	3		x					**5**
mebeverine										x								**1**
meclizine = meclozine	x		x	x		x	z					3	x			3		**8**
melperone = methylperone										x								**1**
memantine										x								**1**
mequitazine													x					**1**
mesoridazine						x			x									**2**
metformin															0,5			**1**
methadone														2				**1**
methantheline	x																	**1**
methocarbamol														1		1		**2**
methscopolamine				x														**1**
methyldopa								x										**1**
methylprednisolone												1						**1**
metoclopramide										x				3		1	detectable	**4**
metopimazine													x					**1**
metoprolol					1									1				**2**
mianserin										x								**1**
midazolam												1						**1**
milnacipran										x								**1**
mirtazapine										x					1	1		**3**
moclobemide										x								**1**
molindone												2						**1**
morphine					1							1		1				**3**
nefazodone										x				1				**2**
neostigmine										x								**1**
nifedipine		x	x				y	x				1					detectable	**6**
nizatidine												1						**1**
nortriptyline	x		x	x					x	x		3		3	2	2		**8**
olanzapine						x			x	x		1		1	2	2		**8**
ondansetron										x								**1**
opipramol											3							**1**
orphenadrine	x			x		x				x	3	3					high	**7**
otilonium										x								**1**
oxazepam		x						x				1						**3**
oxcarbazepine												2						**1**
oxomemazine													x					**1**
oxybutynin	x		x	x		x		x		x	3	3	x		2	3	high	**12**
oxycodone		x						x				1		1				**4**
pancuronium		x						x				1						**3**
paroxetine					2				x	x		1		2	2	1		**7**
periciazine = propericiazine													x				high	**2**
perphenazine	x								x			1	x	2		3		**6**
pethidine = meperidine			x	x	2							2						**4**
phenelzine	x	x						x				1						**4**
phenindamine						x												**1**
pheniramine													x					**1**
phenobarbital		x						x						1				**3**
phenytoin															0,5			**1**
phloroglucinol										x								**1**
pilocarpine										x								**1**
pimethixene													x					**1**
pimozide						x			x	x		2						**4**

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pinaverium										x								**1**
piperacillin		x						x				1						**3**
pipotiazine													x					**1**
pramipexole										x						1		**2**
pramiverine										x								**1**
prednisolone		x	x					x				1						**4**
prednisone							y					1						**2**
prifinium										x								**1**
procainamide				x														**1**
prochlorperazine	x			x					x			1		2		2	detectable	**7**
procyclidine				x		x						3						**3**
promazine						x			x									**2**
promethazine	x		x	x		x				x		3	x			3		**8**
propantheline	x			x								3		2				**4**
propinoxate = propinox										x								**1**
propiverine										x								**1**
propoxyphene														2	0,5			**2**
protriptyline	x			x		x						3						**4**
pseudoephedrine-triprolidine																2		**1**
pyridostigmine										x								**1**
pyrilamine = mepyramine				x								3						**2**
quetiapine									x	x				2	1	1		**5**
quinidine	x		x	x			y										detectable	**5**
quinupramine										x								**1**
ranitidine		x	x		2		y	x				2		2	1	1	detectable	**10**
reboxetine										x								**1**
risperidone					1				x	x				1		1		**5**
robitussin = dextromethorphan or guaifenesin														1				**1**
scopolamine = hyoscine	x			x		x						3	x	3				**6**
selegiline										x						1		**2**
sertindole										x								**1**
sertraline									x	x		1		1				**4**
solifenacin													x					**1**
sulpiride										x								**1**
temazepam												1			1			**2**
theophylline		x	x				y	x			2	1					detectable	**7**
thioridazine	x	x		x	3	x		x	x	x		3		3	3	3		**12**
thiothixene	x			x					x			1				3		**5**
tianeptine										x								**1**
tiapride										x								**1**
ticrocillin		x						x										**2**
tiemonium iodide										x			x					**2**
timolol										x								**1**
tiropramide										x								**1**
tizanidine										x						3		**2**
tobramycin		x						x										**2**
tolterodine										x		3	x	3	3	2	detectable	**7**
topiramate															0,5			**1**
tramadol												1		2			detectable	**3**
trandolapril														1				**1**
trazodone	x		x							x				1		1		**5**
triamcinolone												1						**1**
triamterene							y	x				1					detectable	**4**
triazolam												1		1				**2**

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trifluoperazine									x	x		1				3		**4**
trifluperidol										x								**1**
triflupromazine						x												**1**
trihexylphenidyl = benzhexol	x			x		x			x	x	3	3		3				**8**
trimebutine										x								**1**
trimethobenzamide				x														**1**
trimipramine	x			x		x				x	3	3	x					**7**
triprolidine						x							x					**2**
tropatepine											3							**1**
tropicamide	x			x														**2**
trospium										x								**1**
valproic acid, divalproex sodium		x						x				1						**3**
vancomycin		x						x				1						**3**
warfarin = coumadin		x	x				y	x				1					detectable	**6**
venlafaxine										x				1				**2**
veralipride										x								**1**
viloxazine										x								**1**
ziprasidone																1		**1**
zotepine										x								**1**
zuclopenthixol										x								**1**