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Antipsychotic Use among Older Persons in
Long-Term Institutional and
Home Care

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UNIVERSITY OF TAMPERE

To those I love

CONTENTS

8

LIST OF ORIGINAL PUBLICATIONS

The present dissertation is based on the following original publications, referred to in the text by the Roman numerals I-V. Some unpublished data are also presented.

I   Alanen HM, Finne-Soveri H, Noro A, Leinonen E (2006): Use of antipsychotic medications among elderly residents in long-term institutional care: a three-year follow-up. Int J Geriatr Psychiatry 21:288-295.

II   Alanen HM, Finne-Soveri H, Noro A, Leinonen E (2006): Use of antipsychotics among nonagenarian residents in long-term institutional care in Finland. Age Ageing 35:508- 513.

III   Alanen HM, Finne-Soveri H, Leinonen E (2007): Factors associated with non-use of antipsychotics among older residents with schizophrenia in long-term institutional care. (Submitted in Int J Geriatr Psychiatry)

IV   Alanen HM, Finne-Soveri H, Noro A, Leinonen E (2007): Use of antipsychotics in older home care patients in Finland 2004. Drugs Aging (in press)

V   Alanen HM, Finne-Soveri H, Fialova D, Topinkova E, Soerbye LW, Bernabei R, Leinonen E (2007): Use of antipsychotic medications in older home care patients – Report from nine European countries. Aging Clin Exp Res (in press)

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ABBREVIATIONS

AD	Alzheimer´s disease
AdHOC	Aged in Home Care
ADL	activities of daily living
ATC	Anatomical and Therapeutic Chemical classification of drugs
BPSD	behavioural and psychological symptoms of dementia
ChEI	cholinesterase inhibitor
CI	confidence interval
CVAV	cerebrovascular adverse event
CVD	cardiovascular disease
DSM-IV	Diagnostic and Statistical Manual of Mental disorders, fourth edition
CPS	Cognitive Performance Scale
DRS	Depression Rating Scale
EMEA	European Agency for the Evaluation of Medicinal Product
EPS	extrapyramidal symptoms
FDA	Food and Drug Administration
HC	home care
ICD-10	International Classification of Disease, tenth edition
LBD	Lewy body dementia
LTCF	long-term care facility
MDS	Minimum Data Set
OR	odds ratio
PD	Parkinson`s disease
RAI	Resident Assessment Instrument
RCT	randomized controlled trial
STAKES	National Research and Development Centre for Welfare and Health
TD	tardive dyskinesia

ABSTRACT

Background: Although antipsychotics are widely used in geriatric patients, there is a paucity of information about the use patterns of antipsychotic medication in home and long-term institutional care, especially among the oldest old and schizophrenic residents.

Aims: The purpose of the present study was to investigate the prevalence of use of antipsychotics and associated factors among elderly persons in long-term institutional and home care.

Materials and methods: The population data in the various studies (I-V) were drawn from the national Resident Assessment Instrument (RAI) database located in STAKES during the period 2001- 2006. The data collection method was the Minimum Data Set (MDS) for long-term care facilities (MDS-LTC) and home care (MDS-HC).

Results: The prevalence of the use of antipsychotics in long-term institutional care decreased from 42% in 2001 to 39% in 2003. The overall confounder-adjusted decrease in antipsychotic use was not statistically significant. However, during the study period the use of antipsychotics decreased significantly among residents with wandering as a behavioural problem. However, the use of antipsychotics increased in those residents who concurrently received anxiolytics (Study I). Antipsychotic medication use among nonagenarians in long-term institutional care was also common (30%) and seemed in many cases to be associated with residents` negative attitudes to others. The major finding was an increasing risk of antipsychotic use among querulous residents. However, this risk was lower among those residents with good social skills (Study II). Approximately 19% of the older residents in long-term institutional care with schizophrenia were not on antipsychotic medication. Any diagnosis of dementia,

severe underweight and severely impaired vision was associated with non-use of antipsychotics (Study III). Antipsychotic use among home care patients in Finland was lower (11.0%) than in long-term institutional care. Several predictive factors such as psychiatric diagnosis, delusions and cognitive impairment were associated with the use of antipsychotics, whereas there was a negative association between age and the use of antipsychotics (Study IV). Of home care patients in nine European countries, 6.2% received antipsychotic medication. Frequency of the use of one or more antipsychotic medications varied widely between study sites, ranging from 3.0% in Denmark to 12.4% in Finland. Certain factors such as delusions, hallucinations, depression, dementia and cognitive impairment as well as youngest age group and concomitant use of other psychotropics explained the use of antipsychotics. Residing in Finland or Italy was also a risk indicator (Study V).

Conclusions: Based on present results and the current literature it seems reasonable to conclude that the use of antipsychotic medication in home and long-term institutional care in Finland was among the highest in the world. The use of antipsychotics was approximately three times more common in long-term institutional care than in home care. The finding that the use of antipsychotics was more common among youngest age group, 65-74 years, contradicts some earlier reports. In many cases antipsychotics were not being prescribed based on clinical indication. The proportion of residents with schizophrenia without any antipsychotic medication was equal to that found in earlier studies.

TIIVISTELMÄ

Tausta: Psykoosilääkkeiden käytöstä vanhusten pitkäaikaisessa koti- ja laitoshoidossa on vähän tutkimustietoa, vaikka vanhusikäisillä käytetään psykoosilääkkeitä runsaasti. Tietoa puuttuu erityisesti kaikkein iäkkäimpien ja skitsofreniaa sairastavien vanhusten psykoosilääkkeiden käytöstä.

Tavoitteet: Tutkimuksen tarkoituksena oli selvittää psykoosilääkkeiden käytön yleisyyttä ja siihen vaikuttavia tekijöitä vanhusten pitkäaikaisessa laitos- ja kotihoidossa.

Aineisto ja menetelmät: Tutkimusaineisto kerättiin eri tutkimuksiin Stakesissa olevasta vuosien 2001–2006 välisestä RAI (Resident Assessment Instrument) -tietokannasta. Laitoshoidossa tutkimusaineiston keräykseen oli käytetty MDS (Minimum Data Set)- LTC (Long-Term Care) ja kotihoidossa MDS-HC (Home Care) tiedonkeruumenetelmää.

Tulokset: Vuosien 2001–2003 välisenä aikana psykoosilääkkeiden käyttö väheni pitkäaikaisessa laitoshoidossa 42 %:sta 39 %:iin. Sekoittavien tekijöiden vakioinnin jälkeen vähenemä ei ollut kuitenkaan tilastollisesti merkitsevä. Psykoosilääkkeiden käyttö väheni niillä potilailla, joilla dementian käytösoireena oli vaeltelua. Toisaalta psykoosilääkkeiden käyttö lisääntyi niillä potilailla, jotka saivat samanaikaisesti rauhoittavaa lääkitystä (Tutkimus I). Yli yhdeksänkymmentävuotiailla potilailla psykoosilääkkeiden käyttö oli myös huomattavan tavallista, psykoosilääkitys oli 30 %:lla. Sen käyttö liittyi potilaan negatiiviseen asenteeseen ympäristöä kohtaan ja tyytymättömillä potilailla riski oli suurempi. Toisaalta hyviin sosiaalisiin taitoihin liittyi vähäisempi psykoosilääkkeen käytön riski (Tutkimus II). Noin 19 % pitkäaikaisessa laitoshoidossa olevista, skitsofreniaa sairastavista vanhuksista oli ilman

psykoosilääkitystä. Dementiadiagnoosi, vaikea alipainoisuus sekä vaikea näön heikentyminen selittivät psykoosilääkkeiden käyttämättömyyttä (Tutkimus III). Kotihoidossa olevilla vanhuksilla käytettiin psykoosilääkkeitä Suomessa vähemmän (11 %) kuin pitkäaikaisessa laitoshoidossa olevilla. Psykoosilääkkeen käyttöä selittivät psykiatrinen diagnoosi, harhaluulot ja kognitiivinen heikentyminen, kun taas iällä ja psykoosilääkkeen käytöllä oli käänteinen yhteys (Tutkimus IV). Yhdeksässä Euroopan maassa psykoosilääkkeitä käytti 6.2 % kotihoidon potilaista. Käyttö vaihteli Tanskan 3 %:sta Suomen 12.4 %:iin. Harhaluulot, aistiharhat, depressio, dementia, kognitiivinen heikentyminen, nuorin ikäryhmä (65–74 vuotta) ja samanaikainen muiden psyykenlääkkeiden käyttö selittivät psykoosilääkkeiden käyttöä. Myös asuminen Suomessa tai Italiassa lisäsi riskiä (Tutkimus V).

Johtopäätökset: Tämä tutkimuksen ja viimeaikaisen kirjallisuuden perusteella voidaan todeta, että Suomessa psykoosilääkkeiden käyttö oli maailman korkeimpia sekä koti- että pitkäaikaisessa laitoshoidossa. Tämän tutkimuksen mukaan psykoosilääkkeiden käyttö oli noin kolme kertaa yleisempää laitoshoidossa kuin kotihoidossa. Psykoosilääkkeitä käytettiin eniten nuoremmissa ikäryhmissä (65–74 vuotta). Tulos oli päinvastainen kuin muutamissa aikaisimmissa tutkimuksissa. Useissa tapauksissa psykoosilääkkeen käyttö ei näyttänyt perustuvan yleisesti hyväksyttyihin indikaatioihin. Psykoosilääkkeitä käyttämättömien skitsofreniapotilaiden osuus oli tässä tutkimuksessa samansuuruinen kuin on raportoitu aikaisemmin.

14

INTRODUCTION

Population aging presents a challenge in all countries of the world, but it is thought that in Finland the changes will come more rapidly than in most other EU countries (Statistics Finland 2007a). It is estimated that by 2035, the proportion of the population aged 65 or over will increase from the current level of 16% to about 27% in Finland (Statistics Finland 2007b). Although an increasing number of older people enjoy good health longer than previously (Sulander et al. 2006), living independently and need no assistance and care, the aging of the population will increase pressure on social and health services.

Dementia affects over 6% of people age 65 and over worldwide (Wimo et al. 2003) and increases sharply with age (Lobo et al. 2000, Ferri et al. 2005). Although improvements in outpatient services, home nursing and home help services in particular, have also enabled to increasing numbers of elderly people with dementia continue to live at home, dementia is the major cause of long-term institutionalisation among older people. At the same time residents in long-term institutional care are ever more frail (Noro et al. 2005). According to earlier reports, about three-quarters of older people in nursing homes are suffering from dementia (Macdonald et al. 2002, Hosia-Randell and Pitkälä 2005).

The need for care is increasing not only by population ageing but also by the longer duration of different diseases. Dementias commonly lead to impaired functional capacity and greatly increase the need for services. Behavioural and psychological symptoms of dementia develop in most elderly patients at some stage (Lawlor 2004).

Older people with psychiatric disorders constitute a significant subgroup of elderly population. According to epidemiological studies the 12-month prevalence rate of any psychiatric disorder was 5.8% among community living

elderly people and 68-94% among elderly residents in long-term care settings (Rovner et al. 1990, Wancata et al. 1998, Hybels and Blazer 2003). The recent epidemiological The Health 2000 Study reported the lifetime prevalence of psychotic disorders to be 3.6% among elderly people in Finland (Perälä et al. 2007). However, the prevalence of schizophrenia is increasing in older individuals as the overall lifespan increases and more individuals with schizophrenia survive into later life. It has been estimated that the absolute number of older patients with schizophrenia will double over the next 30 years (Cohen et al. 2000).

Antipsychotics are widely used in geriatric disorders. The proportion of residents receiving antipsychotic medication in long-term institutional care has varied widely, 15-42% (Liperoti et al. 2003, Hosia-Randell and Pitkälä 2005). Excessive prescribing of antipsychotic therapy is a concern owing to their potential to cause serious adverse events.

In this dissertation the prevalence and associated factors of antipsychotic use among elderly people in long-term institutional and home care were studied.

1 REVIEW OF THE LITERATURE

1.1 Social and health services for older people

1.1.1 Older population proportions and trends

The proportions of older persons out of the total population are increasing in most countries. At the end of 2005, the number of over-65s accounted for 16% of the Finnish population, over-75s for 7.5% and over-85s for 1.7% (STAKES 2007). By 2035, the number of over -65s is estimated to grow to 27%. The population share over-75s will increase to 15% and over-85s at nearly 5%. The growth of the older population can partly be explained by the fact that people live longer than ever before.

Preliminary data for 2005 indicate that the average life expectancy of the Finnish population was 75.5 years for men and 82.3 years for women. By 2035, the life expectancy will rise to 81.3 years for men and 85.8 years for women (Statistics Finland 2006, STAKES 2007). With the worldwide aging of the population the number of disabled older persons in and out of institutions will approximately triple from 1985 to 2050 (Manton 1997).

1.1.2 Long-term care for older people

The aim is to promote older people's functional capacity and independent living, with the main aim that as many older people as possible can continue to live in their own homes and their familiar environments. In Finland services provided in the person's home are provided by the social welfare authorities (home-help service units) or health care authorities (home-nursing units) either jointly or separately. At the end of 2005, living at home accounted for 89.6% of all over-75s. Of population aged 65 years and over 6.5% were having regularly home

care services, of population aged 75 and over 11.5% and of those aged 85 and over 20.9% (STAKES 2007).

At the same time as the older population is growing, an increasingly low proportion of older people live in long-term institutional care. Long-term institutional care for older people is mostly provided in residential homes and health-care inpatients wards. At the end of 2005 in Finland, those living at residential homes accounted for 2.2% and those living in inpatient care in health centres accounted for 1.3% for all over-65s (STAKES 2007). Results from long-term care facilities in 10 nations showed that institutionalization rates among the nations studied varied between 2% and 5% (Ribbe et al. 1997). In 2004 the proportions of over-65s in institutional care and housing services for older people in Nordic countries were: in institutional care in Finland 6.8%, in Sweden 7.3%, in Norway 11.8%, in Denmark 8.2% and in Iceland 9.4% (STAKES 2007). The proportions receiving home-help services were: 9.8% in Finland, 8.5% in Sweden, 14.1% in Norway, 21.6% in Denmark and 19.2% in Iceland.

1.2 Psychotic and organic mental disorders in later life

1.2.1 Psychotic symptoms and disorders

1.2.1.1 Epidemiology

For having at least one psychotic symptom, the estimated point prevalence in community living elderly people has been reported to be 3.2% to 5.7% (Henderson et al. 1998, Forsell et al. 2003). The prevalence rate of psychotic symptoms in individuals older than 85 without dementia has been found to be 10.1% (Östling and Skoog 2002). Two studies on individuals aged above 70 have reported a cumulative incidence of psychotic symptoms 4.8% (Henderson et al. 1998, Östling et al. 2007). Psychotic symptoms in older persons are important because of their clinical significance and social impact. According to

18

earlier studies there may be a twofold mortality risk in individuals above 70 years with psychotic symptoms (Henderson and Kay 1997).

The prevalence of psychotic disorders in the elderly has ranged from 0.1-5.1% in community based samples patients to 10%- 63% in a nursing home population (Junginger et al. 1993, Copeland et al. 1998, Zayas and Grossberg 1998, Ritchie et al. 2004, Skoog 2004). The point prevalence of psychotic disorders seems to increase with age: 1.0% in the population aged 70 and 5.1% in the population aged 85 and more (Skoog 2004). The recent The Finnish Health 2000 Study reported that the lifetime prevalence of all psychotic disorders was 3.06% in general population (Perälä et al. 2007). The prevalence of psychotic disorders was highest in the age group 65 and over, 3.55% (2.80 % in men, 3.98% in women). These prevalences accord with an earlier study by Ritchie et al. stating that lifetime prevalence of psychosis among elderly people was 4.7% (Ritchie et al. 2004). However, longitudinal epidemiological studies of psychiatric disorders in the very old are rare.

1.2.1.2 Risk factors for psychosis

The risk factors that are described as being associated with the development of psychotic symptoms in older people include the following: cognitive dysfunction, a higher level of social isolation than others in the community, being divorced or never married, being female, being old, having depressive symptoms and using psychotropic drugs (Forsell and Henderson 1998, Henderson et al. 1998, Zayas and Grossberg 1998). In the recent study hearing impairment in older people, however, was not a risk factor for psychosis (van der Werf et al. 2007), in contrast to previous reports (Prager and Jeste 1993, Stein and Thienhaus 1993, Almeida et al. 1995).

1.2.2 Schizophrenia

1.2.2.1 Diagnosis of schizophrenia

Schizophrenia is defined almost identically in the two major psychiatric classification systems, the American Psychiatric Association's Diagnostic and Statistical Manual of Mental disorders, 4th edition (DSM-IV; 1994) and the World Health Organization's International Classification of Diseases, 10th edition (ICD-10; 1997). There are some differences between these criteria. In ICD-10, severe symptoms should have been present for 1 month, but DSM-IV requires 6 months` duration (Schultz and Andreasen 1999).

Three broad types of symptoms characterize schizophrenia: positive symptoms, negative symptoms and cognitive impairment (Mueser and McGurk 2004). Positive or psychotic symptoms include extraordinary beliefs, delusions, hallucinations and incoherence or looseness of associations in thought and speech, grossly disturbed behaviour or affect. Long-term functioning is predominantly influenced by negative symptoms – such as flattening of affect, amotivation, anhedonia – and cognitive problems (Andreasen 1995). These cognitive deficits involve impaired executive functioning that affects planning, abstract thinking, rule flexibility, processing deficits, attention impairments and short- and long-term memory difficulties.

There are two distinct groups of individuals with late life schizophrenia. The first and larger group comprises patients with onset of schizophrenia early in life (early-onset schizophrenia) who are now elderly. The other group defined by onset of symptoms after age 40 or age 45 (late-onset schizophrenia) and onset of symptoms after age 60 (very-late-onset schizophrenia-like psychosis). Approximately 80% have early-onset schizophrenia (Cohen et al. 2000) with the remaining 20% including those with late-onset schizophrenia (Howard et al. 2000). However, this classification is included neither in ICD-10 nor in DSM-IV.

1.2.2.2 Prevalence of schizophrenia

Schizophrenia is among the most severe psychiatric disorders, affecting nearly 1% of the world's population (Schultz and Andreasen 1999). For individuals over 65 years of age, community prevalence estimates for schizophrenia have been reported to vary from 0.1% to 0.6% (Nielsen and Nielsen 1989, Keith and Matthews 1991, Copeland et al. 1998). Other studies have suggested that the actual prevalence of schizophrenia in later life is higher, approximately 1.0% (Gurland and Cross 1982, Cohen 1990). In the recent population based Health 2000 study in Finland the lifetime prevalence of schizophrenia has been reported to be 0.92% among elderly people over 65 years of age (Perälä et al. 2007). It has been estimated that at least 0.1% of the world's elderly population have a diagnosis of schizophrenia that started late in life (Arunpongpaisal et al. 2003). Late onset schizophrenia accounts for about 15-23% of older adults with schizophrenia (Harris and Jeste 1988, Howard et al. 2000).

Approximately 85% of people with schizophrenia aged 65 and over are living in the community (Cohen et al. 2000). With the aging of the population and the downsizing of psychiatric institutions, nursing homes and equivalent settings have become increasingly common places of residence for patients with schizophrenia in the later stages of life. It has been reported that residents with schizophrenia account for 6-7% up to 12% of all nursing home residents (Gurland and Cross 1982, Tariot et al. 1993, McAlpine and Mechanic 2000, Snowdon et al. 2005).

1.2.2.3 Course of schizophrenia in later life

Mental disorders in general are life shortening (Hannerz et al. 2001). In addition to psychiatric symptoms, patients with schizophrenia often lack basic medical care and thus suffer from greater severity of comorbid medical disorders which may have a negative impact on both psychiatric and physical outcomes (Meyer et al. 2005). Compared with the general population, individuals with schizophrenia have an increased risk of death from medical causes and an up to 20% shorter lifespan (Harris and Jeste 1988). Mortality rates among people with

schizophrenia have been estimated to be two to four times higher than that in general population (Jeste et al. 1996). The prevalence of schizophrenia is increasing in older individuals as the overall lifespan increases and more individuals with schizophrenia survive into later life (Cohen et al. 2000).

Schizophrenia is an illness with a low rate of full recovery and characterised by considerable heterogeneity in symptomatology, course and outcome. For years it has been believed that in later life the severity of psychotic symptoms of schizophrenia is markedly reduced. There are essentially no long-term studies of the course of psychotic symptoms in schizophrenia that use formal assessments of symptom severity. In a cross-sectional study of patients with schizophrenia ranging in age from 25 to 95, all of whom were chronically institutionalized at the time of assessment, the severity of positive and negative symptoms was assessed (Davidson et al. 1995). The oldest patients in the study (aged 75 and over) still had considerable psychotic symptoms. By contrast, Jeste et al. have claimed an inverse association of age and the severity of psychotic symptoms (Jeste et al. 2003). Several longitudinal studies have shown that there is no evidence of improvement in psychotic symptoms with advancing age (Putnam et al. 1996, Harvey et al. 2003).

Because of sample heterogeneity, there is more controversy about improvement in negative symptoms; some investigators believe that negative symptoms dominate the picture in later life, whereas others contend that such symptoms remit (Cohen 1990, McGlashan and Fenton 1992, Davidson et al. 1995, Schultz et al. 1997, Cohen et al. 2000, Jeste et al. 2003). Cohen et al. note that in elderly schizophrenic patients negative symptoms may be difficult to identify because of the confounding effects of depression, medications and institutionalization (Cohen et al. 1996, Cohen and Talavera 2000). Negative symptoms have been found to correlate with cognitive deficits (Lindenmayer et al. 1997) and to be inversely correlated with functional status (Palmer et al. 2002). Institutionalized schizophrenic patients have demonstrated an age related pattern of cognitive change different from that observed for Alzheimer`s disease (AD) and healthy individuals (Friedman et al. 2001).

22

Cognitive impairment is a prominent feature of schizophrenia after the onset of psychosis and increases in severity and prevalence with age (Davidson et al. 1995, Harvey et al. 1995a, Harvey et al. 1995b). Although it has been reported that two thirds of elderly institutionalized patients with schizophrenia had cognitive impairments (Dwork et al. 1998), several studies have reported that AD and AD-like neuropathology does not occur more often in chronic schizophrenia than in general population (Dwork et al. 1998, Murphy et al. 1998, Purohit et al. 1998, Jellinger and Gabriel 1999). The prevalence of AD in elderly patients with chronic schizophrenia ranges from 2% to 9%, (Dwork et al. 1998, Murphy et al. 1998, Purohit et al. 1998, Jellinger and Gabriel 1999) showing that the frequency of AD may be equal or even less than in the general population.

Schizophrenia in general is a chronic debilitating disease that is often characterized by frequent relapses associated with exacerbation of psychosis and the need for psychiatric rehospitalization. Only 8% of schizophrenic patients (40-70 years) living independently met the criteria for sustained remission (Auslander and Jeste 2004). Sustained remission was recently defined as a state in which patients have experienced an improvement in core sign and symptoms such as psychoticism, disorganization and negative symptoms to the extent that any remaining symtomatology is of such low intensity that it no longer interferes significantly with behaviour (Andreasen et al. 2005). It is below the threshold typically utilized in justifying an initial diagnosis of schizophrenia. With regard to symptom severity, these experts defined a score of mild or better [the Positive and Negative Syndrome Scale (PANSS): ≤ 3, the Brief Psychiatric Rating Scale (BPRS): ≤ 3, the Scale for the Assessment of Positive Symptoms (SAPS): ≤ 2 and the Scale for the Assessment of Negative Symtoms (SANS): ≤ 2)] simultaneusly on all these items as representative of an impairment level consistent with symptomatic remission of illness. Six months was identified as the minimum period that a patient had to sustain this low level of symptomalogy to be considered as in remission (Andreasen et al. 2005).

Most patients with schizophrenia are at very high risk of relapse in the absence of antipsychotic treatment. Unfortunately, there is no reliable indicator

to differentiate the minority who will not from the majority who will relapse without contained medication (Lehman et al. 2004). Antipsychotics can reduce the risk of relapse in the stable phase of illness to less than 30% per year (Gilbert et al. 1995, Leucht et al. 2003). Without maintenance treatment, 60-70% of patients relapse within 1 year, and almost 90% relapse within 2 years. While many of these studies included younger adults with schizophrenia, the rates of relapse following withdrawal of antipsychotics seemed to be comparable in those studies that included elderly patients (Jeste et al. 1993).

1.2.3 Dementia

It is estimated that there are over 24 million people with dementia worldwide (Ferri et al. 2005). The prevalence of dementia varies between 5.9% and 9.4% in European populations aged over 65 (Lobo et al. 2000, Berr et al. 2005) and increases sharply with age: it doubles every five years, being 0.8-1.5% in the age group of 65-69 years, and 24.8-28.5% in the age group of 85 years and older (Lobo et al. 2000, Ferri et al. 2005). In Finnish population-based studies a prevalence of 6.7-9.6% for all dementia has been reported (Sulkava et al. 1985, Koivisto 1995, Löppönen et al. 2003). In a recent study in Finland the prevalence of dementia was 22.8% in subjects aged over 75 years (Rahkonen et al. 2003). It has been reported that the prevalence of dementia among nonagenarians varied 26.7% to 38.6% (Juva et al. 1993, Juva et al. 2000, Polvikoski et al. 2001) and among centenarians 51-58% respectively in population based studies (Sobel et al. 1995, Andersen-Ranberg et al. 2001).

Dementia is an incurable disease with marked effects on cognition, activities of daily living and behaviour and it is a major cause of long-term institutionalization among older people. Dementia affects approximately three-quarters of older people in specialist nursing homes in UK and at least one third of residents had severe cognitive impairment (Macdonald et al. 2002). Figures of between 61 and 78% have been reported from Canada, Denmark and Australia (Brodaty et al. 2001, Sorensen et al. 2001, Hagen et al. 2005). Accordingly, in an previous study in Finland approximately 70% of the residents in nursing homes had been diagnosed with dementia (Hosia-Randell and Pitkälä 2005).

1.2.3.1 Behavioural and psychological symptoms and signs

Although cognitive dysfunction is the hallmark of dementia, behavioural and psychological symptoms of dementia (BPSD), such as psychosis, aggression, sleep disturbance, agitation, and mood disorders, develop in most elderly patients at some stage (Lawlor 2004). Agitation is a descriptive term applied to nonspecific physical and verbal behaviours that are commonly found in nursing home residents with dementia: these include symptoms of aggression, wandering, irritability, restlessness, shouting and pacing, usually in the context of distress and anxiety (Cohen-Mansfield and Billig 1986, Howard et al. 2001).

The prevalence of BPSD in both community and clinical settings is very high. In community-dwelling patients with dementia, more than 80% exhibit some BPSD from the onset of cognitive impairment, with apathy (45.3%), depression (43.6%), and agitation/aggression (40.1%) showing the highest cumulative prevalence (Lyketsos et al. 2002). For up to 60% of these patients, the level of BPSD will be in the clinically significant range (Lyketsos et al. 2002). The prevalence of clinically significant BPSD rises more than 80% for residents in nursing homes (Brodaty et al. 2001, Margallo-Lana et al. 2001, Pitkälä et al. 2004, Zuidema et al. 2007). Prevalence estimates for BPSD vary widely because of the heterogeneity of patients populations studied in terms of settings and type of dementia and the different definitions used for BPSD.

Psychotic symptoms develop in about half (30-60%) of patients with Alzheimer`s disease during the course of their dementia (Zayas and Grossberg 1998, Jeste and Finkel 2000, Ballard et al. 2001, Brodaty et al. 2001, Paulsen et al. 2000, Wilson et al. 2000). Delusions and hallucinations are prevalent in patients with dementia in 12-49% and 5-39% respectively (Wagner et al. 1995, Margallo-Lana et al. 2001, Pitkälä et al. 2004, , Zuidema et al. 2007). Psychotic symptoms in dementia are variable, but may be persistent, with lasting symptoms present in 39-62% after 3 months and in 43-57% after 1 year (Schneider and Dagerman 2004). Psychotic symptoms have a clinical impact because psychotic symtoms in dementia may impair functional ability (Schneider et al. 2003) and

predict earlier institutionalization (Gonzalez-Salvador et al. 1999, Lopez et al. 1999, Pang et al. 2002).

Most of these symptoms and behaviours do not occur in isolation but tend to occur together in clusters or syndromes. For example, delusions have been associated with agitation, aggression and insomnia (Lachs et al. 1992, Gormley et al. 1998), while depression has been associated with psychotic symptoms (Lyketsos et al. 1999).

Moreover, the development of BPSD is a major risk for caregiver burden (Coen et al. 1997, Gonzalez-Salvador et al. 1999) and may be more important in this regard than are cognitive deficits of the disease process (Steele et al. 1990). The development of BPSD is also associated with a poorer prognosis, a more rapid rate of cognitive decline, illness progression (Paulsen et al. 2000), greater impairment in activities of daily living (Lyketsos et al. 1997) and impaired quality of life (Gonzalez-Salvador et al. 2000). In addition, it has been shown that BPSD adds significantly to the direct and indirect costs of care (Jönsson et al. 2006).

1.3 Antipsychotic medications

1.3.1 Definitions of antipsychotic medications

Antipsychotic medications are the mainstay of treatment for psychotic illnesses. Antipsychotic medications are broadly derived into conventional or typical neuroleptics and newer or atypical antipsychotics depending on their pharmacological profile. Conventional neuroleptics include e.g. haloperidol, chlorpromazine, thioridazine, block dopamine-D_2 receptors, and atypical antipsychotics e.g. clozapine, risperidone, olanzapine and quetiapine block both dopamine –D_2 and serotonin-$5HT_2$ receptors.

Atypical antipsychotics have suggested to work more effectively than conventional neuroleptics for treating the negative symptoms of schizophrenia

and for treating patients who show treatment-resistance and do not respond to conventional neuroleptics (Salokangas et al. 2001).

1.3.2 Indications for using antipsychotics in older patients

According to the Expert Consensus Guidelines (US 2004), antipsychotics in the elderly are indicated for disorders with psychotic symptoms, that is schizophrenia, mania with psychosis, agitated dementia with delusions, psychotic major depression and delusional disorder (Alexopoulos et al. 2004). Experts have suggested that antipsychotics are sometimes indicated for mania without psychosis, delirium, and agitated dementia without delusions. By contrast, they do not recommend antipsychotics for irritability and hostility in the absence of a major psychiatric syndrome, non-psychotic major depression without severe anxiety, generalized anxiety disorder, panic disorder, hypochondrias or insomnia/sleep disturbance without a major psychiatric syndrome, severe nausea and vomiting, neuropathic pain or motion sickness. For patients with dementia and elderly patients with schizophrenia atypical antipsychotics are recommended (Salokangas et al. 2001, Alexopoulos et al. 2004, Lehman et al. 2004). Most "good practice" guidelines recommend non-pharmacological interventions as the first-line treatment approach for behavioural and psychiatric symptoms in people with dementia (Lawlor 2004, Pirttilä et al. 2006).

These guidelines also recommend limiting antipsychotic treatment of people with dementia to the short-term treatment (up to three months) of severe neuropsychiatric symptoms associated with severe distress or serious risk (Alexopoulos et al. 2004, Ballard and Howard 2006). American experts recommend a duration of antipsychotic treatment after response before trying to discontinue the antipsychotic in agitated dementia with and without delusions – tapering should start at 3-6 months to determine the lowest effective maintenance dose. In the same guidelines they recommend that the lowest effective dose of antipsychotics may continue indefinitely time among older patients with schizophrenia (Alexopoulos et al. 2004).

1.3.3 Use of antipsychotic medications among elderly people

1.3.3.1 Use of antipsychotics in the home-dwelling elderly

Epidemiological studies in general population from different countries have shown the use of antipsychotics to vary from 1.0% to 1.4% (Alonso et al. 2004, Percudani et al. 2005, Trifiro et al. 2005) and to increase progressively with increasing age (Percudani et al. 2005, Trifiro et al. 2005). The proportion of patients taking antipsychotics among the home-dwelling elderly has ranged 3-11% in Europe (Giron et al. 2001, Linjakumpu et al. 2002, Fahey et al. 2003, Hartikainen et al. 2003b, Linden et al. 2004, Rapoport et al. 2005) being as low as 1.8% rates in the United States (Aparasu et al. 2003).

The use of antipsychotics has been found to be six times more common in demented individuals than among non-demented subjects (Giron et al. 2001, Hartikainen et al. 2003b). The associations between the use of antipsychotics and the level of cognitive functioning as well as the activities of daily living in elderly patients have been ether negative or positive (Sorensen et al. 2001, Craig et al. 2003, Lindesay et al. 2003). There are some reports of antipsychotic medication use in nondemented elderly people without any clear clinical indications such as psychotic symptoms (Hartikainen et al. 2003b).

1.3.3.2 Use of antipsychotics in long-term institutional care

Surveys have documented a high use of antipsychotic medication (15-42%) among elderly people in long-term institutional care (Liperoti et al. 2003, Hosia-Randell and Pitkälä 2005). Studies on antipsychotic use in long-term institutional care are presented in Table 1.

Table 1. Prevalence of antipsychotic use in long-term care facilities in various countries since 2000.

Reference	No. of patients	Age (years)	Country	Mean % of residents taking antipsychotics
Furniss L et al. (2000)	330		UK	28
Van Dijk KN et al. (2000)	2355	65+	The Netherlands	35
Draper B et al. (2001)	647	24-111	Australia	21.3
Margallo-Lana M et al. (2001)	231	-	UK	41
Sorensen L et al. (2001)	288	65+	Denmark	21
Ruths S et al. (2001)	1552	39-111	Norway	23
Oborne CA et al. (2002)	934	65+	UK	24.5
Macdonald A et al. (2002)	445	65+	UK	15.3
Fahey T et al. (2003)	172	65+	UK	28
Holmquist I et al. (2003)	225	65+	Sweden	16
Liperoti R et al. (2003)	139 714	65+	USA	15
Lindesay J et al. (2003)	4226	65+	UK	21.9
Nygaard HA et al. (2003)	1027	65+	Norway	21.9
Bronskill SE et al. (2004)	19 870	65+	Canada	24
Briesacher BA et al. (2005)	1096	65+	United States	27.6
Hosia-Randell H and Pitkälä K (2005)	1987	65+	Finland	42.6
Champoux N et al. (2005)	2460	65+	Canada	25.2
Snowdon J et al. (2005)	2302	-	Australia	25.1
Rochon PA et al. (2007)	47 322	66+	Canada	32.4

1.3.3.3 Use of antipsychotics among the oldest old

Only a few studies have reported on the overall prevalence of antipsychotic medication use in the oldest old (85 years and older). In a Swedish study the use of antipsychotics among individuals 85 years and older has been reported to be 10.4% among those living in institutions and 4.8% living in the community (Skoog et al. 1993). Of those oldest-old elderly with psychotic disorders only 8.7% received antipsychotics (Skoog et al. 1993). In another study among individuals at 85 years of age with psychotic symptoms (hallucinations or delusions) one fifth were prescribed neuroleptics. In addition those oldest-old with no psychotic symptoms 5.1% were taking antipsychotics (Östling and Skoog 2002).

1.3.3.4 Use of antipsychotics in older patients with schizophrenia

Antipsychotic medications are the key role of treatment for schizophrenia. It has been reported that in Australian nursing homes 6.1% of patients had been diagnosed as having schizophrenia and to 81% of them were prescribed antipsychotic medications (Snowdon et al. 2005). Some earlier studies on older schizophrenic residents in nursing homes have shown that 15-19% were not receiving any antipsychotic medication (Bowie et al. 2001, Snowdon et al. 2005).

Elderly patients with schizophrenia are more sensitive to the adverse effects of antipsychotic medications than younger patients and they are also more likely to be taking other medications that may increase the likelihood of adverse drug interactions. It is challenging for the clinician to decide whether or not to continue antipsychotic treatment: continued use of the drug is associated with serious adverse effects such as tardive dyskinesia (TD) and metabolic syndrome while discontinuing the drug can bring about a schizophrenic relapse.

1.3.3.5 Use of antipsychotics among patients with dementia

The behavioural and psychological symptoms of dementia (BPSD) are very common and antipsychotic medications are widely used to controll these symptoms. Surveys have documented a frequent use of antipsychotics (23-48%) among patient with dementia in nursing homes (Lindesay et al. 2003, Nygaard et al. 2003, Hosia-Randell and Pitkälä 2005, Kim and Whall 2006, Raivio et al. 2007). Pitkälä et al. have stated that of the patients with dementia in acute geriatric wards and nursing homes in Helsinki, 42% were on conventional antipsychotics and 13% were on atypical antipsychotics (Pitkälä et al. 2004). In contrast to schizophrenia, no medications have been specifically approved for the psychotic or behavioural manifestations of dementia. Studies on randomized controlled trials (RCT) and meta-analysis of RCTs antipsychotic use in patients with dementia are presented in Table 2.

30

Table 2. Principal studies of typical and atypical antipsychotics: study characteristics.

Source	No. of Patients	Study Design	Lenght of Study	Drug	Patient residence
Typical					
Stotsky, 1984	358	RCT	4 wk	Thioridazine	Nursing home and hospital
Schneider et al. 1990	252	Meta-analysis of 7 RCTs	3-8 wk	Haloperidol, thioridazine, thiothixene clorpromatzine, trifluoperazine, acetophenazine	Mostly nursing home
Lonergan et al. 2002	573	Meta-analysis of 5 RCTs	3-16 wk	Haloperidol	Community and nursing home
Atypical					
De Deyn et al. 1999	229	RCT	12 wk	Risperidone	Nursing home
Katz et al. 1999	625	RCT	12 wk	Risperidone	Nursing home
Street et al. 2000	206	RCT	6 wk	Olanzapine	Nursing home
Clark rt al. 2001	206	RCT	6 wk	Olanzapine	Nursing home
Brodaty et al. 2003	345	RCT	12 wk	Risperidone	Nursing home
De Deyn et al. 2004	652	RCT	10 wk	Olanzapine	Nursing home
De Deyn et al. 2005	208	RCt	10 wk	Aripiprazole	Community living
Zhong et al. 2007	333	RCT	10 wk	Quetiapine	Mostly nursing home

RCT= randomized controlled trial

1.3.4 Adverse effects of antipsychotics

The adverse effects of antipsychotic medications, which can cause difficulties in any patient population, are particularly troublesome in elderly patients, who experience many age-related changes that may exacerbate the adverse effects of medication (Masand 2000). Alterations in pharmacokinetics and pharmacodynamics, however, complicate pharmacotherapy in older patients. Moreover, elderly patients frequently have comorbid illnesses, such as cardiovascular disease and dementia, and take multiple medications. In comparison with younger patients, geriatric patients show an increased

variability of response and an increased sensitivity to medication (Salzman 1990, Avorn et al. 1992).

Adverse effects of particular concern in the older individuals include anticholinergic toxicity/reactions (which can lead to urinary retention, constipation, dry mouth, worsening of glaucoma, and confusion), neurological symptoms [e.g. extrapydamidal symptoms (EPS) and tardive dyskinesia (TD)], orthostatic hypotension, cardiac conduction disturbances (e.g. corrected QT interval prolongation), reduced bone mineral density, sedation, and cognitive slowing (Masand 2000). In a recent systematic review antipsychotic drug as a group seemed to be associated with an increased risk of falling (Hartikainen et al. 2007). Both conventional and atypical antipsychotics have been reported to increase the risk of fractures (Takkouche et al. 2007) and to increase the risk of hospitalization for femur fracture in institutionalized elderly patients (Liperoti et al. 2007). In the 1990s, the newer atypical antipsychotic therapies were introduced. These agents were thought to be safer than the earlier conventional antipsychotic therapy, leading to widespread use of atypical agents in nursing homes (Bronskill et al. 2004, Briesacher et al. 2005).

1.3.4.1 Neurological

Extrapyramidal symptoms include parkinsonism, akathisia and dystonia. Older individuals are particularly prone to develop parkinsonism (Wilson and MacLennan 1989), which is a frequent neuroleptic adverse effect that has a triad of symptoms: resting tremor, rigidity, and bradykinesia. Akathisia is characterized by increased restlessness, psychomotor activity, and agitation, an inability to sit still.

Tardive dyskinesia is a movement disorder characterized by involuntary, irregular or repetitive abnormal movements more frequently observed in the peribuccal, periocular areas, but also perceptible in the hands, legs, and feet. Tardive dyskinesia, one of the most serious adverse effects of treatment with conventional antipsychotics, is 5 to 6 times more prevalent in older than in younger adults (Caligiuri et al. 1999, Jeste et al. 1999). In addition to age, other

32

risk factors for tardive dyskinesia include early EPS, cumulative amounts of antipsychotics, duration of antipsychotics treatment, and history of alcohol abuse and/or dependence (Jeste et al. 1999, Jeste et al. 2000). Severe TD can be especially troublesome to the elderly, because orofacial TD can impair eating and swallowing and also result in dental problems that may progress to mouth infection and/or unintelligible speech. The gait disturbances of patients with severe limbtruncal dyskinesia may lead to falls and injuries (Jeste et al. 2000).

Although atypical antipsychotics have lower ability for EPS than conventional antipsychotics, atypical antipsychotics have been reported to be associated with parkinsonism (Rochon et al. 2005), other movement disorders (Lee et al. 2005) and are likely to also have low potential for tardive dyskinesia (Jeste et al. 2000), despite the paucity of controlled studies in elderly people. However, in younger patients with schizophrenia the prevalences for antipsychotic-induced movement disorders in schizophrenia patients are usually in the range 29% to 74% (Van Harten et al. 1996, Muscettola et al. 1999, Modestin et al. 2000). In an Estonian patient sample of 99 chronic schizophrenia patients in a state nursing home aged 18-65 years (mean age 49.7 years), nearly two-thirds suffered from a antipsychotic-induced movement disorder (Janno et al. 2004). The prevalence of antipsychotic-induced movement disorders in the patients receiving clozapine was 35% and in those receiving conventional antipsychotics 68%.

1.3.4.2 Metabolic

Antipsychotic medication may contribute to the development of metabolic syndrome by causing weight gain (Allison et al. 1999, Koponen et al. 2002), lipid abnormalities (Koro et al. 2002, Casey 2004) and abnormalities in glucose regulation (Haupt and Newcomer 2002, Leslie and Rosenheck 2004). In a Finnish study Suvisaari et al. showed that typical antipsychotic medications were associated with high prevalence of metabolic syndrome (Suvisaari et al. 2007). However, the prevalence among those aged 55 and over did not differ from that in the general population. A recent meta-analysis showed that clozapine and

olanzapine were consistently associated with increased risk for diabetes, in contrast to risperidone and quetiapine treatment (Scheen and De Hert 2007). The estimate for new-onset diabetes mellitus in the 10-year naturalistic study in clozapine-treated patients has been reported to be approximately 43% (Henderson et al. 2005).

In elderly patients with dementia atypical antipsychotics have been not shown to be associated with weight gain, glucose intolerance, diabetes or hyperlipidaemia (Gurevitz et al. 2004, Herrmann and Lanctot 2006). In the Clinical Antipsychotic Trial of Intervention Effectiveness study for Alzheimer's disease (CATIE-AD), patients with AD gained weight with olanzapine and risperidone and lost weight with placebo (Schneider et al. 2006). Schneider et al. have suggested that the possibility that antipsychotics cause metabolic syndrome in the elderly requires further investigation (Schneider et al. 2006).

1.3.4.3 Cardiovascular

The metabolic syndrome (obesity, dyslipidemia, impaired glucose tolerance and hypertension) has been shown to be an important risk factor in the development of both type 2 diabetes mellitus and cardiovascular disease (the combination of cerebrovascular disease, coronary heart disease, and peripheral vascular disease). Cardiovascular disease is the leading cause of death in patients with schizophrenia (Brown 1997).

Some antipsychotics have been suspected to of causing increased risk of ventricular arrythmias and sudden cardiac death (Shader and Greenblatt 1998, Straus et al. 2004). Users of antipsychotics are over-presented in registries of sudden death (Mehtonen et al. 1991). Recently, epidemiological studies have reported a direct relationship between conventional antipsychotics and the risk of sudden death (Ray et al. 2001, Hennessy et al. 2002). A QTc interval > 500 ms (as measured in ECG) increases the risk of potentially lethal arrytmias such as torsades pointes and sudden death (Roden 2004). Both typical and atypical antipsychotics have been associated with cardiac conduction abnormalities, with

the magnitude of QTc prolongation being slightly smaller with atypical antipsychotics (Herrmann and Lanctot 2006). A large case-controlled study of patients >65 years of age using antipsychotics examined the risk of hospitalisation for ventricular arrythmias or cardiac arrest (Liperoti et al. 2005). There was no increase risk associated with treatment with atypical antipsychotics compared with no use, while treatment with typical antipsychotics increased the risk by 86% compared with no use and more than doubled the risk compared with treatment with atypical antipsychotics. However, it has been reported that antipsychotic-treated elderly psychiatric inpatients did not have a higher rate of cardiac morbidity compared to patients who had not received antipsychotics (Barak et al. 2007).

In 2005, responding to several studies (De Deyn et al. 1999, Katz et al. 1999, Street et al. 2000, Brodaty et al. 2003, De Deyn et al. 2004), the Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA) issued a warning regarding atypical antipsychotic medications, noting that the drugs might increase the risk of cerebrovascular adverse events (CVAEs) in elderly patients with dementia-related behaviour disturbances. There is limited evidence regarding the long-term safety of atypical antipsychotics in elderly patients with dementia. The potential for increased risk of stroke and mortality is a serious concern (Carson et al. 2006). Conventional antipsychotics have been shown in a meta-analysis to have modest efficacy in BPSD (Schneider et al. 1990), but their contribution to CVAEs has not so far been examined.

1.3.4.4 Mortality

Atypical antipsychotics have also been linked to death among elderly patients with dementia (Schneider et al. 2005, Wang et al. 2005). In a recent study Gill et al. stated that the use of atypical antipsychotics was associated with an increased risk for death compared with non-use among older adults with dementia (Gill et al. 2007). However, the risk for death may be greater with conventional antipsychotics than with atypical antipsychotics. In a population-based study in

Canada the risk of death associated with conventional antipsychotic medications was comparable to the risk of death associated with atypical antipsychotics (Schneeweiss et al. 2007). In a Finnish study in patients with dementia Raivio et al. stated that neither the use of atypical antipsychotics nor the use of conventional neuroleptics increased mortality. The use of restrain doubled the mortality (Raivio et al. 2007).

2 AIMS OF THE STUDY

The general purpose of the present study was to investigate the prevalence of antipsychotic use among older persons in long-term institutional and home care.

The specific aims of the present study were:

1 To investigate the use of antipsychotic medications, change over time and associated factors in a three-year follow-up among residents in long-term institutional care in 2001-2003 (Study I).
The main question was: Is there any change of the prevalence of antipsychotic use during the study period and which factors would explain the change?

2 To investigate the use of antipsychotic medications and associated factors among nonagenarian residents in long-term institutional care in 2003 (Study II).
The main question was: What is the prevalence of antipsychotic use among nonagenarian institution residents and which factors associate such use?

3 To investigate the factors associated with non-use of antipsychotics among older residents with schizophrenia in long-term institutional care in 2006 (Study III).
The main question was: What is the prevalence of older residents with schizophrenia not having any antipsychotics at the time of the data gathering and which factors are associated with non-use of antipsychotics?

4 To investigate the use of antipsychotic medications and factors associated with such use in elderly patients in home care in Finland in 2004 (Study IV).
The main question was: What is the prevalence of antipsychotic use among home care patients in Finland and which factors are associated with such use?

5 To investigate the use of antipsychotic medications and associated factors in nine European countries in 2001-2002 (Study V).
The main question was: Is there any variation in antipsychotic use among home care patients in nine European countries and which factors contribute to such variation?

3 MATERIALS AND METHODS

Multidimensional functional assessment is the basis of individualized care. It is especially important in the care of elderly, with complex symptoms and often with cognitive impairment. An assessment intrument for elderly people used in this study is the Resident Assessment Instrument (RAI), which was developed in the United States in the late 1980s to improve individual care planning and the quality of care in nursing homes (Morris et al. 1990). In addition, it was designed to estimate the need for resources and develop the payment system. The RAI consists of three basic components: 1. a questionnaire (Minimum Data Set, MDS), 2. a help tool for care planning (Residents` Assessments Protocol, RAPs) and 3. a user manual. Since 1990, interRAI (www.interrai.org), a non-profit international research organisation, has been copyright holder and developer of this system. The interRAI assessment instruments have been introduced in over 30 countries.

The "Benchmarking and the Implementation of the RAI System in Elderly Care" project was lauched in Finland in 2000 on the initiative of STAKES (National Research and Development Centre for Welfare and Health) and the Chydenius Institute in collaboration with the staff of private and public service housing facilities and residential homes and with public health centre wards (Noro et al. 2005).

3.1 Materials

The population data in the various studies (I-V) were drawn from the national RAI database located in STAKES for the period 2001 to 2006.

Every unit in the RAI database joined on a voluntary basis. The recruitment process was through web-page announcements by STAKES and the common interest of the units to improve their caring patterns. Only long-term elderly care units were included in the data. Long-term institutional care includes only hospital-based long-term care units (non-acute ward) and residential homes. All types of institutional setting were included: small and large, urban and rural.

In 2001 there were 16 hospital-based long-term institutions and 25 residential homes that comprised approximately 17% of long-term institutional care for the elderly. In 2006, the data consisted of a total of 24 hospital-based long-term care institutions (103 wards) and 52 residential homes (239 wards). Units in 29 municipalities located in different parts of Finland with 7611 resident assessments represent approximately a crude third of all residents in long-term institutional care. During the study period the same long-term care units remained, only a small proporton was different. The data of each study were derived from the latest available complete national database.

Home care patients in the present study include only regular home-care clients who revieved home nursing or both home nursing and home help services and also had a valid service and care plan. For each of the home care units, each patient who had one assessment was included in the dataset. In order to present reliable outcomes from home care, assisted living was excluded. In addition, the data were derived only from areas where all or almost all patients had been assessed.

3.1.1 Long-term institutional care

The only exclusion criterion was age ≤ 65 years, except that the Study II exclusion criterion was ≤ 90 years. Every person residing in the unit was assessed. Since assessments were part of the care process there were no resident refusals. For each resident only one assessment was included in the data set. In Finland the semi-annual data collection was adapted as optimal to monitor changes in caring patterns.

3.1.1.1 Three-year follow-up (I)

The population data were derived from 16 hospital-based long-term care institutions (55 wards) and 25 residential homes (102 wards) in 14 municipalities. The data were derived from three different timepoints representing the same services. Firstly, the units in the database during the period 1 July to 31 December, 2001 were identified and the individual assessments for relevant parts were included in the analysis. Secondly the same units with their current assessments were identified during the periods 1 July to 31 December, 2002 and 2003. In the study, instead of residents, the units were followed with varying numbers of individuals in each year.

3.1.1.2 Nonagenarians (II)

The population data were derived from 23 hospital-based long-term care institutions (69 wards) and 43 residential homes (190 wards) in 26 municipalities. Every resident aged 90 or older was included in the extracted set. The extracted dataset covered the period from 1 January to 30 June 2003.

3.1.1.3 Residents with schizophrenia (III)

The population data were derived from 7,611 total assessments, of which 2,629 (34.5 %) were hospital-based long-term care institutions (103 wards) and 4,982 (65.5%) residential homes (239 wards) in 29 municipalities. Every resident with a diagnosis of schizophrenia aged 65 years or more was included in the extracted set. Data from all residents with a diagnosis of schizophrenia were gathered and these data comprised 53 hospital-based long-term care wards and 108 residential home wards in 22 municipalities. The extracted data set covered the period from 1 January to 30 June 2006.

3.1.2 Home care

The population data were derived from home care units caring for patients in a certain geographical area in Finland and also in several European countries. The

exclusion criterion was aged <65 years. In addition, those who were no longer resident in their original homes or temporarely residing in institutional settings at the time of the assessment were excluded.

3.1.2.1 Home care in Finland (IV)

The data were derived from 5 home care units in 4 municipalities located in different parts of Finland. The extracted dataset covered the period from 1 July to 31 December in 2004. The data were derived from the latest available full database.

3.1.2.2 Home care in nine European countries (V)

The study population consisted of a random sample of elderly people admitted to the home care programmes in 11 different European Home Health Agencies between 2001 and 2003 and who participated in the The Aged in Home Care (AdHOC) project, under the sponsorship of the European Union (Carpenter et al. 2004). The AdHOC project analysed the structure and organisational characteristics of home care services in 11 European countries along with the clinical and functional characteristics of their patients.

   The population data of Study V were derived from AdHOC Study during the September 2001 – January 2002 11 European countries, from which the data from two countries (Sweden and France) were excluded due to lack of data on medication or inconsistent recording of antipsychotics. The AdHOC Study was designed to compare outcomes of different models of community care using a structured comparison of services and a comprehensive standardised assessment instrument. The samples in each of the countries were gathered from identified municipalities providing formal home care services and a population considered representative of the country's urban area was selected. The participating home care patients were randomly selected from home care agencies serving a certain geographical area. This register led to the creation of a cross-national population-based data set in nine European countries (the Czech Republic, Denmark,

Finland, Germany, Iceland, Italy, the Netherlands, Norway and the United Kingdom).

3.2 Methods

The data collection method was RAI with its care assessment component known as the Minimum Data Set (MDS) for Long-Term Care Facilities (LTCF) and Home Care (HC).

3.2.1 Minimum Data Set (MDS)

The MDS is a standardized primary screening and comprehensive assessment tool for the health care status of residents in nursing homes (Hawes et al. 1995). It was introduced in the United States in response to the United States Congress in the Omnibus Budget Reconciliation Act of 1987. It consists of 18 sections, with items including defined codes concerning physical, psychological and psychosocial functioning. All parts of the RAI are described in the Training Manual (Morris et al. 1995), which gives additional information and precise instructions on how to carry out the assessment.

The MDS was intended for clinical, quality assurance and research purposes. The MDS has been tested for validity and reliability in the US (Hawes et al. 1995) and in other countries such as Sweden and Denmark (Sgadari et al. 1997) and also in Finland (Björkgren et al. 1999). The use of the MDS: the instrument is intended to facilitate communications across disciplines, to inquire about the patient's status over a relevant time period, e.g. seven or 90 days, and to use multiple sources of information from the patient himself/herself, relatives, staff and from medical and nursing records. The assessment is recommended to be originated by nurse, based on interactions between patient and staff in daily contacts, with conversation and the observations of the patient, and performed in co-operation between different professions. On average the assessment takes 60-90 minutes to complete, depending on factors such as the complexity of the patients needs and ability to communicate. The personnel conducting the MDS

42

assessments on each of the wards and home care units had received a minimum of 20 hours` standardized education that included assessments step-by-step according to the training manual (Morris et al. 1995) and the use of software (Boholm 2005).

In addition to interviews with and observations of patients, data were collected from the medical and nursing documents, and from the patients` caregivers including the home care professionals. The diagnoses (ICD-10) were taken from the medical records as recorded by treating physicians (mostly GPs). Due to the high prevalence of dementia in long-term care facilities and in order to ascertain the prevalence of the psychiatric diseases not linked with dementia, the psychiatric diagnoses available in the database were reclassified into a hierarchical order as follows (Studies I-III): 1) all residents with any diagnosed form of dementia, 2) residents without dementia and with schizophrenia, 3) residents without dementia and without schizophrenia but with diagnoses of mood disorders and 4) residents without the above diagnoses but with a diagnosis of anxiety. Medical diagnoses were noted if they were the subject of active treatment or monitoring or if they affected the patient`s current condition.

Information on drug use was collected for 7 days prior to the assessment and included the ACT codes (Anatomical and Therapeutic Chemical code) of antipsychotics N05A, anxiolytics N05B, antidepressants N06A (with the eception of lithium) and hypnotics N05C. Only regularly used prescription drugs were included in the analysis. In addition Studies IV-V included the name and ATC code, formulation, dosage, frequency and mode of administration. Apart from medications for dizziness and/or nausea and lithium, all medications with an ATC code of N05A were coded as antipsychotics. After that the antipsychotics were divided into two categories, conventional (chlorpromazine, chlorprotixene, fluphenazine, flupentixol, haloperidol, levomepromazine, melperone, perphenazine, periciazine, sulpiride, thioridazine, zuclopenthixol) and atypical (clozapine, olanzapine, quetiapine, risperidone). In addition, chlorpromazine equivalents of antipsychotics were calculated using a table as published by Schatzberg (Study IV).

3.2.1.1 Assessment system for the Long Term Care Facility

The first assessment system created by the members of interRAI was the Long Term Care Facility (LTCF). The interRAI LTCF was originally developed in 1988-90 under the US Health Care Financing Administration. The development of MDS/RAI was mandated by the 1987 Nursing Home Reform Law, which also required that it be implemented in all US nursing homes. The MDS-LTCF is a 6 page tool consisting of core screening and assessment items in the following areas: sociodemographic information, prior customary routine, cognition, communication/hearing, vision, mood and behaviour, psychosocial well-being, physical functioning and structural problems, bladder and bowel continence, disease diagnoses, health conditions, oral/nutritional status, dental status, skin condition, activity pursuits, medications, special treatments and procedures, and discharge potential. The condition is coded for whether present or not. The usability of the variables has been tested and validated (Casten et al. 1998, Lawton et al. 1998).

3.2.1.2 Assessment system for Home Care

The Home Care assessment system was developed in 1993-94 to provide a common language for assessing the health status and care needs of frail elderly and disabled individuals living in the community (www.interRAI.org). The system was designed to be comparatible with the Long Term Care Facility system. The HC was designed to highlight issues to functioning and quality of life for community-residing individuals. It consists of the Minimum Data Set for Home Care (MDS-HC) and Client Assessment Protocols (CAPs).

The MDS- HC tool is a 5-page tool designed to collect standardized information on a broad range of domains critical to caring for individuals in the community, including items related to cognition; communication/hearing, vision, mood and behaviour, social functioning, informal support services, physical functioning, continence, disease diagnoses, health conditions, preventive health measures, nutrition/hydration, dental status, skin condition, environment/home safety, service utilization, medications and socio-demographic/background information.

The reliability and validity of the MDS-HC data elements and its embedded scales have been demonstrated through a series of on-going international studies (Landi et al. 2000, Morris et al. 1997). In addition to interviewing and observing the patients, data were collected from the medical and nursing documents, and from the patients' caregivers including the home care professionals.

3.2.1.3 Scales

The Cognitive Performance Scale (CPS) was combined within the hierarchical seven-category from five of the RAI/MDS items from different sections MDS with the levels 0-6 (intact-very severe impairment) (Morris et al. 1994, Hartmaier et al. 1995). The CPS includes the RAI/MDS items: short-term memory, cognitive skills for daily decision-making, ability to be understood by others, self-performance in eating, and comatose. The CPS has been evaluated against two standard cognitive assessment tools, The Mini Mental State Examination (MMSE) (Folstein et al. 1975) and the Test for Severe Impairment (TSI) (Albert and Cohen 1992), with a high degree of reliability (Morris et al. 1994, Hartmaier et al. 1995, Paquay et al. 2007).

The Activities of Daily Living Hierarchy Scale (ADL) groups activities of daily living according the stage of the disablement process in which they occur. The ADL Hierarchy Scale ranges from 0 (low impairment) to 6 (total dependence) (Morris et al. 1999). The four items used to score the hierarchical ADL-scale (0-6) are personal hygiene, toileting, locomotion and eating. Early loss ADL`s (e.g. dressing) are assigned lower scores than late loss ADL`s (e.g., eating)

The Depression Rating Scale (DRS) was used to screen for depression in nursing home residents where at least 3 points refer to probability of depression (Burrows et al. 2000). The 7-item scale was derived from mood and behavioural items in the Minimum Data Set. The DRS validated against two interview-based criterion measures, the Hamilton Depression Rating Scale and the Cornell Scale for Depression in Dementia, both of which have been tested and validated in geriatric populations (Burrows et al. 2000). The DRS items are: 1. residents

made negative statements 2. persistent anger and irritability with self and others 3. expression of what appear to be unrealistic fears 4. repetitive health complaints 5. repetitive anxious complaints/concerns (non-health-related) 6. sad, pained, worried facial expressions 7. crying, tearfulness.

3.3 Statistical methods

In all studies the associations of the use of antipsychotics with selected explanatory variables were tested using chi-square tests for the dichotomous variables and t-tests for the continuous variables. Continuous variables were first categorized and then dichotomized to form 0 or 1 dummy variables. The associations between these variables and the use of antipsychotics were then tested using chi-square test. Statistically significant factors according to univariate tests were included one by one in the multiple logistic regression model to test the independently associated factors.

Specifics of different studies are given:

Study I. After identifying the significant associates of use of antipsychotics in 2001, these variables were entered into a multiple logistic regression model that represented 2001 only. The following step was to separately test this model using the same variables that provided significance in 2001, using data from 2002 and then data from 2003. R-square for variance explanation was recorded in each of the multiple logistic regression analyses. Finally, the interactions between the independent variables and time-points were tested for the whole population to identify the most potent predictors of use of antipsychotics (see e.g. Häkkinen et al. 1996, Häkkinen 2002). Changes over time (i.e. level of prevalence of antipsychotics use compared to 2001) were estimated in the multiple logistic regression model using data from all three time-points and creating dummy variables for each of the years and each of the predictors identified for use of antipsychotics, which thus allowed the monitoring of confounder adjusted changes. All the procedures were performed step by step.

46

Study II. In addition to existing variables a summary scale was formed in which the new dichotomous variables was 0 if no sign in any individual item of entities "sense of initiative/involvement" or " unsettled relationships" was found and 1 if any of them was present. These new variables were likewise first tested separately.

Study III. All associations in both dichotomous and continuous variables as well as multivariate analysis were calculated for non-use of antipsychotics.

Study IV. The significant dichotomous and continuous variables were also analysed in multivariate model separately within the groups of both atypical and conventional antipsychotics.

Study V. The site at which the frequency of antipsychotic use was lowest was used as a reference. After testing for the associations between chosen variables and total number of antipsychotics, the same tests (dichotomuos, continuous and multivariate) were performed using typical and atypical antipsychotics separately as dependent variables.

p-values less than 0.05 were considered statistically significant. The data was analysed at STAKES and all statistical analyses were performed using SAS version 8.2 (SAS Institute Inc., Cary, North Carolina, USA).

3.2 Ethical considerations

The study was conducted according to the guidelines of the Declaration of Helsinki, and the Ethical Commitee of Tampere University Hospital. The STAKES Ethical Commitee and the Ministry of Social Welfare and Health have approved the RAI data collection.

4 RESULTS

4.1 Long-term institutional care (I, II, III)

4.1.1 Characteristics of residents

Sociodemographic and main clinical background data of the residents in Studies I-III are given in Table 3 and Table 4.

Table 3. Sociodemographic characteristics of residents in long-term institutional care according to Studies I-III.

	Three-year follow-up, 2001 (I)	Three-year follow-up, 2002 (I)	Three -year follow-up, 2003 (I)	Nonagenarian residents, 2003 (II)	Residents with schizophrenia 2006 (III)
N	3662	3969	3867	1334	356
Mean age in years	82.9 $\pm$7.74	83.0 $\pm$7.56	83.1$\pm$7.69	92.9 $\pm$ 2.7	78.2 $\pm$ 7.5
Age group, %					
65-74	16.0	14.9	14.7	-	32.9
75-84	38.6	39.6	39.1	-	46.9
85-94	40.0	40.5	40.8	76.0 (90-94 y)	13.2
95+	5.4	5.0	5.4	24.0	7.0
Sex, %					
Women	75.5	75.4	75.9	87.8	77.5
Previous mental health history	12.6	11.0	10.0	5.5	72.2
Arrived from a psychiatric hospital	4.9	4.2	3.6	1.5	23.9

Table 4. Clinical data of residents in long-term institutional care according to Study I-III.

	A three-year follow-up, 2001 (I)	A three-year follow-up, 2002 (I)	A three-year follow-up, 2003 (I)	Nonagenarian residents, 2003 (II)	Residents with schizophrenia, 2006 (III)
Documented diagnoses, %					
Any dementia	54.9	57.4	57.5	58.6	24.2[*]
Schizophrenia [a]	4.6	3.9	3.9	1.0	100[*]
Depression[b]	15.3	15.6	15.7	11.5	8.4[*]
Anxiety disorder[c]	2.2	2.4	2.0	2.2	2.5[*]
Psychiatric and behavioural symptoms, %					
Delusions	10.4	10.6	10.5	9.5	37.4
Hallucinations	14.7	14.4	14.4	12.8	40.5
Reason to suspect depression (DRS= 3+)[§]	22.0	22.9	21.9	21.1	21.6
Wandering	18.0	19.0	18.4	15.1	17.4
Verbally abusive	21.3	20.2	19.2	14.8	35.7
Physically abusive	11.6	11.6	11.3	9.1	14.3
Socially disruptive	22.9	22.4	21.9	20.7	36.8
Resists care	30.0	30.5	30.0	30.7	43.3
Recurring anxious complaints	-	-	-	21.9	27.5
Recurring physical movements	-	-	-	28.9	35.7
Cognition and physical functions, %					
CPS[#] 0	9.1	8.1	7.1	8.8	6.2
CPS 1-2	21.0	18.9	19.4	19.5	32.3
CPS 3-6	69.9	72.0	73.5	71.4	61.5
ADL[##] 0	7.2	8.1	7.1	6.2	7.9
ADL 1-2	18.1	18.9	19.4	15.2	26.4
ADL 3-6	74.7	73.0	73.5	78.6	65.7
Psychotropic medication, %					
Antipsychotics	41.6	40.4	38.6	29.5	81.5
Antidepressants	41.6	42.4	41.5	33.8	27.3
Anxiolytics	35.0	34.6	32.8	26.4	46.6
Hypnotics	41.0	37.5	33.2	33.7	21.9

a: without dementia, **b**: without dementia and schizophrenia, **c**: without dementia, schizophrenia and depression, [*]: Concomitant with schizophrenia, **§** DRS: Depression Rating Scale ≥3 indicates depression, **#** CPS: Cognitive Performance Scale: 0 no cognitive impairment, 1-2 mild cognitive impairment, 3-6 moderate to severe cognitive impairment, **##** ADL: Activities of Daily Living Scale: 0 no dependence on assistance with daily living, 1-2 mild degree of dependence on assistance with daily living, 3-6 moderate to severe degree of dependence on assistance with daily living

4.1.2 Prevalence of antipsychotic use

The prevalence of antipsychotic use was 41.7% in 2001, 40.4% in 2002, and 38.6% in 2003 (I). However, the overall confounder-adjusted decrease in antipsychotic use was not statistically significant. The proportion of nonagenarian residents prescribed one or more antipsychotics was 29.5% of the study population in 2003 (II). The prevalence of antipsychotic use among older schizophrenia residents in 2006 was 81.5%, thus 18.5% of residents with schizophrenia were not on antipsychotic medication (III).

4.1.3 Multivariate results

In 2001-2003 the use of antipsychotics decreased with among residents who had wandering as a behavioural problem [odds ratio (OR) 0.79, 95%CI 0.63-0.99] and increased among residents with concomitant use of anxiolytic medications (OR 1.23, 95%CI 1.03-1.48) (I).

Factors independently associated with the use of antipsychotics among nonagenarian residents were: socially inappropriate or disruptive behavioural symptoms (OR 1.86, 95%CI 1.36-2.54), concomitant anxiolytic medication (OR 1.83, 95%CI 1.39-2.42), recurring anxious complaints (OR 1.61, 95%CI 1.17-2.22), recurring physical movements (OR 1.43, 95%CI 1.08-1.91) and unsettled relationships (OR 1.35, 95%CI 1.15-1.57) (II). A good sense of initiative or involvement were significantly less likely to be associated with antipsychotics (OR 0.86, 95%CI 0.80-0.94). There were no associations between any psychiatric diagnoses or symptoms and the use of antipsychotics.

Factors independently associated with non-use of antipsychotics among residents with schizophrenia were: severe degree of functional impairment (OR 3.21, 95%CI 1.61-6.42), severely impaired vision (OR 2.62, 95%CI 1.26-6.61), any diagnosis of dementia (OR 2.58, 95%CI 1.38-4.81) and severe underweight (OR 2.20, 95%CI 1.15-4.17) (III). There was a negative association between non-use of antipsychotics and a factor "had arrived from a psychiatric hospital" (OR 0.31, 95%CI 0.12-0.81).

4.2 Home care (IV, V)

4.2.1 Characteristics of patients

The sociodemographic and main clinical background data of the patients in Studies IV-V are given in Table 5.

4.2.2 Prevalence of antipsychotic use

The prevalence of antipsychotic use was 11.0% among home care patients in Finland in 2004 (IV). Of the home care patients in nine European countries (the Czech Republic, Denmark, Finland, Germany, Iceland, Italy, the Netherlands, Norway and the United Kingdom) 6.2% received antipsychotic medication (V). The prevalence of the use of one or more antipsychotics varied widely between study sites, ranging from 3.0% in Denmark to 12.4% in Finland.

4.2.3 Multivariate results

Factors independently associated with the use of antipsychotics in Finland were: any psychiatric diagnosis (OR 6.62, 95%CI 4.19-10.45), delusions (OR 4.19, 95%CI 2.22-7.90), parkinsonism (OR 3.08, 95%CI 1.07-8.87), not at ease interacting with others (OR 1.88, 95%CI 1.06-3.36), and moderate to severe cognitive impairment (OR 1.47, 95%CI 1.06-2.04) (IV). By contrast, patients 85 years and older were significantly less likely to be taking antipsychotics (OR 0.59, 95%CI 0.43-0.81). The use of atypical antipsychotic medication was associated in the logistic regression model with delusions (OR 4.05, 95%CI 2.01-8.17), parkinsonism (OR 3.66, 95%CI 1.10-12.19), any psychiatric diagnosis (OR 3.06, 95%CI 1.66-5.63), moderate to severe cognitive impairment (OR 2.0, 95%CI 1.32-3.03) and age 85 and older (OR 0.66, 95%CI 0.44-0.99).

Table 5. Sociodemographic characteristics and main clinical data of patients in home care according to Studies IV and V.

	Home care in Finland (IV)	Home care in nine European countries (V)
N	1106	3251
Mean age in years	81.2 (±6.9)	82.2 (±7.3)
Age group, %		
65-74	15.8	17.7
75-84	51.5	44.8
85-94	31.0	38.1 (85+ y)
95+	1.6	
Sex, %		
Women	74.4	74.4
Documented diagnoses, %		
Any dementia	17.5	12.3
Any psychiatric	13.1	13.2
Parkinsonism	2.0	4.9
Psychiatric and behavioural symptoms, %		
Delusions	5.8	2.3
Hallucinations	3.1	2.5
Reason to suspect depression (DRS= 3+)[§]	17.5	16.1
Wandering	4.0	0.8
Verbally abusive	3.6	0.7
Physically abusive	0.5	0.3
Socially disruptive	1.7	0.4
Resists care	5.0	1.0
Not at ease interacting with others	9.6	11.6
Cognition and physical functions, %		
CPS[#] 0	40.8	53.2
CPS 1-2	47.3	28.6
CPS 3-6	11.8	18.2
ADL[##] 0	77.5	69.6
ADL 1-2	13.5	10.8
ADL 3-6	9.0	19.6
Psychotropic medication, %		
Antipsychotics	11.0	6.2
Antidepressants	24.3	14.9
Anxiolytics	12.7	11.1
Hypnotics	44.2	19.7

§ DRS: Depression Rating Scale ≥3 indicates depression, # CPS: Cognitive Performance Scale: 0 no cognitive impairment, 1-2 mild cognitive impairment, 3-6 moderate to severe cognitive impairment, ## ADL: Activities of Daily Living Scale: 0 no dependence on assistance with daily living, 1-2 mild degree of dependence on assistance with daily living, 3-6 moderate to severe degree of dependence on assistance with daily living

However, the use of conventional antipsychotics was only associated with any psychiatric diagnosis (OR 8.88, 95%CI 5.05-15.61) and age 85 and older (OR 0.65, 95%CI 0.44-0.98) (see Study IV Table 2).

Factors independently associated with the use of antipsychotics in nine European countries were: delusions (OR 3.09, 95%CI 1.66-5.76), any diagnosis of dementia (OR 2.57, 95%CI 1.70-3.87), youngest age group (65-74 years) (OR 2.37, 95%CI 1.53-3.66), and hallucinations (OR 2.28, 95%CI 1.17-4.45). Concomitant use of anxiolytics (OR 2.32, 95%CI 1.58-3.41), hypnotics (OR 2.08, 95%CI 1.44-3.03) and antidepressants (OR 2.06, 95%CI 1.41-3.00) likewise signs of depression (OR 1.78, 95%CI 1.24-2.56), moderate to severe cognitive impairment (OR 1.30, 95%CI 1.12-1.51), and residing in Finland (OR 2.52, 95%CI 1.21-5.24) or Italy (OR 2.15, 95%CI 1.10-4.19) were associated with the use of antipsychotics (see Study V Table 3).

4.3 Summary of the results

Statistically significant findings of the different studies are listed in Table 6.

Table 6. Summary of final statistically significant findings.

	Three-year follow-up in long-term institutional care, (I)	Nonagenarian residents in long-term institutional care, (II)	Residents with schizophrenia in long-term institutional care, (III)[#]	Home care in Finland (IV)	Home care in nine European countries (V)
Age group					
Age group 65-74					+
Age group 85+				-	
Diagnosis					
Any psychiatric				+	
Dementia			+		+
Parkinsonism				+	
Psychiatric and behavioural symptoms					
Socially disruptive		+			
Delusions				+	+
Hallucinations					+
Depression					+
Wandering	-				
Recurring anxious complaints		+			
Recurring physical movements		+			
Unsettled relationships		+			
Sense of initiative/involvements		-			
Not at ease interacting with others				+	
Concomitant psychotropics					
Anxiolytic	+	+			+
Hypnotic					+
Antidepressants					+
Cognitive and functional impairment					
Moderate to severe cognitive impairment				+	+
Severe degree of functional impairment			+		
Others					
Arrived from a psychiatric hospital			-		
Impaired vision			+		
Underweight			+		
Finland					+
Italy					+

= Association with the non-use of antipsychotics

+ = Positive association, **-** = Negative association

5 DISCUSSION

5.1 Main findings

The prevalence of the use of one or more antipsychotic medications in long-term institutional care in Finland was high, up to 42% (Study I). In the recent studies from various countries, the prevalence of use of antipsychotic medication among nursing home residents has varied between 15% (Liperoti et al. 2003) and 41% (Margallo-Lana et al. 2001). The findings of the present study are in accordance with an earlier Finnish study in which the prevalence of antipsychotic use among nursing home residents in Helsinki was 42.6% (Hosia-Randell and Pitkälä 2005). The prevalence of antipsychotic use in long-term institutional care decreased from 42% in 2001 to 39% in 2003. However, the overall confounder-adjusted decrease in antipsychotic use was not statistically significant.

In the present study the prevalence of antipsychotic use was constantly high and the caring patterns in 2001-2003 were quite stable. Adequate indications may not have been fulfilled in all cases. According to quality indicators based on the RAI the limit of good care in long-term institutional care has defined such that the prevalence of use of antipsychotics without any psychotic disorder or symptom should be below 13.4% (Zimmerman et al. 1995, Noro et al. 2005). The limit of excellent care is 5.4% among those residents without a psychotic disorder or psychotic symptoms. In high risk residents (impaired cognition and behavioural symptoms), the limit of good care is respectively 21.3% and excellent care 8.4% (Noro et al. 2005).

Antipsychotic medication use among institutionalized nonagenarian residents was also very common, almost 30% (Study II). This finding concurs with that of Hosia-Randell and Pitkälä, who found that 31% of nonagenarian residents in nursing homes were taking antipsychotics (Hosia-Randell and Pitkälä 2005).

Although studies on antipsychotic medication use frequency in such very high age populations are rare, there are some earlier studies reporting 25-28% prevalence of antipsychotic medication use (Oborne et al. 2002, Briesacher et al. 2005). The residents in these earlier studies have been somewhat younger than the population in the present Study II. In any case, Lindesay et al. reported lower use (17%) of antipsychotics in nursing home residents aged >85 years (Lindesay et al. 2003). Accordingly, in Study II the antipsychotic use was three times more common than one earlier study from Sweden (Skoog et al. 1993).

The main finding of the study on older residents with schizophrenia in long-term institutional care was that approximately every fifth was not on any antipsychotic medication at all (Study III). Although the studies on antipsychotic medication use frequency in older residents with schizophrenia are sparse, this finding concurs with some earlier studies on older schizophrenic residents in nursing homes, where 15-19% were not receiving any antipsychotic medication (Bowie et al. 2001, Snowdon et al. 2005).

The main finding of the study of home care patients in Finland (Study IV) was more frequent use of antipsychotics (11.0%) than previously reported in home-dwelling elderly people in Finland and Sweden (3% to 9%) (Giron et al. 2001, Linjakumpu et al. 2002, Hartikainen et al. 2003a). Of home care patients in nine European countries 6.2% received antipsychotic medication (Study V), which was in line with earlier reports on home-dwelling elderly people (3% to 11%) (Giron et al. 2001, Linjakumpu et al. 2002, Hartikainen et al. 2003a, Linden et al. 2004, Rapoport et al. 2005). Frequency of use of one or more antipsychotic varied widely between study sites, ranging from 3.0% in Denmark to 12.4% in Finland. The mean consumption was somewhat higher than has been reported in the general population (from 1% to 1.4%) (Alonso et al. 2004, Percudani et al. 2005, Trifiro et al. 2005).

5.2 Specific findings

5.2.1 Long-term institutional care

There were several factors associated with the use of antipsychotics in a single study and some factors in more than one study.

5.2.1.1 Wandering and anxiolytics in institutionalized residents (I)

In 2001-2003 the use of antipsychotics decreased among residents who had wandering as a behavioural problem. However, the use of antipsychotics increased in those residents concurrently taking anxiolytics. There is surprisingly little published information about change in antipsychotic medications use and associated factors over time in nursing homes. In one earlier study in the UK Lindesay et al. have reported that the prescription rate of antipsychotics increased from 18% in 1990 to 22% in 1997 (Lindesay et al. 2003). In that report the only significant change in antipsychotic prescribing practice was an increase in the prescription rate in cognitively unimpaired residents in 1997, possibly related to mental hospital closures.

Wandering behaviour prevalence in the present Study I at 19% roughly matches the prevalence of 15-28% previously reported (Dawson and Reid 1987, Cooper et al. 1990, Cooper and Mungas 1993, Klein et al. 1999, Schonfeld et al. 2007) though as low rates as 6.5% (Sloane et al. 1998) and high as 63% (Hope et al. 1994) have also been reported. The different patient populations such as severity and type of dementia, as well as the different definitions of wandering may account for this variation. Although definitions vary, wandering refers to seemingly aimless or disoriented ambulation throughout a facility, often with obserable patterns such as lapping, pacing or random ambulation (Algase et al. 2003). The MDS procedural manual describes wandering as "locomotion with no discernible, rational purpose" and differentiates wandering from purposeful movement.

Wandering behaviour and antipsychotic medication use have been associated in several earlier studies (Klein et al. 1999, Lövheim et al. 2006, Schonfeld et al. 2007). However, the prevalence of reported antipsychotic use associated with wandering behaviour has been 23% (Klein et al. 1999) compared to prevalences of 55% to 63% in Study I. The management of BPSD represents a significant part of the day-to-day workload of clinicians treating with dementia patients in institutional settings. Of all behavioural symptoms associated with dementia, wandering is among the most problematic from the perspective of resident management and safety. It has been reported that wandering, use of antipsychotics and also anxiolytics, were all correlated with falls (French et al. 2007b), causing e.g. hip fractures, especially in female patients (Cohen-Mansfield et al. 1991, Colon-Emeric et al. 2003).

Although the use of antipsychotics decreased between 2001 and 2003 among wandering residents, more than half of the wandering residents were still taking antipsychotic medication in 2003. Antipsychotics frequently have harmful adverse effects and show only modest efficacy in managing many behavioural problems in dementia (Ballard and O'Brien 1999, Howard et al. 2001). It is possible that in some cases antipsychotic adverse effects may be rated as wandering instead of akathisia (Wise and Tierney 1992), affective instability or general restlessness due to diverse neurological or psychiatric conditions.

The overall high use of antipsychotics among the present residents with wandering-related behaviour (55-63%) suggests a need to review the indications themselves. However, not all wandering should be deemed problematic in the sense that the resident keeps active (Cohen-Mansfield and Werner 1998, Yao and Algase 2006). Within institutions, a variety of environmental manipulations are often introduced to decrease the behaviours (Robinson et al. 2007). Fossey and co-workers have demonstrated that antipsychotic therapy was reduced by 19% following the introduction of a training and support intervention that focused on alternatives to drug use for the management of agitated behaviour (Fossey et al. 2006). Key elements in that programme involved initial skill training, behavioural management techniques, and ongoing training and support.

There was a positive association between the change in the use of antipsychotics and concomitant use of anxiolytics in the present residents. During the follow-up period this use increased in those residents who concomitantly used anxiolytics. Approximately every third residents was taking anxiolytics and more than half of them received concomitant antipsychotics. In 1990-1991 among the home-dwelling elderly in Finland, the prevalence of a combination of hypnotic/sedative and antipsychotic medications was only 3% (Linjakumpu et al. 2002). However, the institution residents in the present Study I were ten years older than those in the study by Linjakumpu et al.

5.2.1.2 Negative attitudes to others in nonagenarians (II)

In this study, factors associated with the use of antipychotics among nonagenarian residents were investigated. The most interesting finding was an increasing risk of antipsychotic use among querulous residents and decreasing risk among those with good social skills. The behavioural items independently associated with the use of antipsychotics among nonagenarian residents were socially inappropriate or disruptive behavioural symptoms, recurring anxious complaints, recurring physical movements and unsettled relationships, all of which are inappropriate indications for antipsychotic use. However, these findings concur with those of Briesacher and coworkers, who stated that nonaggressive behavioural problems, such as restlessness (51.7%), unsociability (34.2%), uncooperativeness (30.4%) and indifference to their surroundings (25.1%), were common among residents receiving inappropriately prescribed antipsychotics (Briesacher et al. 2005). Individuals who have a good sense of initiative or involvement were less likely to receive antipsychotic medication. They could interact easily with others and were involved in group activities and responded positively to new activities. However, there were no associations between any psychiatric diagnoses or symptoms and the use of antipsychotics among nonagenarian residents. Furthermore, there was no association between diagnosis of dementia or cognitive impairment and the use of antipsychotics.

Clearly defined indications for antipsychotic use among nonagenarian residents in the present study may not be fulfilled in many cases. In a recent study a large discrepancy has been reported between mental health diagnoses and the use of antipsychotics (French et al. 2007). However, the frequent use of antipsychotics among the present residents does not necessarily indicate misuse of these drugs, but there is a considerable gap between the recommendations for antipsychotic medication and clinical practice (Alanen et al. 2006). According to some recommendations, 18% to 19% would be appropriate use of antipsychotic medications (Oborne et al. 2002, Briesacher et al. 2005). In a recent Canadian study one out of six residents in nursing homes received antipsychotics without appropriate clinical indication (Rochon et al. 2007). Rather, the decision to prescribe an antipsychotic medication appeared to be related to the nursing home environments, with some environment being more permissive than others regarding antipsychotic use. Prescribing decisions in practice was usually based on clinical information provided by the nursing home staff. Sorensen et al. have reported that staff perceptions of psychiatric morbidity and norms may have a greater impact on the prescription of antipsychotics than standardised clinical criteria (Sorensen et al. 2001).

The risk of inappropriate use of antipsychotics might be especially high in those nonagenarian residents who were querulous or were involved in staff-resident friction. However, it may possible to make a reliable distinction of these attitudes from behavioural symptoms. In a recent Swedish study, Lövheim and co-workers suggested that antipsychotic treatment among dementia patients in geriatric care is determined not only by the resident's symptoms but also by factors related more closely to the caregiver and the caring situations (Lövheim et al. 2006).

There is concern that once antipsychotic medication has started it is rarely discontinued despite adverse effects. The average length of time that residents in long-term care facilities in Canada had been receiving antipsychotic medications was 0.87 years (Hagen et al. 2005). In that study only 16% of all antipsychotic prescriptions demonstrated evidence of dose reduction within six months of the

60

prescription being written. However, it has been recommended that when antipsychotics are administered to patients with dementia, long-term treatment should be avoided if at all possible and that treatments should be reviewed regularly, preferably with trial discontinuation at 3-6 monthly intervals (Alexopoulos et al. 2004, Ballard and Howard 2006, Pirttilä et al. 2006). It has suggested that approximately 25% of patients on antipsychotic therapy in the nursing home could have their antipsychotics safely discontinued (Courtney 1994). Three recent placebo-controlled withdrawal studies among patients with dementia reported that in many cases there is no deterioration of behaviour when antipsychotic medications were discontinued (Bridges-Parlet et al. 1997, Cohen-Mansfield et al. 1999, Ballard et al. 2004). In the present Study III the portion of nonagenarian residents whose antipsychotic medication had been experimentally discontinued was unknown.

5.2.1.3 Dependence and functional impairment in residents with schizophrenia (III)

The proportion of nursing home residents with schizophrenia has varied from 6% to 7% in the US and Australia, whereas according to this study it was 4.8% in Finland (Gurland and Cross 1982, McAlpine and Mechanic 2000, Snowdon et al. 2005). Interestingly, the present proportion of those residents with schizophrenia without any antipsychotic medication (19%) concurs with earlier studies (15-19%) (Bowie et al. 2001, Snowdon et al. 2005). The results suggested that residents with schizophrenia in later life without any antipsychotic medication were those with greater dependence and impaired functional capacity. Any diagnosis of dementia, severe underweight and severely impaired vision was associated with non-use of antipsychotics among these residents.

Harvey et al. found that nursing home residence was associated with more severe negative and cognitive, as well as greater functional impairment than among community dwellers and psychiatric inpatients (Harvey et al. 1999). In the present study approximately two out of three residents with schizophrenia had a severe degree of cognitive and functional impairment. Among the nonusers of antipsychotics this prevalence was even higher, 76% and 80% respectively. It

has also been reported that the severity of negative symptoms correlated inversely with functional status in older schizophrenic residents (Palmer et al. 2002). In the present study population, however, negative symptoms may be difficult to identify because of confounding effects such as cognitive impairment, depression and institutionalization.

Malnutrition is a common problem among older people living in nursing homes (Suominen et al. 2005, Wojszel 2006). According to an earlier Finnish study one third of nursing home residents were suffering from malnutrition (Suominen et al. 2005). Accordingly, 42% of the nonusers of antipsychotics in the present study were severely underweight (body mass index <20) compared to 19% of users of antipsychotics. It has been reported that risk factors for being underweight are cognitive and functional decline, eating dependencies and swallowing difficulties (Suominen et al. 2005, Wojszel 2006). Nutrition in geriatric psychiatry has been stated to be a neglected field (Bhat et al. 2005), although undernutrition appears to be an independent risk factor for morbidity and mortality (Pirlich and Lochs 2001, Guigoz et al. 2002). Research on Alzheimer`s disease suggests that weight loss precedes the clinical onset of the dementia in Alzheimer`s disease (Barrett-Connor et al. 1996). However, present residents with schizophrenia who were not receiving any antipsychotics often also had dementia and a severe degree of functional impairment and may have had swallowing difficulties. Some of the non-users may have needed to be fed.

The reason for the association between impaired vision and non-use of antipsychotics in the present study is unknown, because of the lack of documentation of medical history. Conventional antipsychotics such as phenothiatzines may cause retinopathies, which may be severe and irreversible (Fornaro et al. 2002). This severe progressive visual loss may occur several years after the cessation of chronic thioridazine treatment for example (Chaudhry et al. 2006). In some of the present non-users of antipsychotics, medication may have been discontinued due to vision problems.

5.2.2 Home care

5. 2.2.1 Problems in social functioning in home care patients (IV)

Several predictive factors such as psychiatric diagnosis, delusions and cognitive impairment were associated with the use of antipsychotics whereas there was a negative association between age and the use of antipsychotics. Of the home care patients in Study IV, one in ten had problems in social functioning indicated by "not at ease interacting with others" (e.g. patients did not like to spend time with others) and 29% of them were taking antipsychotics. Antipsychotics might be used in many cases to relieve symptoms associated with lack of social contacts or poor life satisfaction. In Study IV two thirds of the patients were living alone. However, this was not independently associated with the use of antipsychotic medication.

Antipsychotic medication use among home care patients in Finland with any psychiatric diagnosis was decidedly high 40% (Study IV). The use of antipsychotics in this group was associated both with conventional and to a lesser extent with atypical antipsychotics. However, the psychiatric diagnoses subsumed under this criterion were heterogeneous, and included diagnoses such as schizophrenia, delusional disorder on the one hand mood and anxiety disorder on the other. In addition, these patients may or may not have had a concomitant diagnosis of dementia.

The prevalence of parkinsonism was 2.1% in the Study IV population and every fourth patient with parkinsonism was on antipsychotic medication. Psychosis is a frequent complication of Parkinson`s disease (PD) affecting 15 to 40% of patients (Aarsland et al. 1999, Fenelon et al. 2000). On the other hand, a recent study has shown that the use of antipsychotic medications, age and disability were strong predictors of developing PD (Noyes et al. 2006). It has been demonstrated that only in a small proportion of elderly patients with PD receiving antipsychotics had their antipsychotic medication been discontinued before starting antiparkinsonian medications (Simon et al. 2005).

In addition to Parkinson`s disease, parkinsonism may complicate many brain disorders such as Alzheimer`s disease and Lewy body dementia (LBD). Postmortem findings suggest that LBD may account for as many as 20% to 34% of all dementia cases and is often underdiagnosed (Luis et al. 1999). It is estimated that 75% of LBD patients will develop parkinsonian features during the course of their illness (McKeith et al. 1999). LBD is important because of the difficult clinical management issues caused by the high frequency of psychiatric symptoms (Baskys 2004) and the risk of severe antipsychotic sensivity reactions (Ballard et al. 1998). Visual hallucinations and delusions are more common in LBD than in AD (McShane et al. 1995, Ballard et al. 2001b).

In Study IV one in two of those patients on antipsychotic treatment were on conventional antipsychotics, whereas in some earlier reports this proportion has been less than 40% (Snowdon et al. 2005, Wang et al. 2005). Conventional antipsychotics especially may cause movement disorders and other motor side effects. However, drug-induced parkinsonism has also been described with a great diversity of other compounds such as antiemetics, drugs used for the treatment of vertigo and antiepileptics (Mena and de Yebenes 2006). At least 10% of patients with drug-induced parkinsonism develop persistent and progressive parkinsonism in spite of the discontinuation of the causative drug (Mena and de Yebenes 2006). Friedman et al. reported that parkinsonism was a very common and underdiagnosed condition among elderly residents taking antipsychotics in nursing homes (Friedman et al. 2004). In Study IV, however, the causal relationship between parkinsonism and antipsychotics was obscure in the elderly receiving home care services. In patients requiring antipsychotic medication, adequate monitoring is needed for early parkinsonian symptoms and rapid discontinuation if these occur. Although the antipsychotic medication doses of both atypical and conventional antipsychotics were low in Study IV (overall mean dose in chlorpromazine equivalents 75.8 mg/day), there is a possibility that a greatly increased total proportions of patients treated with (atypical) antipsychotics in a growing population might paradoxically even lead to increased total numbers of patients with EPS and TD (Lohr et al. 2004).

Patients with severe mood disorders may be especially at risk also when using atypical antipsychotics (Kane 1999).

5.2.2.2 Antipsychotic use in home care patients in Finland and Italy (V)

Antipsychotic use among home care patients in nine European countries varied widely (3.0% to 12.4%). This wide variation may primarily be attributable to the differences in health care systems and in care practices, or to different attitudes to antipsychotic therapy in different countries. In Finland (12.4%) and Italy (11.2%) antipsychotic use was more than twice as common as in Denmark (3.0%) when adjusted for confounders. In accordance with these results, a high prevalence of antipsychotic medication use in the elderly has also been previously reported in institutional care in Finland as well as in Italy (Hughes et al. 2000, Hosia-Randell and Pitkälä 2005). The high level of use of antipsychotics both in home and long-term institutional care may reflect the overall prescribing tradition pertaining to the use of antipsychotic medications for elderly people in Finland and Italy.

Around 3% of the patients in Study V had hallucinations, which matches the prevalence of hallucinatory symptoms 4% previously reported among dementia sufferers living in resident care environments in the UK (Margallo-Lana et al. 2001). However, the rate of hallucinations in the present study was substantially lower than reported in the review of 55 studies of AD patients where the median prevalence of hallucinations was 18% (Ropacki and Jeste 2005). Interestingly, only one fourth of subjects with hallucinations in the present study were on antipsychotic treatment, which concurs with one earlier report (Östling and Skoog 2002). However, hallucinations may lead to subjective distress on the part of the patients and have adverse effects on caregivers. The early recognition of hallucinations and interpretation of underlying etiologies coupled with the initiation of appropriate treatment interventions will reduce morbidity and improve the quality of life for these patients.

Depression in the present patients was also associated with the use of antipsychotics this concurs with several earlier studies (Giron et al. 2001,

Lövheim et al. 2006). Altogether 12% of the present patients with depression symptoms were taking antipsychotics. In one report from nine European centres, depressive psychosis prevalence ranged from 2% to 11% (Copeland et al. 1999). However, the exact proportion of psychotically depressed patients in the present study is unknown. Concomitant use of antipsychotics and other psychotropics was common in the present population, which concurs with earlier studies (Hughes et al. 2000, Hartikainen et al. 2003a, Hartikainen et al. 2003b, Holmquist et al. 2005, Kim and Whall 2006). In a Finnish study on the home-dwelling elderly the proportion of psychotropic combinations was 10% among elderly people without dementia and as high as 26% among those with dementia (Hartikainen et al. 2003b).

5.2.3 Other important factors and antipsychotic use

5.2.3.1 Younger age in elderly people and antipsychotic use (IV, V)

Based on the results of home care Studies IV and V the likelihood of receiving antipsychotic treatment was more common in the youngest age group (65-74 years). In Study IV, the patients 85 years and older in home care in Finland were significantly less likely to be taking antipsychotics. This may conflict with some earlier studies in which the likelihood for the use of antipsychotics increased with age (Hartikainen et al. 2003a, Percudani et al. 2005, Trifiro et al. 2005). However, the results of the present study agree with some other studies in which the frequency of antipsychotic use was lower among the oldest age groups in nursing homes (Liperoti et al. 2003, Hosia-Randell and Pitkälä 2005). Differences in the study populations may explain this discrepancy and one explanation for the more common antipsychotic use in the youngest age group may be the more frequently troublesome disruptive behaviour in this age group. Medications may thus have been given for purposes of social control. Another explanation for the lower use in the oldest age group may be that these medications are considered especially harmful to the oldest patients. Indeed,

these individuals are the most sensitive to antipsychotic medication adverse effects and the relevant indications should be more carefully evaluated.

5.2.3.2 Dementia and antipsychotic use (III, IV, V)

Severe degree of cognitive impairment was associated with use of antipsychotics in Studies IV and V. Diagnosis of dementia was associated with antipsychotic use among home care patients in nine European countries (Study V) and with non-use of antipsychotics among residents with schizophrenia in long-term institutional care (Study III).

The prevalence of Alzheimer`s disease in community living elderly patients with chronic schizophrenia has ranged from 2% to 9% (Dwork et al. 1998, Murphy et al. 1998, Purohit et al. 1998, Jellinger and Gabriel 1999). In the present study this prevalence in generally was higher, up to 20%. However, this was even higher among those residents with schizophrenia who did not take any antipsychotics (44%). The schizophrenia residents without antipsychotics were relatively old, more commonly demented and had a high level of dependence on assistance with daily living.

The patients with moderate to severe cognitive impairment (CPS 3-6) took antipsychotics twice as commonly (22.3%) as cognitively intact (CPS 0) patients (8.4%) in home care in Finland (Study IV). However, in the study of nine European countries (V) the subjects with moderate to severe cognitive impairment took antipsychotics as much as four times more often than the cognitively sound patients (13.4% vs. 3.4%). In some earlier reports, the use of antipsychotics has been 6-times more frequent among individuals with dementia than among those without dementia (Giron et al. 2001, Hartikainen et al. 2003b). Although one out of two patients in the European Study (V) and at least 60% of home care patients in Finland (Study IV) were assessed to have some degree of cognitive impairment, only 12% to 18% respectively were recorded as having a diagnosis of dementia. This discrepancy may be due to the fact that the cause of cognitive impairment among home care patients is only seldom ascertained. This may imply insufficient diagnostic procedures as to neurodegenerative disease, or

that cognitive impairment was caused by stroke or depression. Another explanation may be that not all diagnoses of dementia have been adequately recorded in the files. As other recent research has reported that less than half of the patients with dementia had their diagnosis documented in primary care medical records (Löppönen et al. 2003).

Recently, serious concerns have been raised regarding the use of antipsychotics in people with dementia, particularly the increased mortality rates, the increased risk of stroke and other cardiovascular adverse events, as well as the increase in parkinsonian symptoms and drowsiness. The main reason for the widespread prescription of antipsychotics in this group could be the limited evidence for alternative treatment approaches (Hermans et al. 2007, Robinson et al. 2007).

In clinical studies, typical antipsychotics have been effective against BPSD, but they were also characterised by their range of adverse effects (Schneider et al. 1990). There have been several randomised, placebo-controlled trials of atypical antipsychotics olanzapine (Street et al. 2000, Clark et al. 2001, De Deyn et al. 2004), risperidone (De Deyn et al. 1999, Tune 2001, Brodaty et al. 2003, Brodaty et al. 2005), quetiapine (Tariot and Ismail 2002, Zhong et al. 2007) and aripiprazole (De Deyn et al. 2005), showing variable efficacy against BPSD. Meta-analysis of atypical antipsychotics has found evidence for the effectiveness of olanzapine and risperidone in dementia (Schneider et al. 2006). Schneider and his collagues analysed the mortality rates in 15 clinical trials in which aripiprazole, olanzapine, quetiapine or risperidone were compared to placebo (Schneider et al. 2005). Overall, in the trials studied, people taking atypical antipsychotics were 1.5 times more likely to die than those taking a placebo.

Cholinesterase inhibitors (ChEIs) are the primary treatment for cognitive symptoms of AD. In a recent Canadian population-based study Herrmann et al. reported that elderly patients with dementia are treated for lengthy periods of time with ChEIs in the community and in long-term care facilities (Herrmann et al. 2007). However, the recent systematic reviews and meta-analysis of the efficacy of ChEIs in the treatment of neuropsychiatric symptoms and functional

impairment in AD have demonstrated only a low or modest beneficial effect on behavioural symptoms and functional abilities (Sink et al. 2001, Trinh et al. 2003, Wild et al. 2003, Grimmer and Kurz 2006). There is only one head-to-head study that compared an atypical antipsychotic (quetiapine) with a ChEI (rivastigmine) and placebo in patients with probable AD found no differences in efficacy between the three treatments (Ballard et al. 2005). However, in a recent report it has been suggested that nursing home residents with AD treated with ChEI have a reduced risk from therapy with antipsychotics compared with these residents without ChEIs (Narayonan et al. 2006). In the present study the data of ChEIs were not available in studies in institutional care and in Study IV the subgroup with that data was too small (n=49) for statistical purposes.

Over the past 4 years, also regulatory authorities in Europe (EMEA) and the US (FDA) have also raised concerns about an apparent increase in cerebrovascular events and deaths associated with atypical antipsychotics. These regulatory authorities warning to physicians and patients stated that off-label use of all atypical antipsychotics could be dangerous to elderly patients with dementia. In contrast to this, several observational studies have found no increase in the risk of cerebrovascular events in patients suffering from different kinds of dementia receiving either atypical or typical antipsychotics (Herrmann et al. 2004, Gill et al. 2005, Layton et al. 2005). There are no head-to-head comparisons of atypical and typical antipsychotics in patients with dementia. However, meta-analysis by Wang and colleagues suggests that typical antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly patients, and that typical medications should not be used to replace atypical agents discontinued in response to the FDA warning (Wang et al. 2005). In addition, Raivio et al. found that neither atypical nor conventional antipsychotics increase mortality among elderly patients with dementia (Raivio et al. 2007), but the use of restraints doubled this risk. In recent studies on elderly patients with and without dementia, the risk of death associated with typical antipsychotic medications is comparable or possibly greater than the risk of death associated with atypical antipsychotics (Gill et al. 2007, Schneeweiss et al. 2007). However, the recent study in community living

patients with AD suggests that the adverse effects of atypical antipsychotics may offset advantages in the efficacy for the treatment of psychosis, aggression or agitation (Schneider et al. 2006).

It has been recommended that atypical antipsychotics should be used as a first-line management strategy only when severe and distressing symptoms of dementia are occurring that cannot be easily contained, and when the individual affected or others are at risk (Ballard and Howard 2006). A careful decision needs to be made on the basis of the distress to the patients and their caregivers as to whether the potential benefits of an atypical antipsychotic might outweigh the risk of adverse effects.

5.2.3.3 Delusions and antipsychotic use (IV, V)

Delusions were associated with antipsychotic use in Studies IV and V.

Around 6% of the patients in home care in Finland (Study IV) and 2% of the patients in the European Study V had delusions which match the point prevalence of psychotic symptoms of 5.7% previously reported in Australian community living elderly (Henderson et al. 1998). However, the rates of delusions in Studies IV and V were substantially lower than those reported in studies among residents with delusions in nursing homes (16-56%) (Brodaty et al. 2001, Margallo-Lana et al. 2001). Risk factors for delusions have been older age (Bassiony et al. 2000) and AD diagnosis (Lyketsos et al. 2000). However, in the recent study hallucinations but not delusions were related to an increased risk of subsequent development of dementia (Östling et al. 2007).

In Study IV 45% of patients with delusions received antipsychotics and 32% in Study V. Delusions as well as hallucinations are well-established indications for antipsychotic treatment and according to earlier studies mortality rate may be double in individuals over 70 with these psychotic symptoms (Henderson and Kay 1997). However, psychotic symptoms have been linked to cognitive and

70

functional decline (Chui et al. 1994, Lopez et al. 1999) and earlier institutionalization (Gonzalez-Salvador et al. 1999, Lopez et al. 1999). Interestingly, the proportion of delusional patients taking no antipsychotics was more than half in Studies IV and V. This concurs with a study in which more than half of nursing home residents with delusions were not on antipsychotics (Brodaty et al. 2001, Margallo-Lana et al. 2001). In addition, Forsell et al. have reported that elderly people with paranoid symptoms often took psychotropic medications, although only 10% took antipsychotics (Forsell and Henderson 1998).

It is also unknown whether the onsets of delusions in the present patients have occured de novo or are associated with pre-existing psychiatric or medical disorders. Delusions may not be severe or persistent enough and may not result in disruption or distress (Studies IV, V). It has also been reported that in more than half of the patients with delusion associated dementia the symptoms do resolve over the year of follow-up independent of pharmacological treatment (Ballard et al. 2001).

5.2.3.4 Anxiolytics and antipsychotic use (I, II, V)

The use of antipsychotics was significantly associated with concomitant use of anxiolytics in Studies I, II and V.

Antipsychotic use among residents in long-term institutional care with concomitant use of anxiolytics was decidedly high. Among the long-term care residents up to 56% used antipsychotic medication concomitantly with anxiolytics (Studies I, II). The use of anxiolytics concomitantly with antipsychotics in home care patients in Europe was 14% (Study V). These percentages seem to be higher or equal to some previously reported (3-13%) (Giron et al. 2001, Gobert and D'hoore 2005). In a population-based Swedish study on very old people with and without dementia one of the most frequent psychotropic combination was antipsychotics and anxiolytics (Giron et al. 2001). Hartikainen et al. have reported that in home-dwelling elderly two out of three nondemented users of antipsychotics were taking at least one other psychotropic

drug (Hartikainen et al. 2003b). In that report the most common combination was hypnotics and antipsychotics among the demented subjects. A population-based study from Finland has reported that half of non-demented people aged 75 and older even used hypnotics or antipsychotics and one out of three used these medications concomitantly (Hartikainen et al. 2005). However, in that study the use of different types of psychotropics or several antipsychotics was a risk factor for death in demented patients.

However, as a general principle it has been recommended that polypharmacy of psychotropics should be avoided among elderly people (Howard et al. 2001). As the possible impact of the growing use of these may include the increased risks of neurological and other adverse effects (Centorrino et al. 2002).

5.3 Limitations and strengths of the study

The major limitations of this study include mostly the limitations in register database. Because of the cross-sectional nature of these studies it was not possible to establish the chronological order of any associations.

5.3.1 Limitations of the MDS

The MDS is a multidimensional assessment tool originally created for both clinical work and for research. This duality leads to compression of all data collection to the minimum necessary to reveal the main problem areas, not to assess these areas fully.

The limitations of the ability of the MDS to reveal the lack of individual indications for the use, doses (except Study IV), duration and discontinuation of antipsychotics are not available. Moreover, generic names of antipsychotics were not available in long-term institutional care studies (I-III), thus, distinguishing between atypical and typical antipsychotics was not possible. Lack of documentation of indications makes it impossible to know whether these drugs were being used for the appropriate reasons. Even though adherence to

72

medications was checked in home care as a routine part of the MDS questionnaire and home care nurses delivered the medications, some uncertainty about the actual consumption cannot be totally excluded (Study IV-V).

Although the MDS is a standardized, comprehensive assessment instrument, the recording of psychiatric symptoms was not its main focus. Psychiatric symptoms were assessed by nursing staff (including the attending physician), and the potential for over- and underestimation remains. In addition the data collected do not include any severity or frequency assessment of psychiatric or behavioural symptoms.

Although the MDS items have demonstrated good to excellent general reliability, it is uncertain how appropriate the MDS is in the nursing home assessment of the oldest old or people with chronic mental illness. In addition, the MDS, however, has not been validated specifically for nursing home residents with schizophrenia. Little is known about the ability of nursing home personnel to accurately recognize the symptoms of schizophrenia. Bowie et al. suggest that symptoms such as thought disorder and hallucinations go almost completely unnoticed by nursing staff when they were asked to give a present-absent rating (Bowie et al. 2001).

Other limitations include uncertainty that not all psychiatric and dementia diagnoses have been adequately recorded in the files. The concern in Study III was the reliability of the database diagnosis of schizophrenia. Earlier studies indicate that Finnish psychiatrists tend to apply a narrow definition of schizophrenia in their clinical practice and that the diagnosis of schizophrenia can be considered reasonably reliable (Salokangas 1993, Isohanni et al. 1997, Kampman et al. 2004).

5.3.2 Reliability

The characteristics, diagnoses and symptoms of residents, residential care systems and clinical practices vary widely between countries making international comparisons and reliability in other populations complex. Despite

the common use of the term "nursing home", there are no generally accepted definitions for the different types of long-term care services. There will be differences in the types of patients who are admitted to these facilities and the ways in which they are diagnosed and treated. Additionally, the more standardized way of assessing residents in long-term institutional and home care might also influence care practice with antipsychotics. Furthermore, the samples in Studies IV and V consisted solely of users of home care services, especially home care patients and the results cannot be generalized to all community-dwelling elderly people. No direct comparison of antipsychotic use between home care patients and community-dwelling individuals is available.

5.3.3 Unstudied factors

These studies did not include antipsychotic medications prescribed "as required". However, some "as required" medications may actually be used quite regularly. Thus, the actual prevalences of antipsychotic medication use may have been higher than is reported here.

There may be an association between facility characteristics and the use of antipsychotics (Hughes et al. 2000) suggesting that the high prevalence of antipsychotic use may be related to low staffing rates in Finnish nursing homes. The mean actual staffing level during the past 5 years in nursing homes in Finland has been 0.43 nurses per resident on weekdays (Noro A et al. 2005). The National Framework for High-Quality Care and Services for Older People suggest an appropriate staffing level of 0.8 nurses per resident. However, there are no comparisons of staffing rates between different countries. In the present study it was impossible to evaluate the influence of staffing rate on the use of antipsychotics. It may be possible that low staffing rates and pressure of work life have affected assessments of patients. Other possible predictors of antipsychotic use such as costs and prescription procedures are beyond of the present thesis.

5.3.4 Strengths of the study

The only exclusion criteria were aged <65 years and assisted living. Every resident in every participating institution and every patient in only home nursing, and common patients for home nursing and home care units were included. In addition, total population sizes were relatively large in all levels studied. The total units comprised approximately 17% of long-term institutional care for the elderly in 2001 in Finland. All types of institutional settings in Finland took part: small and large, from cities and from rural areas, nursing homes and hospital-based beds. These study populations can be considered to be representative of older populations in long-term care in Finland. Thus, the spectrum of cognitive and physical impairment together with essential psychiatric disorders and symptoms prevalent was likely to be captured.

5.4 Implications for future research

More studies on elderly people are needed in order to identify the factors that associated with the type and doses of antipsychotics in long-term care settings. This study also points to the importance of studying the longitudinal changes in prescribing patterns of antipsychotics for elderly people both in long-term institutional and home care. More attention should be paid to the appropriate use of antipsychotics and especially staff training including intervention studies for the care of the elderly. More studies are also needed on antipsychotic use based on prospective long-term follow-up design to ascertain the factors associated with such use. Future research should also address the question of whether there are predictors to differentiate the older patients with schizophrenia who will not relapse with discontinuation of antipsychotics.

6 SUMMARY

The prevalences of antipsychotic use were high in all the studies.

The present study focused on five specific questions as follows.

1. *Is there any change of the prevalence of antipsychotic use during the study period and which factors would explain the change? (Study I)*
Findings: The prevalence of antipsychotic use in long-term institutional care decreased from 42% in 2001 to 39% in 2003. The overall confounder-adjusted decrease in antipsychotic use was not statistically significant. During the study period the use of antipsychotics decreased among residents with wandering as a behavioural problem. On the other hand, the use of antipsychotics increased in those residents concurrently receiving anxiolytics.

2. *What is the prevalence of antipsychotic use among nonagenarian institution residents and which factors associate with such use? (Study II)*
Findings: Antipsychotic medication use among nonagenarians in long-term institutional care was common (30%) and seemed in many cases to be associated with residents` negative attitudes to others. Thus, there was an increasing risk of antipsychotic use among querulous residents and decreasing risk among those with good social skills.

3. *What is the prevalence of older residents with schizophrenia not having any antipsychotics at the time of the data gathering and which factors associate with non-use of antipsychotics? (Study III)*
Findings: Approximately 19% of the older residents with schizophrenia in long-term institutional care were not on antipsychotic medication. Any diagnosis of dementia, severe underweight and severely impaired vision was associated with non-use of antipsychotics among these residents.

4. *What is the prevalence of antipsychotic use among home care patients in Finland and which factors are associated with such use? (Study IV)*

Findings: Antipsychotic use among home care patients in Finland was lower (11.0%) than that in long-term institutional care. Several factors such as psychiatric diagnosis, delusions and cognitive impairment were associated with the use of antipsychotics whereas there was a negative association between age and the use of antipsychotics.

5. *Is there any variation of antipsychotic use among home care patients in nine European countries and which factors contribute to such variation? (Study V)*

Findings: Of home care patients in nine European countries 6.2% were taking antipsychotic medication. The frequency of the use of one or more antipsychotic varied widely between study sites, ranging from 3.0% in Denmark to 12.4% in Finland. Certain factors such as delusions, hallucinations, depression, dementia and cognitive impairment as well as youngest age group and concomitant use of other psychotropics explained the use of antipsychotics. Residing in Finland and Italy was also a risk indicator.

The use of antipsychotic medications in long-term institutional and home care in Finland was among the highest in the world.

7 ACKNOWLEDGEMENTS

8 REFERENCES

Aarsland D, Larsen JP, Cummins JL and Laake K (1999): Prevalence and clinical correlates of psychotic symptoms in Parkinson disease: a community-based study. Arch Neurol 56:595-601.

Alanen HM, Finne-Soveri H, Noro A and Leinonen E (2006): Reply. Age Ageing 36(1):108-109.

Albert M and Cohen C (1992): The Test for Severe Impairment: an instrument for the assessment of patients with severe cognitive dysfunction. J Am Geriatr Soc 40:449-453.

Alexopoulos GS, Streim J, Carpenter D, Docherty JP and Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients (2004): Using antipsychotic agents in older patients. J Clin Psychiatry 65 (Suppl 2):5-99; discussion 100-102; quiz 103-104.

Algase DL, Beel-Bates C and Beattie ER (2003): Wandering in long-term care. Ann Long Term Care 11:33-39.

Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC and Weiden PJ (1999): Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 156:1686-1696.

Almeida OP, Howard RJ, Levy R and David AS (1995): Psychotic states arising in late life (late paraphrenia). The role of risk factors. Br J Psychiatry 166:215-228.

Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, de Girolamo G, Graaf R, Demyttenaere K, Gasquet I, Haro JM, Katz SJ, Kessler RC, Kovess V, Lepine JP, Ormel J, Polidori G, Russo LJ, Vilagut G, Almansa J, Arbabzadeh-Bouchez S, Autonell J, Bernal M, Buist-Bouwman MA, Codony M, Domingo-Salvany A, Ferrer M, Joo SS, Martinez-Alonso M, Matschinger H, Mazzi F, Morgan Z, Morosini P, Palacin C, Romera B, Taub N, Vollebergh WA and ESEMeD/MHEDEA 2000 Investigators, European Study of the Epidemiology of Mental Disorders (ESEMeD) Project (2004): Psychotropic drug utilization in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand 420:55-64.

American Psychiatric Association (1994): Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington DC.

Andersen-Ranberg K, Vasegaard L and Jeune B (2001): Dementia is not inevitable: a population-based study of Danish centenarians. J Gerontol B Psychol Sci Soc Sci 56:152-159.

Andreasen NC (1995): Symptoms, signs, and diagnosis of schizophrenia. Lancet 346:477-481.

Andreasen NC, Carpenter WT Jr, Kane JM, Lasser RA, Marder SR and Weinberger DR (2005): Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry 162(3):441-449.

Aparasu RR, Mort JR and Brandt H (2003): Psychotropic prescription use by community-dwelling elderly in the United States. J Am Geriatr Soc 51(5):671-677.

Arunpongpaisal S, Ahmed I, Aqeel N and Suchat P (2003): Antipsychotic drug treatment for elderly people with late-onset schizophrenia. Cochrane Database Syst Rev 2(2):CD004162.

Auslander LA and Jeste DV (2004): Sustained remission of schizophrenia among community-dwelling older outpatients. Am J Psychiatry 161(8):1490-1493.

Avorn J, Soumerai S, Everitt DE, Ross-Degnan D, Beers MH, Sherman D, Salem-Schatz SR and Fields D (1992): A randomized trial of a program to reduce the use of psychoactive drugs in nursing homes. N Engl J Med 327 (3):168-173.

Ballard C, Grace J, McKeith I and Holmes C (1998): Neuroleptic sensitivity in dementia with Lewy bodies and Alzheimer's disease. Lancet 351(9108):1032-1033.

Ballard C and O'Brien J (1999): Treating behavioural and psychological signs in Alzheimer's disease. BMJ 319(7203):138-139.

Ballard C and Howard R (2006): Neuroleptic drugs in dementia: benefits and harm. Nat Rev Neurosci 7(6):492-500.

Ballard CG, Margallo-Lana M, Fossey J, Reichelt K, Myint P, Potkins D and O'Brien J (2001a): A 1-year follow-up study of behavioral and psychological symptoms in dementia among people in care environments. J Clin Psychiatry 62(8):631-636.

Ballard CG, O'Brien JT, Swann AG, Thompson P, Neill D and McKeith IG (2001b): The natural history of psychosis and depression in dementia with Lewy bodies and Alzheimer's disease: persistence and new cases over 1 year of follow-up. J Clin Psychiatry 62(1):46-49.

Ballard CG, Thomas A, Fossey J, Lee L, Jacoby R, Lana MM, Bannister C, McShane R, Swann A, Juszczak E and O'Brien JT (2004): A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the neuropsychiatric inventory median cutoff is a predictor of clinical outcome. J Clin Psychiatry 65(1):114-119.

Ballard C, Margallo-Lana M, Juszczak E, Douglas S, Swann A, Thomas A, O'Brien J, Everratt A, Sadler S, Maddison C, Lee L, Bannister C, Elvish R and Jacoby R (2005): Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. BMJ 330(7496):874.

Barak Y, Baruch Y, Mazeh D, Paleacu D and Aizenberg D (2007): Cardiac and cerebrovascular morbidity and mortality associated with antipsychotic medications in elderly psychiatric inpatients. Am J Geriatr Psychiatry 15(4):354-356.

Barrett-Connor E, Edelstein SL, Corey-Bloom J and Wiederholt WC (1996): Weight loss precedes dementia in community-dwelling older adults. J Am Geriatr Soc 44(10):1147-1152.

Baskys A (2004): Lewy body dementia: the litmus test for neuroleptic sensitivity and extrapyramidal symptoms. J Clin Psychiatry 65(Suppl 11):16-22.

Bassiony MM, Steinberg MS, Warren A, Rosenblatt A, Baker AS and Lyketsos, CG (2000): Delusions and hallucinations in Alzheimer's disease: prevalence and clinical correlates. Int J Geriatr Psychiatry 15(2): 99-107.

Hennessy S, Bilker WB, Knauss JS, Margolis DJ, Kimmel SE, Reynolds RF, Glasser DB, Morrison MF and Strom BL (2002): Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. BMJ 325(7372):1070.

Berr C, Wancata J and Ritchie K (2005): Prevalence of dementia in the elderly in Europe. Eur Neuropsychopharmacol 15(4):463-471.

Bhat RS, Chiu E and Jeste DV (2005): Nutrition and geriatric psychiatry: a neglected field. Curr Opin Psychiatry 18(6):609-614.

Björkgren MA, Häkkinen U, Finne-Soveri UH and Fries BE (1999): Validity and reliability of Resource Utilization Groups (RUG-III) in Finnish long-term care facilities. Scand J Public Health 27(3):228-234.

Boholm J (2005). RAIsoft software development. In: Quality and Productivity in Institutional Care of Elderly Residents - Benchmarking with the RAI, pp.39-45. Eds. Noro A, Finne-Soveri H, Björkgren M and Vähäkangas P STAKES, Gummerus, Helsinki.

Bowie CR, Moriarty PJ, Harvey PD, Parrella M, White L and Davis KL (2001): Aggression in elderly schizophrenia patients: a comparison of nursing home and state hospital residents. J Neuropsychiatry Clin Neurosci 13(3):357-366.

Bridges-Parlet S, Knopman D and Steffes S (1997): Withdrawal of neuroleptic medications from institutionalized dementia patients: results of a double blind, baseline-treatment-controlled pilot study. J Geriatr Psychiatry Neurol 10(3):119-126.

Briesacher BA, Limcangco MR, Simoni-Wastila L, Doshi JA, Levens SR, Shea DG and Stuart B (2005): The quality of antipsychotic drug prescribing in nursing homes. Arch Intern Med 165(11):1280-1285.

Brodaty H, Draper B, Saab D, Low LF, Richards V, Paton H and Lie D (2001): Psychosis, depression and behavioural disturbances in Sydney nursing home residents: prevalence and predictors. Int J Geriatr Psychiatry 16(5):504-512.

Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, Lee E, Lyons B and Grossman F (2003): A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 64(2):134-143.

Brodaty H, Ames D, Snowdon J, Woodward M, Kirwan J, Clarnette R, Lee E and Greenspan A (2005): Risperidone for psychosis of Alzheimer's disease and mixed dementia: results of a double-blind, placebo-controlled trial. Int J Geriatr Psychiatry 20(12):1153-1157.

Bronskill SE, Anderson GM, Sykora K, Wodchis WP, Gill S, Shulman KI and Rochon PA (2004): Neuroleptic drug therapy in older adults newly admitted to nursing homes: incidence, dose, and specialist contact. J Am Geriatr Soc 52(5):749-755.

Brown S (1997): Excess mortality of schizophrenia. A meta-analysis. Br J Psychiatry 171:502-508.

Burrows AB, Morris JN, Simon SE, Hirdes JP and Phillips C (2000): Development of a minimum data set-based depression rating scale for use in nursing homes. Age Ageing 29(2):165-172.

Caligiuri MP, Lacro JP and Jeste DV (1999): Incidence and predictors of drug-induced parkinsonism in older psychiatric patients treated with very low doses of neuroleptics. J Clin Psychopharmacol 19(4):322-328.

Carpenter I, Gambassi G, Topinkova E, Schroll M, Finne-Soveri H, Henrard JC, Garms-Homolova V, Jonsson P, Frijters D, Ljunggren G, Sorbye LW, Wagner C, Onder G, Pedone C and Bernabei R (2004): Community care in Europe. The Aged in Home Care project (AdHOC). Aging Clin Exp Res 16(4):259-269.

Carson S, McDonagh MS and Peterson K (2006): A systematic review of the efficacy and safety of atypical antipsychotics in patients with psychological and behavioral symptoms of dementia. J Am Geriatr Soc 54(2):354-361.

Casey DE (2004): Dyslipidemia and atypical antipsychotic drugs. J Clin Psychiatry 65(Suppl 18):27-35.

Casten R, Lawton MP, Parmelee PA and Kleban MH (1998): Psychometric characteristics of the minimum data set I: confirmatory factor analysis. J Am Geriatr Soc 46(6):726-735.

Centorrino F, Eakin M, Bahk WM, Kelleher JP, Goren J, Salvatore P, Egli S and Baldessarini RJ (2002): Inpatient antipsychotic drug use in 1998, 1993, and 1989. Am J Psychiatry 159(11):1932-1935.

Champoux N, Monette J, Monette M, Galbaud du Fort G, Wolfson C and Le Cruguel JP (2005): Use of neuroleptics: study of institutionalized elderly people in Montreal, Que. Can Fam Physician 51:696-697.

Chaudhry IA, Shamsi FA and Weitzman ML (2006): Progressive severe visual loss after long-term withdrawal from thioridazine treatment. Eur J Ophthalmol 16(4):651-653.

Chui HC, Lyness SA, Sobel E and Schneider LS (1994): Extrapyramidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer's disease. Arch Neurol 51(7):676-681.

Clark WS, Street JS, Feldman PD and Breier A (2001): The effects of olanzapine in reducing the emergence of psychosis among nursing home patients with Alzheimer's disease. J Clin Psychiatry 62(1):34-40.

Coen RF, Swanwick GR, O'Boyle CA and Coakley D (1997): Behaviour disturbance and other predictors of carer burden in Alzheimer's disease. Int J Geriatr Psychiatry 12(3):331-336.

Cohen CI (1990): Outcome of schizophrenia into later life: an overview. Gerontologist 30(6):790-797.

Cohen CI and Talavera N (2000): Functional impairment in older schizophrenic persons. Toward a conceptual model. Am J Geriatr Psychiatry 8(3):237-244.

Cohen CI, Talavera N and Hartung R (1996): Depression among aging persons with schizophrenia who live in the community. Psychiatr Serv 47(6):601-607.

Cohen CI, Cohen GD, Blank K, Gaitz C, Katz IR, Leuchter A, Maletta G, Meyers B, Sakauye K and Shamoian C (2000): Schizophrenia and older adults. An overview: directions for research and policy. Am J Geriatr Psychiatry 8(1):19-28.

Cohen-Mansfield J and Billig N (1986): Agitated behaviors in the elderly. A conceptual review. J Am Geriatr Soc 34(10):711-721.

Cohen-Mansfield J, Werner P, Marx MS and Freedman L (1991): Two studies of pacing in the nursing home. J Gerontol 46(3):M77-83.

Cohen-Mansfield J and Werner P (1998): The effects of an enhanced environment on nursing home residents who pace. Gerontologist 38(2):199-208.

Cohen-Mansfield J, Lipson S, Werner P, Billig N, Taylor L and Woosley R (1999): Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing home: a controlled, double-blind study. Arch Intern Med 159(15):1733-1740.

Colon-Emeric CS, Biggs DP, Schenck AP and Lyles KW (2003): Risk factors for hip fracture in skilled nursing facilities: who should be evaluated? Osteoporos 14(6):484-489.

Cooper JK and Mungas D (1993): Risk factor and behavioral differences between vascular and Alzheimer's dementias: the pathway to end-stage disease. J Geriatr Psychiatry Neurol 6(1):29-33.

Cooper JK, Mungas D and Weiler PG (1990): Relation of cognitive status and abnormal behaviors in Alzheimer's disease. J Am Geriatr Soc 38(8):867-870.

Copeland JR, Dewey ME, Scott A, Gilmore C, Larkin BA, Cleave N, McCracken CF and McKibbin PE (1998): Schizophrenia and delusional disorder in older age: community prevalence, incidence, comorbidity, and outcome. Schizophr Bull 24(1):153-161.

Copeland JR, Chen R, Dewey ME, McCracken CF, Gilmore C, Larkin B and Wilson KC (1999): Community-based case-control study of depression in older people. Cases and sub-cases from the MRC-ALPHA Study. Br J Psychiatry 175:340-347.

Courtney DL (1994): Effects of antipsychotic withdrawal in elderly nursing home residents. Kans Med 95(11):246-247.

Craig D, Passmore AP, Fullerton KJ, Beringer TR, Gilmore DH, Crawford VL, McCaffrey PM and Montgomery A (2003): Factors influencing prescription of CNS medications in different elderly populations. Pharmacoepidemiol Drug Saf 12(5):383-387.

Davidson M, Harvey PD, Powchik P, Parrella M, White L, Knobler HY, Losonczy MF, Keefe RS, Katz S and Frecska E (1995): Severity of symptoms in chronically institutionalized geriatric schizophrenic patients. Am J Psychiatry 152(2):197-207.

Dawson P and Reid DW (1987): Behavioral dimensions of patients at risk of wandering. Gerontologist 27(1):104-107.

Draper B, Brodaty H, Low LF, Saab D, Lie D, Richards V and Paton H (2001): Use of psychotropics in Sydney nursing homes: associations with depression, psychosis, and behavioral disturbances. Int Psychogeriatr 13(1):107-20.

De Deyn PP, Rabheru K, Rasmussen A, Bocksberger JP, Dautzenberg PL, Eriksson S and Lawlor BA (1999): A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 53(5):946-955.

De Deyn PP, Carrasco MM, Deberdt W, Jeandel C, Hay DP, Feldman PD, Young CA, Lehman DL and Breier A (2004): Olanzapine versus placebo in the treatment of psychosis with or without associated behavioral disturbances in patients with Alzheimer's disease. Int J Geriatr Psychiatry 19(2):115-126.

De Deyn P, Jeste DV, Swanink R, Kostic D and Breder C (2005): Aripiprazole for the treatment of psychosis in patients with Alzheimer's disease: a randomized, placebo-controlled study. J Clin Psychopharmacol 25(5):463-467.

Dwork AJ, Susser ES, Keilp J, Waniek C, Liu D, Kaufman M, Zemishlany Z and Prohovnik I (1998): Senile degeneration and cognitive impairment in chronic schizophrenia. Am J Psychiatry 155(11):1536-1543.

Fahey T, Montgomery AA, Barnes J and Protheroe J (2003): Quality of care for elderly residents in nursing homes and elderly people living at home: controlled observational study. BMJ 326(7389):580.

Fenelon G, Mahieux F, Huon R and Ziegler M (2000): Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain 123 (Pt 4):733-745.

Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M and Alzheimer's Disease International (2005): Global prevalence of dementia: a Delphi consensus study. Lancet 366(9503):2112-2117.

Folstein MF, Folstein SE and McHugh PR (1975): "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12(3):189-198.

Fornaro P, Calabria G, Corallo G and Picotti GB (2002): Pathogenesis of degenerative retinopathies induced by thioridazine and other antipsychotics: a dopamine hypothesis. Doc Ophthalmol 105(1):41-49.

Forsell Y and Henderson AS (1998): Epidemiology of paranoid symptoms in an elderly population. Br J Psychiatry 172:429-432.

Forsell Y, Palmer K and Fratiglioni L (2003): Psychiatric symptoms/syndromes in elderly persons with mild cognitive impairment. Data from a cross-sectional study. Acta Neurol Scand Suppl 179:25-28.

Fossey J, Ballard C, Juszczak E, James I, Alder N, Jacoby R and Howard R (2006): Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia: cluster randomised trial. BMJ 332(7544):756-761.

French DD, Campbell RR, Spehar AM and Accomando J (2007a): How well do psychotropic medications match mental health diagnoses? A national view of potential off-label prescribing in VHA nursing homes. Age Ageing 36(1): 107-8; author reply 108-9.

French DD, Werner DC, Campbell RR, Powell-Cope GM, Nelson AL, Rubenstein LZ, Bulat T and Spehar AM (2007b): A multivariate fall risk assessment model for VHA nursing homes using the minimum data set. J Am Med Dir Assoc 8(2):115-122.

Friedman JI, Harvey PD, Coleman T, Moriarty PJ, Bowie C, Parrella M, White L, Adler D and Davis KL (2001): Six-year follow-up study of cognitive and functional status across the lifespan in schizophrenia: a comparison with Alzheimer's disease and normal aging. Am J Psychiatry 158(9):1441-1448.

Friedman JH, Fernandez HH and Trieschmann MM (2004): Parkinsonism in a nursing home: underrecognition. J Geriatr Psychiatry Neurol 17(1):39-41.

Furniss L, Burns A, Craig SK, Scobie S, Cooke J and Faragher B. Effects of a pharmacist's medication review in nursing homes. Randomised controlled trial. Br J Psychiatry 176:563-567.

Gilbert PL, Harris MJ, McAdams LA and Jeste DV (1995): Neuroleptic withdrawal in schizophrenic patients. A review of the literature. Arch Gen Psychiatry 52(3):173-188.

Gill SS, Rochon PA, Herrmann N, Lee PE, Sykora K, Gunraj N, Normand SL, Gurwitz JH, Marras C, Wodchis WP and Mamdani M (2005): Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. BMJ 330(7489):445.

Gill SS, Bronskill SE, Normand SL, Anderson GM, Sykora K, Lam K, Bell CM, Lee PE, Fischer HD, Herrmann N, Gurwitz JH and Rochon PA (2007): Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 146(11):775-786.

Giron MS, Forsell Y, Bernsten C, Thorslund M, Winblad B and Fastbom J (2001): Psychotropic drug use in elderly people with and without dementia. Int J Geriatr Psychiatry 16(9):900-906.

Gobert M and D'hoore W (2005): Prevalence of psychotropic drug use in nursing homes for the aged in Quebec and in the French-speaking area of Switzerland. Int J Geriatr Psychiatry 20(8):712-721.

Gonzalez-Salvador MT, Arango C, Lyketsos CG and Barba AC (1999): The stress and psychological morbidity of the Alzheimer patient caregiver. Int J Geriatr Psychiatry 14(9):701-710.

Gonzalez-Salvador T, Lyketsos CG, Baker A, Hovanec L, Roques C, Brandt J and Steele C (2000): Quality of life in dementia patients in long-term care. Int J Geriatr Psychiatry 15(2):181-189.

Gormley N, Rizwan MR and Lovestone S (1998): Clinical predictors of aggressive behaviour in Alzheimer's disease. Int J Geriatr Psychiatry 13(2):109-115.

Grimmer T and Kurz A (2006): Effects of cholinesterase inhibitors on behavioural disturbances in Alzheimer's disease: a systematic review. Drugs Aging 23(12):957-967.

Guigoz Y, Lauque S and Vellas BJ (2002): Identifying the elderly at risk for malnutrition. The Mini Nutritional Assessment. Clin Geriatr Med 18(4):737-757.

Gurevitz SL, Costakis T and Leiter J (2004): Do atypical antipsychotics cause weight gain in nursing home dementia residents? Consult Pharm 19(9):809-812.

Gurland BJ and Cross PS (1982): Epidemiology of Psychopathology in old age. Some implications for clinical services. Psychiatr Clin North Am 5(1):11-26.

Hagen B, Esther CA, Ikuta R, Williams RJ, Le Navenec CL and Aho M (2005): Antipsychotic drug use in Canadian long-term care facilities: prevalence, and patterns following resident relocation. Int Psychogeriatr 17(2):179-193.

Hannerz H, Borga P and Borritz M (2001): Life expectancies for individuals with psychiatric diagnoses. Public Health 115(5):328-337.

Harris MJ and Jeste DV (1988): Late-onset schizophrenia: an overview. Schizophr Bull 14(1):39-55.

Hartikainen S, Rahkonen T, Kautiainen H and Sulkava R (2003a): Kuopio 75+ study: does advanced age predict more common use of psychotropics among the elderly? Int Clin Psychopharmacol 18(3):163-167.

Hartikainen S, Rahkonen T, Kautiainen H and Sulkava R (2003b): Use of psychotropics among home-dwelling nondemented and demented elderly. Int J Geriatr Psychiatry 18(12):1135-1141.

Hartikainen S, Rahkonen T, Kautiainen H and Sulkava R (2005): The use of psychotropics and survival in demented elderly individuals. Int Clin Psychopharmacol 20(4):227-231.

Hartikainen S, Lönnroos E and Louhivuori K (2007): Medication as a risk factor for falls: critical systematic review. J Gerontol A Biol Sci Med Sci 62(10):1172-1181.

Hartmaier SL, Sloane PD, Guess HA, Koch GG, Mitchell CM and Phillips CD (1995): Validation of the Minimum Data Set Cognitive Performance Scale: agreement with the Mini-Mental State Examination. J Gerontol A Biol Sci Med Sci 50(2):M128-33.

Harvey PD, Lombardi J, Kincaid MM, Parrella M, White L, Powchik P and Davidson M (1995): Cognitive functioning in chronically hospitalized schizophrenic patients: age-related changes and age disorientation as a predictor of impairment. Schizophr Res 17(1):15-24.

Harvey PD, White L, Parrella M, Putnam KM, Kincaid MM, Powchik P, Mohs RC and Davidson M (1995): The longitudinal stability of cognitive impairment in schizophrenia. Mini-mental state scores at one- and two-year follow-ups in geriatric in-patients. Br J Psychiatry 166(5):630-633.

Harvey PD, Silverman JM, Mohs RC, Parrella M, White L, Powchik P, Davidson M and Davis KL (1999): Cognitive decline in late-life schizophrenia: a longitudinal study of geriatric chronically hospitalized patients. Biol Psychiatry 45(1):32-40.

Harvey PD, Bertisch H, Friedman JI, Marcus S, Parrella M, White L and Davis KL (2003): The course of functional decline in geriatric patients with schizophrenia: cognitive-functional and clinical symptoms as determinants of change. Am J Geriatr Psychiatry 11(6):610-619.

Haupt DW and Newcomer JW (2002): Abnormalities in glucose regulation associated with mental illness and treatment. J Psychosom Res 53(4):925-933.

Hawes C, Morris JN, Phillips CD, Mor V, Fries BE and Nonemaker S (1995): Reliability estimates for the Minimum Data Set for nursing home resident assessment and care screening (MDS). Gerontologist 35(2):172-178.

Henderson AS and Kay DW (1997): The epidemiology of functional psychoses of late onset. Eur Arch Psychiatry Clin Neurosci 247(4):176-189.

Henderson AS, Korten AE, Levings C, Jorm AF, Christensen H, Jacomb PA and Rodgers B (1998): Psychotic symptoms in the elderly: a prospective study in a population sample. Int J Geriatr Psychiatry 13(7):484-492.

Henderson DC, Nguyen DD, Copeland PM, Hayden DL, Borba CP, Louie PM, Freudenreich O, Evins AE, Cather C and Goff DC (2005): Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-year naturalistic study. J Clin Psychiatry 66(9):1116-1121.

Hermans DG, Htay UH and McShane R (2007): Non-pharmacological interventions for wandering of people with dementia in the domestic setting. Cochrane Database Syst Rev 1(1):CD005994.

Herrmann N and Lanctot KL (2006): Atypical antipsychotics for neuropsychiatric symptoms of dementia: malignant or maligned? Drug Saf 29(10):833-843.

Herrmann N, Mamdani M and Lanctot KL (2004): Atypical antipsychotics and risk of cerebrovascular accidents. Am J Psychiatry 161(6):1113-1115.

Herrmann N, Gill SS, Bell CM, Anderson GM, Bronskill SE, Shulman KI, Fischer HD, Sykora K, Shi HS and Rochon PA (2007): A population-based study of cholinesterase inhibitor use for dementia. J Am Geriatr Soc 55(10):1517-1523.

Holmquist IB, Svensson B and Höglund P (2003): Psychotropic drugs in nursing- and old-age homes: relationships between needs of care and mental health status. Eur J Clin Pharmacol 59(8-9):669-676.

Holmquist IB, Svensson B and Höglund P (2005): Perceived anxiety, depression, and sleeping problems in relation to psychotropic drug use among elderly in assisted-living facilities. Eur J Clin Pharmacol 61(3):215-224.

Hope T, Tilling KM, Gedling K, Keene JM, Cooper SD and Fairburn CG (1994): The structure of wandering in dementia. Int J Geriatr Psychiatry 9:149-155.

Hosia-Randell H and Pitkälä K (2005): Use of psychotropic drugs in elderly nursing home residents with and without dementia in Helsinki, Finland. Drugs Aging 22(9):793-800.

Howard R, Rabins PV, Seeman MV and Jeste DV (2000): Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group. Am J Psychiatry 157(2):172-178.

Howard R, Ballard C, O'Brien J, Burns A and UK and Ireland Group for Optimization of Management in dementia (2001): Guidelines for the management of agitation in dementia. Int J Geriatr Psychiatry 16(7):714-717.

Hughes CM, Lapane KL and Mor V (2000): Influence of facility characteristics on use of antipsychotic medications in nursing homes. Med Care 38(12):1164-1173.

Hughes CM, Lapane KL, Mor V, Ikegami N, Jonsson PV, Ljunggren G and Sgadari A (2000): The impact of legislation on psychotropic drug use in nursing homes: a cross-national perspective. J Am Geriatr Soc 48(8):931-937.

Hybels CF and Blazer DG (2003): Epidemiology of late-life mental disorders. Clin Geriatr Med 19(4):663-96.

Häkkinen U, Rosenquist G, Aro S (1996): Economic depression and the use of physician services in Finland. Health Econ 5:421-434.

Häkkinen U (2002): Change in determinants of use of physician services in Finland between 1987 and 1996. Soc Sci Med 55:1523-1537.

Isohanni M, Mäkikyrö T, Moring J, Räsänen P, Hakko H, Partanen U, Koiranen M and Jones P (1997): A comparison of clinical and research DSM-III-R diagnoses of schizophrenia in a Finnish national birth cohort. Clinical and research diagnoses of schizophrenia. Soc Psychiatry Psychiatr Epidemiol 32(5):303-308.

Janno S, Holi M, Tuisku K and Wahlbeck K (2004): Prevalence of neuroleptic-induced movement disorders in chronic schizophrenia inpatients. Am J Psychiatry 161(1):160-163.

Jellinger K and Gabriel E (1999): No increased incidence of Alzheimer's disease in elderly schizophrenics. Acta Neuropathol 97(2):165-169.

Jeste DV, Lacro JP, Gilbert PL, Kline J and Kline N (1993): Treatment of late-life schizophrenia with neuroleptics. Schizophr Bull 19(4):817-830.

Jeste DV, Gladsjo JA, Lindamer LA and Lacro JP (1996): Medical comorbidity in schizophrenia. Schizophr Bull 22(3):413-430.

Jeste DV, Lacro JP, Bailey A, Rockwell E, Harris MJ and Caligiuri MP (1999): Lower incidence of tardive dyskinesia with risperidone compared with haloperidol in older patients. J Am Geriatr Soc 47(6):716-719.

Jeste DV and Finkel SI (2000): Psychosis of Alzheimer's disease and related dementias. Diagnostic criteria for a distinct syndrome. Am J Geriatr Psychiatry 8(1):29-34.

Jeste DV, Okamoto A, Napolitano J, Kane JM and Martinez RA (2000): Low incidence of persistent tardive dyskinesia in elderly patients with dementia treated with risperidone. Am J Psychiatry 157(7):1150-1155.

Jeste DV, Twamley EW, Eyler Zorrilla LT, Golshan S, Patterson TL and Palmer BW (2003): Aging and outcome in schizophrenia. Acta Psychiatr Scand 107(5):336-343.

Junginger J, Phelan E, Cherry K and Levy J (1993): Prevalence of psychopathology in elderly persons in nursing homes and in the community. Hosp Community Psychiatry 44(4):381-383.

Juva K, Sulkava R, Erkinjuntti T, Valvanne J and Tilvis R (1993): Prevalence of dementia in the city of Helsinki. Acta Neurol Scand 87(2):106-110.

Juva K, Verkkoniemi A, Viramo P, Polvikoski T, Kainulainen K., Kontula K and Sulkava R (2000): Apolipoprotein E, cognitive function, and dementia in a general population aged 85 years and over. Int Psychogeriatr 12(3):379-387.

Jönsson L, Eriksdotter Jonhagen M, Kilander L, Soininen H, Hallikainen M, Waldemar G, Nygaard H, Andreasen N, Winblad B and Wimo A (2006): Determinants of costs of care for patients with Alzheimer's disease. Int J Geriatr Psychiatry 21(5):449-459.

Kampman O, Kiviniemi P, Koivisto E, Väänänen J, Kilkku N, Leinonen E and Lehtinen K (2004): Patient characteristics and diagnostic discrepancy in first-episode psychosis. Compr Psychiatry 45(3):213-218.

Kane JM (1999): Tardive dyskinesia in affective disorders. J Clin Psychiatry 60 (Suppl 5):43-7; discussion 48-9.

Katz IR, Jeste DV, Mintzer JE, Clyde C, Napolitano J and Brecher M (1999): Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. Risperidone Study Group. J Clin Psychiatry 60(2):107-115.

Keith SJ and Matthews SM (1991): The diagnosis of schizophrenia: a review of onset and duration issues. Schizophr Bull 17(1):51-67.

Kim H and Whall AL (2006): Factors associated with psychotropic drug usage among nursing home residents with dementia. Nurs Res 55(4):252-258.

Klein DA, Steinberg M, Galik E, Steele C, Sheppard JM, Warren A, Rosenblatt and Lyketsos CG (1999): Wandering behaviour in community-residing persons with dementia. Int J Geriatr Psychiatry 14(4):272-279.

Koivisto K (1995): Population-based dementia screening program in the city of Kuopio, eastern Finland: evaluation of screening methods, prevalence of dementia and dementia subtypes. Thesis. University of Kuopio, Kuopio.

Koponen H, Saari K, Savolainen M and Isohanni M (2002): Weight gain and glucose and lipid metabolism disturbances during antipsychotic medication: a review. Eur Arch Psychiatry Clin Neurosci 252(6):294-298.

Koro CE, Fedder DO, L'Italien GJ, Weiss S, Magder LS, Kreyenbuhl J, Revicki D and Buchanan RW (2002): An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. Arch Gen Psychiatry 59(11):1021-1026.

Lachs MS, Becker M, Siegal AP, Miller RL and Tinetti ME (1992): Delusions and behavioral disturbances in cognitively impaired elderly persons. J Am Geriatr Soc 40(8):768-773.

Landi F, Tua E, Onder G, Carrara B, Sgadari A, Rinaldi C, Gambassi G, Lattanzio F, Bernabei R and SILVERNET-HC Study Group of Bergamo (2000): Minimum data set for home care: a valid instrument to assess frail older people living in the community. Med Care 38(12):1184-1190.

Lawlor BA (2004): Behavioral and psychological symptoms in dementia: the role of atypical antipsychotics. J Clin Psychiatry 65(Suppl 11):5-10.

Lawton MP, Casten R, Parmelee PA, Van Haitsma K, Corn J and Kleban MH (1998): Psychometric characteristics of the minimum data set II: validity. J Am Geriatr Soc 46(6):736-744.

Layton D, Harris S, Wilton LV and Shakir SA (2005): Comparison of incidence rates of cerebrovascular accidents and transient ischaemic attacks in observational cohort studies of patients prescribed risperidone, quetiapine or olanzapine in general practice in England including patients with dementia. J Psychopharmacol 19(5):473-482.

Lee PE, Sykora K, Gill SS, Mamdani M, Marras C, Anderson G, Shulman KI, Stukel T, Normand SL and Rochon PA (2005): Antipsychotic medications and drug-induced movement disorders other than parkinsonism: a population-based cohort study in older adults. J Am Geriatr Soc 53(8):1374-1379.

Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO and Kreyenbuhl J. American Psychiatric Association. Steering Committee on Practice Guidelines. Am J Psychiatry 161(Suppl 2):1-56.

Leslie DL and Rosenheck RA (2004): Incidence of newly diagnosed diabetes attributable to atypical antipsychotic medications. Am J Psychiatry 161(9):1709-1711.

Leucht S, Barnes TR, Kissling W, Engel RR, Correll C and Kane JM (2003): Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. Am J Psychiatry 160(7):1209-1222.

Linden M, Bar T and Helmchen H (2004): Prevalence and appropriateness of psychotropic drug use in old age: results from the Berlin Aging Study (BASE). Int Psychogeriatr 16(4):461-480.

Lindenmayer JP, Negron AE, Shah S, Lowinger R, Kennedy G, Bark N and Hyman R (1997): Cognitive deficits and psychopathology in elderly schizophrenic patients. Am J Geriatr Psychiatry 5(1):31-42.

Lindesay J, Matthews R and Jagger C (2003): Factors associated with antipsychotic drug use in residential care: changes between 1990 and 1997. Int J Geriatr Psychiatry 18(6):511-519.

Linjakumpu T, Hartikainen S, Klaukka T, Koponen H, Kivelä SL and Isoaho R (2002): Psychotropics among the home-dwelling elderly--increasing trends. Int J Geriatr Psychiatry 17(9):874-883.

Liperoti R, Mor V, Lapane KL, Pedone C, Gambassi G and Bernabei R (2003). The use of atypical antipsychotics in nursing homes. J Clin Psychiatry 64(9):1106-1112.

Liperoti R, Gambassi G, Lapane KL, Chiang C, Pedone C, Mor V and Bernabei R (2005): Cerebrovascular events among elderly nursing home patients treated with conventional or atypical antipsychotics. J Clin Psychiatry 66(9):1090-1096.

Liperoti R, Onder G, Lapane KL, Mor V, Friedman JH, Bernabei R and Gambassi G (2007): Conventional or atypical antipsychotics and the risk of femur fracture among elderly patients: results of a case-control study. J Clin Psychiatry 68(6):929-934.

Lobo A, Launer LJ, Fratiglioni L, Andersen K, Di Carlo A, Breteler MM, Copeland JR, Dartigues JF, Jagger C, Martinez-Lage J, Soininen H and Hofman A (2000): Prevalence of dementia and major subtypes in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. Neurology 54(11) Suppl 5:S4-9.

Lohr JB, Kuczenski R and Niculescu AB (2003): Oxidative mechanisms and tardive dyskinesia. CNS Drugs. 17(1):47-62.

Lonergan E, Luxenberg J and Colford J (2002): Haloperidol for agitation in dementia. Cochrane Database Syst Rev (4):CD002852.

Lopez OL, Wisniewski SR, Becker JT, Boller F and DeKosky ST (1999): Psychiatric medication and abnormal behavior as predictors of progression in probable Alzheimer disease. Arch Neurol 56(10):1266-1272.

Luis CA, Mittenberg W, Gass CS and Duara R (1999): Diffuse Lewy body disease: clinical, pathological, and neuropsychological review. Neuropsychol Rev 9(3):137-150.

Lyketsos C, Steele, C, Baker L, Galik E, Kopunek S, Steinberg M and Warren A (1997): Major and minor depression in Alzheimer's disease: prevalence and impact. J Neuropsychiatry Clin Neurosci 9(4):556-561.

Lyketsos CG, Steele C, Galik E, Rosenblatt A, Steinberg M, Warren A and Sheppard JM (1999): Physical aggression in dementia patients and its relationship to depression. Am J Psychiatry 156(1):66-71.

Lyketsos CG, Steinberg M, Tschanz JT, Norton MC, Steffens DC and Breitner JC (2000): Mental and behavioral disturbances in dementia: findings from the Cache County Study on Memory in Aging. Am J Psychiatry 157(5):708-714.

Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J and DeKosky S (2002): Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. JAMA 288(12):1475-1483.

Löppönen M, Räihä I, Isoaho R, Vahlberg T and Kivelä SL (2003): Diagnosing cognitive impairment and dementia in primary health care -- a more active approach is needed. Age Ageing 32(6):606-612.

Lövheim H, Sandman PO, Kallin K, Karlsson S and Gustafson Y (2006): Relationship between antipsychotic drug use and behavioral and psychological symptoms of dementia in old people with cognitive impairment living in geriatric care. Int Psychogeriatr 18(4):713-726.

Macdonald AJ, Carpenter GI, Box O, Roberts A and Sahu S (2002): Dementia and use of psychotropic medication in non-'Elderly Mentally Infirm' nursing homes in South East England. Age Ageing 31(1):58-64.

Manton KG (1997): Future trends in chronic disability and institutionalization: implications for long-term care needs. Health Care Manag 3(1):177-191.

Margallo-Lana M, Swann A, O'Brien J, Fairbairn A, Reichelt K, Potkins D, Mynt P and Ballard C (2001): Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. Int J Geriatr Psychiatry 16(1):39-44.

Masand PS (2000): Side effects of antipsychotics in the elderly. J Clin Psychiatry 61(Suppl 8):43-9; discussion 50-1.

McAlpine DD and Mechanic D (2000): Utilization of specialty mental health care among persons with severe mental illness: the roles of demographics, need, insurance, and risk. Health Serv Res 35(1):277-292.

McGlashan TH and Fenton WS (1992): The positive-negative distinction in schizophrenia. Review of natural history validators. Arch Gen Psychiatry 49(1):63-72.

McKeith IG, O'Brien JT and Ballard C (1999): Diagnosing dementia with Lewy bodies. Lancet. 354(9186):1227-1228.

McShane R, Gedling K, Reading M, McDonald B, Esiri MM and Hope T (1995): Prospective study of relations between cortical Lewy bodies, poor eyesight, and hallucinations in Alzheimer's disease. J Neurol Neurosurg Psychiatry 59(2):185-188.

Mehtonen OP, Aranko K, Malkonen L and Vapaatalo H (1991): A survey of sudden death associated with the use of antipsychotic or antidepressant drugs: 49 cases in Finland. Acta Psychiatr Scand 84(1):58-64.

Mena MA and de Yebenes JG (2006): Drug-induced parkinsonism. Expert Opin Drug Saf 5(6):759-771.

Meyer JM, Nasrallah HA, McEvoy JP, Goff DC, Davis SM, Chakos M, Patel JK, Keefe RS, Stroup TS and Lieberman JA (2005): The Clinical Antipsychotic Trials Of Intervention Effectiveness (CATIE) Schizophrenia Trial: clinical comparison of subgroups with and without the metabolic syndrome. Schizophr Res 80(1):9-18.

Modestin J, Stephan PL, Erni T and Umari T (2000): Prevalence of extrapyramidal syndromes in psychiatric inpatients and the relationship of clozapine treatment to tardive dyskinesia. Schizophr Res 42(3):223-230.

Morris JN, Hawes C, Fries BE, Phillips CD, Mor V, Katz S, Murphy K, Drugovich ML and Friedlob AS (1990): Designing the national resident assessment instrument for nursing homes. Gerontologist 30(3):293-307.

Morris JN, Fries BE, Mehr DR, Hawes C, Phillips C, Mor V and Lipsitz LA (1994): MDS Cognitive Performance Scale. J Gerontol 49(4):M174-82.

Morris JN, Hawes C, Murphy K, Nonemaker S (1995). Long Term Care Resident Assessment Instrument User`s Manual Version 2.0. Health Care Financing Administration.

Morris JN, Fries BE, Steel K, Ikegami N, Bernabei R, Carpenter GI, Gilgen R, Hirdes JP and Topinkova E (1997): Comprehensive clinical assessment in community setting: applicability of the MDS-HC. J Am Geriatr Soc 45(8):1017-1024.

Morris JN, Fries BE and Morris SA (1999): Scaling ADLs within the MDS. J Gerontol A Biol Sci Med Sci 54(11):M546-53.

Mueser KT and McGurk SR (2004): Schizophrenia. Lancet 363(9426):2063-2072.

Murphy GM Jr, Lim KO, Wieneke M, Ellis WG, Forno LS, Hoff AL and Nordahl T (1998): No neuropathologic evidence for an increased frequency of Alzheimer's disease among elderly schizophrenics. Biol Psychiatry 43(3):205-209.

Muscettola G, Barbato G, Pampallona S, Casiello M and Bollini P (1999): Extrapyramidal syndromes in neuroleptic-treated patients: prevalence, risk factors, and association with tardive dyskinesia. J Clin Psychopharmacol 19(3):203-208.

Narayanan S, Beusterien KM, Thomas SK, Musher J and Strunk B (2006): Antipsychotic drug use among nursing home residents taking rivastigmine. J Am Med Dir Assoc 7(1):12-16.

Nielsen JA and Nielsen J (1989): Prevalence investigation of mental illness in the aged in 1961, 1972 and 1977 in a geographically delimited Danish population group. Acta Psychiatr Scand Suppl 348:95-104; discussion 167-78.

Noro A, Finne-Soveri H, Björkgren M and Vähäkangas P (2005): Quality and Productivity in Institutional Care of Elderly Residents - Benchmarking with the RAI. STAKES, Helsinki.

Noyes K, Liu H and Holloway RG (2006): What is the risk of developing parkinsonism following neuroleptic use? Neurology 66(6):941-943.

Nygaard HA, Naik M, Ruths S and Straand J (2003): Nursing-home residents and their drug use: a comparison between mentally intact and mentally impaired residents. The Bergen district nursing home (BEDNURS) study. Eur J Clin Pharmacol 59(5-6):463-469.

Oborne CA, Hooper R, Li KC, Swift CG and Jackson SH (2002): An indicator of appropriate neuroleptic prescribing in nursing homes. Age Ageing 31(6):435-439.

Palmer BW, Heaton RK, Gladsjo JA, Evans JD, Patterson TL, Golshan S and Jeste DV (2002): Heterogeneity in functional status among older outpatients with schizophrenia: employment history, living situation, and driving. Schizophr Res 55(3):205-215.

Pang FC, Chow TW, Cummings JL, Leung VP, Chiu HF, Lam LC, Chen QL, Tai CT, Chen LW, Wang SJ and Fuh JL (2002): Effect of neuropsychiatric symptoms of Alzheimer's disease on Chinese and American caregivers. Int J Geriatr Psychiatry 17(1):29-34.

Paquay L, De Lepeleire J, Schoenmakers B, Ylieff M, Fontaine O and Buntinx F (2007): Comparison of the diagnostic accuracy of the Cognitive Performance Scale (Minimum Data Set) and the Mini-Mental State Exam for the detection of cognitive impairment in nursing home residents. Int J Geriatr Psychiatry 22(4):286-293.

Paulsen JS, Ready RE, Stout JC, Salmon DP, Thal LJ, Grant I and Jeste DV (2000): Neurobehaviors and psychotic symptoms in Alzheimer's disease. J Int Neuropsychol Soc 6(7):815-820.

Percudani M, Barbui C, Fortino I and Petrovich L (2005): Epidemiology of first- and second-generation antipsychotic agents in Lombardy, Italy. Pharmacopsychiatry 38(3):128-131.

Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, Partonen, T, Tuulio-Henriksson A, Hintikka J, Kieseppä T, Härkänen T, Koskinen S and Lönnqvist J (2007): Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry 64(1):19-28.

Pirlich M and Lochs H (2001): Nutrition in the elderly. Best Pract Res Clin Gastroenterol 15(6):869-884.

Pirttilä T, Alhainen K, Erkinjuntti T, Koponen H, Puurunen M, Raivio M, Rosenvall A, Suhonen J and Vataja R (2006): Alzheimerin taudin diagnostiikka ja lääkehoito. Käypä Hoito-suositus. Duodecim 122(12):1532-1544.

Pitkälä KH, Laurila JV, Strandberg TE and Tilvis RS (2004): Behavioral symptoms and the administration of psychotropic drugs to aged patients with dementia in nursing homes and in acute geriatric wards. Int Psychogeriatr 16(1):61-74.

Polvikoski T, Sulkava R, Myllykangas L, Notkola IL, Niinistö L, Verkkoniemi A, Kainulainen K, Kontula K, Perez-Tur J, Hardy J and Haltia M (2001): Prevalence of Alzheimer's disease in very elderly people: a prospective neuropathological study. Neurology 56(12):1690-1696.

Prager S and Jeste DV (1993): Sensory impairment in late-life schizophrenia. Schizophr Bull 19(4):755-772.

Purohit DP, Perl DP, Haroutunian V, Powchik P, Davidson M and Davis KL (1998): Alzheimer disease and related neurodegenerative diseases in elderly patients with schizophrenia: a postmortem neuropathologic study of 100 cases. Arch Gen Psychiatry 55(3):205-211.

Putnam KM, Harvey PD, Parrella M, White L, Kincaid M, Powchik P and Davidson M (1996): Symptom stability in geriatric chronic schizophrenic inpatients: a one-year follow-up study. Biol Psychiatry 39(2):92-99.

Rahkonen T, Eloniemi-Sulkava U, Rissanen S, Vatanen A, Viramo P and Sulkava R (2003): Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. J Neurol Neurosurg Psychiatry 74(6):720-724.

Raivio MM, Laurila JV, Strandberg TE, Tilvis RS and Pitkälä KH (2007): Neither atypical nor conventional antipsychotics increase mortality or hospital admissions among elderly patients with dementia: a two-year prospective study. Am J Geriatr Psychiatry 15(5):416-424.

Rapoport M, Mamdani M, Shulman KI, Herrmann N and Rochon PA (2005): Antipsychotic use in the elderly: shifting trends and increasing costs. Int J Geriatr Psychiatry 20(8):749-753.

Ray WA, Meredith S, Thapa PB, Meador KG, Hall K and Murray KT (2001): Antipsychotics and the risk of sudden cardiac death. Arch Gen Psychiatry 58(12):1161-1167.

Ribbe MW, Ljunggren G, Steel K, Topinkova E, Hawes C, Ikegami N, Henrard JC and Jonnson PV (1997): Nursing homes in 10 nations: a comparison between countries and settings. Age Ageing 26(Suppl 2):3-12.

Ritchie K, Artero S, Beluche I, Ancelin ML, Mann A, Dupuy AM, Malafosse A and Boulenger JP (2004): Prevalence of DSM-IV psychiatric disorder in the French elderly population. Br J Psychiatry 184:147-152.

Robinson L, Hutchings D, Dickinson HO, Corner L, Beyer F, Finch T, Hughes J, Vanoli A, Ballard C and Bond J (2007): Effectiveness and acceptability of non-pharmacological interventions to reduce wandering in dementia: a systematic review. Int J Geriatr Psychiatry 22(1):9-22.

Rochon PA, Stukel TA, Sykora K, Gill S, Garfinkel S, Anderson GM, Normand SL, Mamdani M, Lee PE, Li P, Bronskill SE, Marras C and Gurwitz JH (2005): Atypical antipsychotics and parkinsonism. Arch Intern Med 165(16):1882-1888.

Rochon PA, Stukel TA, Bronskill SE, Gomes T, Sykora K, Wodchis WP, Hillmer M, Kopp A, Gurwitz JH and Anderson GM (2007): Variation in nursing home antipsychotic prescribing rates. Arch Intern Med 167(7):676-683.

Roden DM (2004): Drug-induced prolongation of the QT interval. N Engl J Med 350(10):1013-1022.

Ropacki SA and Jeste DV (2005): Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. Am J Psychiatry 162(11):2022-2030.

Rovner BW, German PS, Broadhead J, Morriss RK, Brant LJ, Blaustein J and Folstein MF (1990): The prevalence and management of dementia and other psychiatric disorders in nursing homes. Int Psychogeriatr 2(1):13-24.

Ruths S, Straand J and Nygaard HA (2001): Psychotropic drug use in nursing homes--diagnostic indications and variations between institutions. Eur J Clin Pharmacol 57(6-7):523-528.

Salokangas RK (1993): First-contact rate for schizophrenia in community psychiatric care. Consideration of the oestrogen hypothesis. Eur Arch Psychiatry Clin Neurosci 242(6):337-346.

Salokangas RK, Honkonen T, Jyväsjärvi S, Koponen H, Närhi P and Wahlbeck K (2001): Skitsofrenia. Käypä Hoito-suositus. Duodecim 117: 2640-2657.

Salzman C (1990): Practical considerations in the pharmacologic treatment of depression and anxiety in the elderly. J Clin Psychiatry 51(Suppl):40-43.

Scheen AJ and De Hert MA (2007): Abnormal glucose metabolism in patients treated with antipsychotics. Diabetes Metab 33(3):169-75.

Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C and Wang PS (2007): Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 176(5):627-632.

Schneider LS and Dagerman KS (2004): Psychosis of Alzheimer's disease: clinical characteristics and history. J Psychiatr Res 38(1):105-111.

Schneider LS, Pollock VE and Lyness SA (1990): A meta-analysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 38(5):553-563.

Schneider LS, Ismail MS, Dagerman K, Davis S, Olin J, McManus D, Pfeiffer E, Ryan JM, Sultzer DL and Tariot PN (2003): Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer's disease trial. Schizophr Bull 29(1):57-72.

Schneider LS, Dagerman KS and Insel P (2005): Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 294(15):1934-1943.

Schneider LS, Dagerman K and Insel PS (2006): Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 14(3):191-210.

Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, Lebowitz BD, Lyketsos CG, Ryan JM, Stroup TS, Sultzer DL, Weintraub D, Lieberman JA and CATIE-AD Study Group (2006): Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 355(15):1525-1538.

Schonfeld L, King-Kallimanis B, Brown LM, Davis DM, Kearns WD, Molinari VA, Werner DH, Beattie ER and Nelson AL (2007): Wanderers with cognitive impairment in Department of Veterans Affairs nursing home care units. J Am Geriatr Soc 55(5):692-699.

Schultz SK and Andreasen NC (1999): Schizophrenia. Lancet 353(9162):1425-1430.

Schultz SK, Miller DD, Oliver SE, Arndt S, Flaum M and Andreasen NC (1997): The life course of schizophrenia: age and symptom dimensions. Schizophr Res 23(1):15-23.

Sgadari A, Morris JN, Fries BE, Ljunggren G, Jonsson PV, DuPaquier JN and Schroll M (1997): Efforts to establish the reliability of the Resident Assessment Instrument. Age Ageing 26(Suppl 2):27-30.

Shader RI and Greenblatt DJ (1998): Potassium, antipsychotic agents, arrhythmias, and sudden death. J Clin Psychopharmacol 18(6):427-428.

Simon SR, Chan KA, Soumerai SB, Wagner AK, Andrade SE, Feldstein AC, Lafata JE, Davis RL and Gurwitz JH (2005): Potentially inappropriate medication use by elderly persons in U.S. Health Maintenance Organizations, 2000-2001. J Am Geriatr Soc 53(2):227-232.

Sink KM, Holden KF and Yaffe K (2001): Pharmacological treatment of neuropsychiatric symptoms of dementia: a review of the evidence. JAMA 293(5):596-608.

Skoog I (2004): Psychiatric epidemiology of old age: the H70 study--the NAPE lecture 2003. Acta Psychiatr Scand 109(1):4-18.

Skoog I, Nilsson L, Landahl S and Steen B (1993): Mental disorders and the use of psychotropic drugs in an 85-year-old urban population. Int Psychogeriatr 5(1):33-48.

Sloane PD, Mitchell CM, Preisser JS, Phillips C, Commander C and Burker E (1998): Environmental correlates of resident agitation in Alzheimer's disease special care units. J Am Geriatr Soc 46(7):862-869.

Snowdon J, Day S and Baker W (2005): Why and how antipsychotic drugs are used in 40 Sydney nursing homes. Int J Geriatr Psychiatry 20(12):1146-1152.

Sobel E, Louhija J, Sulkava R, Davanipour Z, Kontula K, Miettinen H, Tikkanen M, Kainulainen K and Tilvis R (1995): Lack of association of apolipoprotein E allele epsilon 4 with late-onset Alzheimer's disease among Finnish centenarians. Neurology 45(5):903-907.

Sorensen L, Foldspang A, Gulmann NC and Munk-Jorgensen P (2001): Determinants for the use of psychotropics among nursing home residents. Int J Geriatr Psychiatry 16(2):147-154.

STAKES. Care and services for older people 2005 (2007). Social Security, National Research and Development Centre for Welfare and Health, Yliopistopaino, Helsinki.

STAKES. Facts about Social Welfare and Health Care in Finland (2006). STAKES, Helsinki.

Statistics Finland (2006). Avalable at http://www.stat.fi/tup/tietotrendit/tt_05_06_ikaantyva_vaesto.html [Accessed 30 September 2007].

Statistics Finland (2007a). Available at http://www.stat.fi/tup/tietotrendit/tt_01_05_nieminen.html [Accessed 30 September 2007].

Statistics Finland (2007b). Available at http://www.stat.fi/tup/suoluk/suoluk_vaesto.html [Accessed 30 September 2007].

Steele C, Rovner B, Chase GA and Folstein M (1990): Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. Am J Psychiatry 147(8):1049-1051.

Stein LM and Thienhaus OJ (1993): Hearing impairment and psychosis. Int Psychogeriatr 5(1):49-56.

Stotsky B (1984): Multicenter study comparing thioridazine with diazepam and placebo in elderly, nonpsychotic patients with emotional and behavioral disorders. Clin Ther 6(4):546-559.

Straus SM, Bleumink GS, Dieleman JP, van der Lei J, 't Jong GW, Kingma JH, Sturkenboom MC and Stricker BH (2004): Antipsychotics and the risk of sudden cardiac death. Arch Intern Med 164(12):1293-1297.

Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN, Mitan SJ, Kadam DL, Sanger TM, Feldman PD, Tollefson GD and Breier A (2000): Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry 57(10):968-976.

Sulander T, Martelin T, Sainio P, Rahkonen O, Nissinen A and Uutela A (2006): Trends and educational disparities in functional capacity among people aged 65-84 years. Int J Epidemiol 35(5):1255-1261.

Sulkava R, Wikström J, Aromaa A, Raitasalo R, Lehtinen V, Lahtela K and Palo J (1985): Prevalence of severe dementia in Finland. Neurology 35(7):1025-1029.

Suominen M, Muurinen S, Routasalo P, Soini H, Suur-Uski I, Peiponen A, Finne-Soveri H and Pitkälä KH (2005): Malnutrition and associated factors among aged residents in all nursing homes in Helsinki. Eur J Clin Nutr 59(4):578-583.

Suvisaari JM, Saarni SI, Perälä J, Suvisaari JV, Härkänen T, Lönnqvist J and Reunanen A (2007): Metabolic syndrome among persons with schizophrenia and other psychotic disorders in a general population survey. J Clin Psychiatry 68(7):1045-1055.

Takkouche B, Montes-Martinez A, Gill SS and Etminan M (2007): Psychotropic medications and the risk of fracture: a meta-analysis. Drug Saf 30(2):171-184.

Tariot PN and Ismail MS (2002): Use of quetiapine in elderly patients. J Clin Psychiatry 63(Suppl 13):21-26.

Tariot PN, Podgorski CA, Blazina L and Leibovici A (1993): Mental disorders in the nursing home: another perspective. Am J Psychiatry 150(7):1063-1069.

Trifiro G, Spina E, Brignoli O, Sessa E, Caputi AP and Mazzaglia G (2005): Antipsychotic prescribing pattern among Italian general practitioners: a population-based study during the years 1999-2002. Eur J Clin Pharmacol 61(1):47-53.

Trinh NH, Hoblyn J, Mohanty S and Yaffe K (2003): Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer disease: a meta-analysis. JAMA 289(2):210-216.

Tune LE (2001): Risperidone for the treatment of behavioral and psychological symptoms of dementia. J Clin Psychiatry 62(Suppl 21):29-32.

Wancata J, Benda N, Hajji M, Lesch OM and Muller C (1998): Prevalence and course of psychiatric disorders among nursing home admissions. Soc Psychiatry Psychiatr Epidemiol 33(2):74-79.

van der Werf M, van Boxtel M, Verhey F, Jolles J, Thewissen V and van Os J (2007): Mild hearing impairment and psychotic experiences in a normal aging population. Schizophr Res 94(1-3):180-186.

van Dijk KN, de Vries CS, van den Berg PB, Brouwers JR and de Jong-van den Berg L (2000): Drug utilisation in Dutch nursing homes. Eur J Clin Pharmacol 55(10):765-71.

van Harten PN, Matroos GE, Hoek HW and Kahn RS (1996): The prevalence of tardive dystonia, tardive dyskinesia, parkinsonism and akathisia The Curacao Extrapyramidal Syndromes Study: I. Schizophr Res 19(2-3):195-203.

Wagner AW, Teri L and Orr-Rainey N (1995): Behavior problems of residents with dementia in special care units. Alzheimer Dis Assoc Disord 9(3);121-127.

Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH and Brookhart MA (2005): Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 353(22):2335-2341.

Wild R, Pettit T and Burns A (2003): Cholinesterase inhibitors for dementia with Lewy bodies. Cochrane Database Syst Rev (3):CD003672.

Wilson JA and MacLennan WJ (1989): Review: drug-induced parkinsonism in elderly patients. Age Ageing 18(3):208-210.

Wilson RS, Gilley DW, Bennett DA, Beckett LA and Evans DA (2000): Hallucinations, delusions, and cognitive decline in Alzheimer's disease. J Neurol Neurosurg Psychiatry 69(2):172-177.

Wimo A, Winblad B, Aguero-Torres H and von Strauss E (2003): The magnitude of dementia occurrence in the world. Alzheimer Dis Assoc Disord 17(2):63-67.

Wise MG and Tierney J (1992): Psychopharmacology in the elderly. J La State Med Soc 144(10):471-476.

Wojszel ZB (2006): Determinants of nutritional status of older people in long-term care settings on the example of the nursing home in Bialystok. Adv Med Sci 51:168-173.

World Health Organization (1995): Tautiluokitus ICD-10 (International Classification of Diseases ICD-10). Rauma, Kirjapaino Oy West Point.

Yao L and Algase D (2006): Environmental ambiance as a new window on wandering. West J Nurs Res 28(1):89-104.

Zayas EM and Grossberg GT (1998): The treatment of psychosis in late life. J Clin Psychiatry 59(Suppl 1):5-10; discussion 11-2.

Zhong KX, Tariot PN, Mintzer J, Minkwitz MC and Devine NA (2007): Quetiapine to treat agitation in dementia: a randomized, double-blind, placebo-controlled study. Curr Alzheimer Res 4(1):81-93.

Zimmerman DR, Karon SL, Arling G, Clark BR, Collins T, Ross R and Sainfort F (1995): Development and testing of nursing home quality indicators. Health Care Financ Rev 16(4):107-127.

Zuidema SU, Derksen E, Verhey FR and Koopmans RT (2007): Prevalence of neuropsychiatric symptoms in a large sample of Dutch nursing home patients with dementia. Int J Geriatr Psychiatry 22(7):632-638.

Östling S and Skoog I (2002): Psychotic symptoms and paranoid ideation in a nondemented population-based sample of the very old. Ach Gen Psychiatry 59(1):53-59.

Östling S, Palsson SP and Skoog I (2007): The incidence of first-onset psychotic symptoms and paranoid ideation in a representative population sample followed from age 70-90 years. Relation to mortality and later development of dementia. Int J Geriatr Psychiatry 22(6):520-528.